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Eptacog alfa activated: a recombinant product to treat rare congenital bleeding disorders

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ABSTRACT

Glanzmann's thrombasthenia (GT) and congenital factor VII deficiency (FVII CD) are rare autosomal recessive bleeding disorders: GT is the most frequent congenital platelet function disorder, and FVII CD is the most common factor-deficiency disease after haemophilia. The frequency of these disorders in the general population ranges from 1:500,000 to 1:2,000,000. Because GT and FVII CD are both rare, registries are the only approach possible to allow the collection and analysis of sufficient observational data. Recombinant activated factor VII (rFVIIa, eptacog alfa activated) is indicated for the treatment of acute bleeding episodes and for surgery coverage in patients with GT who are refractory to platelets and have antiplatelet or anti-human leukocyte antigen (HLA) antibodies, and for the prevention and treatment of bleeding in patients with FVII CD. This article summarises published data on the mechanism of action and use of rFVIIa in these disorders from two international, prospective, observational registries: the Glanzmann's Thrombasthenia Registry (GTR) for GT; and the Seven Treatment Evaluation Registry (STER) for FVII CD. Haemostatic effectiveness rates with rFVIIa were high across all patients with GT and those with FVII CD, and treatment with rFVIIa in the GTR and STER registries was well tolerated. The GTR and the STER are the largest collections of data in GT and FVII CD, respectively, and have expanded our knowledge of the management of these two rare bleeding disorders.

1. Introduction

Glanzmann's thrombasthenia (GT) and congenital factor VII deficiency (FVII CD) are rare autosomal recessive bleeding disorders, caused by platelet dysfunction in GT [1], and by structurally abnormal or deficient FVII in FVII CD [2]. Because both GT and FVII CD are rare, it is not possible to carry out controlled, prospective clinical trials [1]; instead, it is necessary to collect and analyse observational data. Patient registries are particularly useful for improving our understanding of the management of rare diseases: the largest patient registries for GT and FVII CD are the Glanzmann's Thrombasthenia Registry (GTR) [3–5] and the Seven Treatment Evaluation Registry (STER) [6,7], respectively.

Physiologically, FVII exerts its haemostatic effect after complexing with tissue factor (TF). In normal individuals, FVIIa-TF complex formation on TF-bearing cells at the site of vascular injury activates FX and FIX to trigger a series of events leading to an initial thrombin generation. The latter activates a variety of clotting factors (e.g., FV, FVIII, FXI) as well as platelets. Thrombin then induces local haemostasis by converting fibrinogen to fibrin, which polymerises and forms a thrombus in conjunction with platelets at the site of vascular injury. Thrombin can also be generated on the surface of activated platelets by the action of recombinant activated factor VII (rFVIIa, eptacog alfa activated, NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark), which is thought to promote haemostasis by activating FIX and FX when complexed with TF.

Recombinant FVIIa is prescribed for the treatment of bleeding episodes and the prevention of bleeding in those undergoing surgery or invasive procedures in patients with GT with refractoriness to platelets (and in some countries where platelets are not available) [8–10]. The objectives of this article are to present the methodologies used for the GTR and the STER, and to summarise published data on the effectiveness of rFVIIa in patients with GT and FVII CD. The article will also highlight the value and feasibility of such patient registries in the collection of data for rare bleeding disorders.

2. Glanzmann's thrombasthenia

2.1. Disease overview

Activated platelets are recruited to the site of vascular injury where they normally aggregate, an event mediated in part by the binding of soluble fibrinogen to the platelet surface α_{IIb}-β_3 integrin (originally termed glycoprotein IIb-IIIa [GPIIb-IIIa]), a fibrinogen receptor. Patients with GT have low levels of, or defective, surface α_{IIb}-β_3 integrin [1,11,12]; as a result, the small amount of thrombin generated leads to the failure of platelets to

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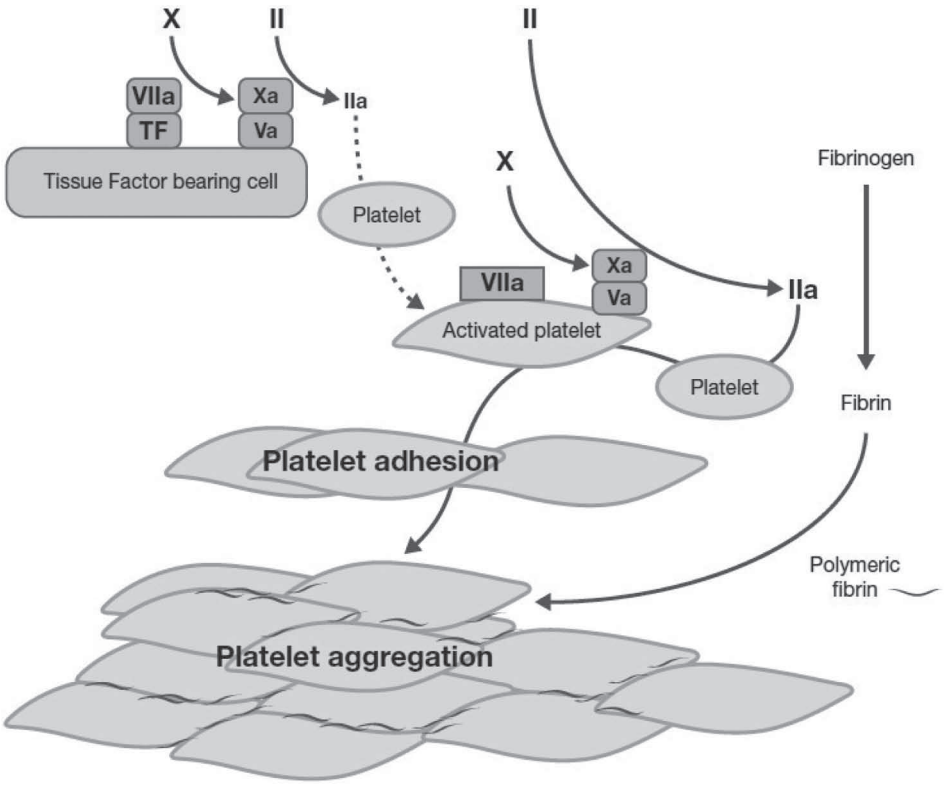

Fig. 1. Schematic tissue factor (TF)-independent, platelet-dependent model of primary haemostatic plug formation in Glanzmann's thrombasthenia (GT) platelets deficient in glycoprotein (GP) IIb-IIIa. Recombinant activated factor VII (rFVIIa) TF complex on TF-bearing cells at the site of vascular injury activates FX to FXa. FXa-FVa on the TF-bearing cells initiates generation of a small amount of thrombin (FIIa) that is insufficient to provide fibrin formation but sufficient to activate GT platelets, causing degranulation and release of FV. FVIIa binds weakly to the negatively charged phospholipid surface [49] of the activated platelets, with the binding enhanced by the GPIb/IX/V complex [50]. FVIIa at high concentration (attained by high-dose rFVIIa therapy) can directly activate FX to FXa to mediate generation of a high concentration of thrombin (thrombin burst). The augmented thrombin generation results in an increased number of activated platelets deposited (adhesion) to the wound site and in an increased available platelet procoagulant surface to facilitate more thrombin generation and more platelet activation. The augmented thrombin generated also converts fibrinogen to fibrin. GT platelets lack the fibrinogen receptor (α_{IIb}-β_3 integrin); therefore, these platelets cannot utilise fibrinogen for aggregation. However, binding of fibrin/polymeric fibrin to an unidentified platelet surface receptor can mediate aggregation of GT platelets at the wound site (albeit less potently than fibrinogen-mediated aggregation of normal platelets), resulting in the formation of a primary haemostatic plug (adapted from Poon [51] with permission)

bind fibrinogen, retract a fibrin clot or aggregate after stimulation by agonists such as adenosine diphosphate, thrombin, epinephrine and collagen at sites of vessel injury. Consequently, clot formation, and in turn retraction, fail. The incidence of GT is approximately 1:1,000,000, but is much higher in populations where consanguineous marriages are common [1,13].

GT is associated with well-defined sites of bleeding, including epistaxis, menorrhagia, gingival haemorrhage, easy bruising and ecchymosis [1]. Gastrointestinal (GI) bleeding and haematuria are less common [1], and haemarthroses and deep haematomas seldom occur [13,14]. In general, spontaneous, unprovoked bleeding is uncommon in patients with GT; rather, haemorrhages are usually associated with physiological or pathological predisposing conditions [1]. In addition, excessive bleeding after trauma or minor/major invasive or dental procedures is a common, major problem in GT [12–14].

Severity and frequency of bleeding in GT is heterogeneous, ranging from minimal bruising, to frequent, severe, potentially fatal haemorrhages [1,12,14]; this variability is seen even in siblings. The expression and functionality of the mutated α_{IIb}-β_3 integrin have been used to classify GT as type 1 (α_{IIb}-β_3 integrin expression <5%), type 2 (5–20%) or variant (>20–100%, but with a dysfunctional α_{IIb}-β_3 integrin) [14]. This classification does not fully predict bleeding phenotype, however, and the risk of severe bleeding remains unpredictable [1].

Standard treatment for GT is platelet transfusion – for persistent or severe bleeding, and for haemostatic cover of major invasive procedures [13–16]. However, platelet transfusion in patients with GT is associated with the potential development of isoantibodies against α_{IIb}-β_3 integrin and/or human leukocyte antigen (HLA), rendering further transfusions ineffective [14,16]. Platelet storage may also result in a series of side-effects such as fever, sepsis, thrombosis and acute lung injury [17]. In addition, platelet transfusion leaves patients at risk of blood-borne pathogen contamination related to the use of blood products [18].

In patients with GT, rFVIIa is recommended, administered as a bolus injection of 90 μg/kg [8–10]. While the mechanism of action of rFVIIa in GT is not fully understood [16], it is thought that rFVIIa improves local thrombin generation by direct activation of FX on the platelet surface (Fig. 1); rFVIIa treatment partially restores platelet aggregation, possibly via other membrane receptor pathways [16,19,20]. Although rFVIIa treatment does not result in a stable platelet plug, it does provide an increase of procoagulant surface at the site of injury, thereby facilitating additional enhancement of thrombin generation and subsequent fibrin formation [16].

2.2. Glanzmann's Thrombasthenia Registry

Prior to the European Medicines Agency (EMA) approval of rFVIIa for GT patients with inhibitors, a small clinical trial of rFVIIa was conducted in four patients [21], and a larger international survey of its efficacy and safety was subsequently conducted in 59 patients with GT (34 surgical/invasive procedures and 108 bleeding episodes) [22]. The results of the

international survey showed that efficacy (bleeding stopped without recurrence within 48 hours) was achieved in 29/31 (94%) evaluable procedures, and 77/103 (75%) evaluable bleeding episodes. Although valuable information was obtained from the survey, the data were not sufficient to define optimal regimens for patients with different types of bleeding or procedures. The GTR is an international, prospective, observational registry; it was created to collect and describe data on the effectiveness and safety of rFVIIa for the treatment of acute and surgical bleeding episodes in patients with GT with past or present refractoriness to platelet transfusions. The GTR also collected information on other haemostatic agents – platelet transfusion and antifibrinolytic agents (AF) – and on all GT patients, regardless of their platelet antibody and refractoriness history [3–5]. The effectiveness of patients' treatment regimens was evaluated by caregivers/patients or physicians as effective, partially effective, ineffective or not evaluable. The assessment of safety included frequency of adverse events during and after treatment, with a particular focus on any complications related to thromboembolic events (TEs).

Data were collected (from December 2004 until the registry was closed in December 2011, following completion of the EMA requirements) from 218 patients (45 sites in 15 countries from four continents). As such, the GTR is the largest observational study reporting on GT patients; as data on haemostatic agents other than rFVIIa were also included, it addresses the issues that remained following the previous GT patient survey. The GTR data were used for the primary analysis performed in 2012 [3,4,23]. Given the nature of data obtained from registries, and following review by the GTR expert panel of the admissions, a post-hoc secondary data analysis was performed in 2014; admissions linked to the same bleeding event in the registry were taken into account, as were two admissions first classified as bleeding episodes that were in fact surgical procedures [24,25]**.** All data were included in the safety analysis.

Data from the GTR described below show that GT patients can present with severe bleeds. Recombinant FVIIa, and other currently available treatments for bleeding in GT, were found to have a good safety and effectiveness profile in most patients. Approximately one-quarter of the non-surgical bleeds reported occurred in patients with a history of platelet antibodies and/or refractoriness [24]. Regardless of the severity of bleeding, or history of antiplatelet antibodies and/or refractoriness to platelets, the median rFVIIa dose and dosing interval aligned with those recommended previously for GT patients (≥80 μg/kg, ≤2.5 hour interval) [24]. In all patient groups, the number of doses reported for severe bleeds was understandably higher than for moderate bleeds, and was associated with longer treatment durations and higher cumulative doses for severe bleeds.

For sections 2.2.1 and 2.2.2 below, treatment is categorised into five groups: rFVIIa alone; rFVIIa + AF; rFVIIa + platelets with or without AF; platelets with or without AF; and AF alone.

2.2.1. Recombinant FVIIa in acute bleeds

2.2.1.1. Effectiveness of rFVIIa treatment

Eight-hundred and twenty nine admissions in the GTR were for acute bleeding episodes in 184 patients (Table 1) [24]. Most patients (71%) had no history of platelet antibodies and/or refractoriness. Platelets with or without AF was the most commonly used treatment (Table 1).

Recombinant FVIIa-based treatment showed broadly similar effectiveness to platelets in the majority of bleeding episodes, regardless of the presence or absence of platelet antibodies/refractoriness (Table 2) [3,24]. Treatment with rFVIIa alone was effective (bleeding stopped and haemostasis achieved for ≥6 h) in 100% of bleeds in patients with only antibodies (vs. 82% of bleeds treated with platelets with or without AF), and in 90.9% (vs. 85.7%), 90.3% (vs. 84.6%) and 88.9% (vs. 64.7%) of bleeds in patients with only refractoriness, no antibodies or refractoriness, and antibodies + refractoriness, respectively (Table 3).

Table 1
Summary of patients with admissions in the Glanzmann's Thrombasthenia Registry for acute bleeding episodes [24]

Number of patients	184
Number of admissions for bleeding episodes	829
History, no. of patients (%)	
Platelet antibodies confirmed	28 (15.2)
Platelet refractoriness confirmed	8 (4.3)
Both confirmed	17 (9.2)
No confirmed platelet antibodies or refractoriness	131 (71.2)
Treatment	
rFVIIa	124 (15.0)
rFVIIa + AF	107 (12.9)
Platelets[a]	312 (37.6)
rFVIIa + Platelets[a]	67 (8.1)
AF	219 (26.4)

rFVIIa, recombinant activated factor VII; AF, antifibrinolytic agents.
[a] With or without AF.

2.2.1.2. Treatment failures and re-bleeds

Overall, treatment failure (i.e., bleeding unchanged or worsened following treatment) occurred in 18 (2%) admissions in the GTR (nine had received AF only; three, rFVIIa + AF; five, platelets with or without AF; and one, rFVIIa + platelets with or without AF) [24]. Of 738 episodes for which re-bleeding data were available, 45 re-bleeds (i.e., bleeds re-starting ≥6 h and <48 h after the initial bleeding stopped) occurred in 25 patients (one had received rFVIIa alone; 23, platelets with or without AF; 12, rFVIIa + platelets with or without AF; and four, AF alone). Of the 45 re-bleeds, 27 occurred in patients with a history of platelet antibodies and refractoriness.

2.2.1.3. Safety of rFVIIa in acute bleeds

Data from the GTR demonstrated that rFVIIa, with or without AF, had a good safety profile for the treatment of acute bleeds [24]. No TEs were reported with any treatment modalities used for acute bleeding episodes [24].

2.2.2. Recombinant FVIIa in surgical procedures

2.2.2.1. Effectiveness of rFVIIa treatment

Ninety-six patients were treated for a total of 206 surgical procedures: 169 (82%) were minor and 37 (18%) major (Table 3) [25]. Nearly half (49%) of patients had no history of platelet antibodies and/or refractoriness. Of the minor procedures, dental was the most frequent (n = 134 [79%]), and the most common major procedures were GI and orthopaedic (n = 9 [24%] for each). The treatment used the most for minor procedures was rFVIIa with or without AF (n = 121 [72%]), and for major procedures, rFVIIa + platelets with or without AF (n = 13 [35%]) [25].

The effectiveness of rFVIIa-based treatment in surgical procedures was similar to that of platelets and rFVIIa + platelets, regardless of platelet antibodies/refractoriness history (Table 4) [25]. In patients with GT without antibodies/refractoriness, rFVIIa showed 100% effectiveness for both minor (n = 24) and major (n = 4) procedures; this was similar to that for platelets with or without AF (minor procedures 11/11 [100%]; major 5/5 [100%]) and rFVIIa + platelets with or without AF (minor procedures 4/4 [100%]; major 6/9 [67%]). In patients with GT and platelet antibodies, refractoriness or both, the effectiveness of rFVIIa (minor procedures 29/32 [91%]; major 2/2 [100%]) was comparable

Table 2
Treatment effectiveness (defined as bleeding stopped/haemostasis achieved for ≥6 hours) of acute bleeding episodes according to bleed severity and history of platelet antibodies and refractoriness in Glanzmann's thrombasthenia: data from the Glanzmann's Thrombasthenia Registry [24]

	Effective treatment, %					
	Bleed severity		History of platelet antibodies and refractoriness			
	Moderate	Severe	Platelet antibodies only	Platelet refractoriness only	Both	Neither
rFVIIa	91.7	0	100	90.9	88.9	90.3
rFVIIa + AF	87.0	74.3	69.2	87.5	66.7	93.6
Platelets[a]	77.8	80.8	82.0	85.7	64.7	84.6
rFVIIa + platelets[a]	85.3	59.4	61.1	50.0	87.5	83.3
AF	85.2	83.0	83.3	88.9	100	84.3
Total	84.1	76.6	78.2	81.1	69.7	86.3

rFVIIa, recombinant activated factor VII; AF, antifibrinolytic agents.
[a] With or without AF.

Table 3
Summary of patients undergoing surgical procedures: data from the Glanzmann's Thrombasthenia Registry [25]

Number of patients	96
Number of all procedures	206
Female, n (%)	
Patients	52/96 (54)
Procedures	114/206 (55)
History, n (%)	
Platelet antibodies confirmed	43 (44.8)
Platelet refractoriness confirmed	23 (24)
Both confirmed	17 (18)
No confirmed platelet antibodies or refractoriness	47 (49)
Number of all procedures, n (%)	206 (100)
Dental	134 (65)
Endoscopy	11 (5.3)
Nasal	8 (3.9)
Gastrointestinal	9 (4.4)
Orthopaedic	9 (4.4)
Other	35 (17.0)
Minor procedures, n (%)	169
Dental	134 (79.0)
Endoscopy	11 (6.5)
Nasal	8 (4.7)
Other	16 (9.5)
Major procedures, n (%)	37
Gastrointestinal	9 (24.3)
Orthopaedic	9 (24.3)
Other	19 (51.4)

to that for platelets with or without AF (minor procedures 10/15 [67%]; major 2/2 [100%]) and rFVIIa + platelets with or without AF (minor procedures 7/9 [78%]; major 2/3[67%]).

Administration of rFVIIa was generally at an initial dose of around 90 μg/kg every 2 hours for both minor and major procedures [25]. For minor procedures, the median number of rFVIIa doses was two to three; for major procedures, the number of doses was higher and more variable.

2.2.2.2. Safety of rFVIIa in surgical procedures

Data from the GTR demonstrated that rFVIIa, with or without AF, had a good safety profile for surgical procedures [25]. One TE was reported; this was in an adult female with platelet refractoriness treated with rFVIIa + platelets + AF for a major surgical procedure (emergency laparotomy for an ovarian cyst and haematoma with bilateral ureteral compressions) and was assessed by the investigator to be probably or possibly related to rFVIIa [23,25].

3. Congenital factor VII deficiency

3.1. Disease overview

Patients with FVII CD have a broad spectrum of mutations in the gene coding FVII (F7) in chromosome 13 [2,26]. These mutations result in structurally abnormal FVII, with decreased secretion or reduced function [26]. Normal FVII is part of the initiating complex of the extrinsic coagulation pathway; thus, FVII CD is the only congenital bleeding disorder characterised by isolated prolonged prothrombin time [2]. FVII CD is the most common of the rare autosomal recessive bleeding disorders [26]. The estimated prevalence is one case per 300,000–500,000 in European countries [27]. According to a worldwide survey, there is wide variation in prevalence, from 1:>2,000,000 (Japan, Sudan and Pakistan), to 1:500,000 (United States and Australia), 1:200,000 (Canada, Italy, Iran and Poland), 1:100,000 (UK, Italy and Croatia), and 1:60,000 (Ireland and Hungary) [26,28]. Similar to GT, the prevalence of FVII CD (especially the severe form) seems to be higher in populations where consanguineous marriages are common [29].

Factor VII CD can range in clinical severity – from life-threatening haemorrhagic episodes to asymptomatic [6,7,30]. A classification of bleeding phenotype has been proposed by the International Registry on Factor VII (IR7)/STER Research Group as follows: haemophilia-like (severe symptoms); platelet-like (mild muco-cutaneous bleedings, including menorrhagia); and asymptomatic [31]. As many as 10–15% of patients with FVII CD experience severe, potentially life- or limb-threatening haemorrhages, including central nervous system (CNS) bleeds, GI bleeds and haemarthroses [27,30]; these patients require aggressive FVII replacement therapy and/or long-term prophylaxis [6,7]. Of note, there is no clear-cut or consistent correlation between FVII levels and bleeding symptoms; some individuals with low/very low FVII coagulant activity (FVII:C) remain asymptomatic throughout their life while other patients with similar levels experience life-threatening bleeds [32]. Differences are seen even in individuals with the same genetic mutation [2,30,33]; it is therefore not possible to predict an individual's propensity to bleed. This is an important issue because patients with a severe bleeding phenotype often become symptomatic at a very young age, and in this clinical setting, prophylaxis may be the most appropriate treatment option. In addition, excessive bleeding after surgical procedures is a major problem in FVII CD, especially in asymptomatic, undiagnosed individuals who represent up to one-third of patients [30,34].

Although not specifically designed for FVII CD, rFVIIa effectively serves as a specific factor replacement therapy to initiate thrombin generation at the site of injury [35]. Preliminary pharmacokinetic data suggested that rFVIIa has a

Table 4
Treatment outcome for surgical procedures in the Glanzmann's Thrombasthenia Registry according to history of platelet antibodies and refractoriness [25]

	Effective treatment, n (%)			
	Platelet antibodies only	Platelet refractoriness only	Both	Neither
Minor surgery				
rFVIIa	9/10 (90)	4/4 (100)	16/18 (88.9)	24/24 (100)
rFVIIa + AF	19/23 (82.6)	3/5 (60)	19/19 (100)	17/17 (100)
Platelets[a]	8/12 (66.7)	0/0 (-)	2/3 (66.7)	11/11 (100)
rFVIIa + platelets[a]	3/4 (75)	1/2 (50)	3/3 (100)	4/4 (100)
AF	1/1 (100)	0/0 (-)	0/0 (-)	4/8 (50)
Total	40/50 (80.0)	8/11 (72.7)	40/43 (93.0)	60/64 (93.8)
Major surgery				
rFVIIa	2/2 (100)	0/0 (-)	0/0 (-)	4/4 (100)
rFVIIa + AF	2/4 (50)	0/0 (-)	0/0 (-)	3/3 (100)
Platelets[a]	1/1 (100)	0/0 (-)	1/1 (100)	5/5 (100)
rFVIIa + platelets[a]	1/1 (100)	1/2 (50)	0/0 (-)	6/9 (66.7)
AF	0/0 (-)	0/0 (-)	0/0 (-)	3/3 (100)
Total	6/8 (75.0)	1/2 (50)	1/1 (100)	21/24 (87.5)

rFVIIa, recombinant activated factor VII; AF, antifibrinolytic agents; n, number of surgical procedures.
[a] With or without AF.

short half-life of approximately 3 hours in patients with FVII CD [36]; however, its haemostatic activity may endure for longer than its plasma kinetics. This may be explained, in part, by its binding to TF in perivascular tissues [37]. Following infusion in mice, rFVIIa was reported to rapidly associate with vascular endothelium, followed by entry into the extravascular space and localisation to regions containing TF-bearing cells [38], where it was then sequestered and retained for prolonged periods [38]. In another study, rFVIIa exposed to platelet-rich plasma from patients with FVII CD was internalised to the platelet cytoplasm with redistribution into the open canalicular system and α-granules, where it was protected from physiological clearance mechanisms [39]. The internalised rFVIIa appeared to improve platelet aggregate formation and fibrin generation in perfusion studies [39]. It has also been demonstrated more recently that rFVIIa has a large volume of distribution in FVII CD [40,41]. These different hypotheses help to explain the observations of a prolonged pharmacological effect of rFVIIa in FVII CD.

The recommended rFVIIa dose range in adults and children is 15–30 μg/kg, administered every 4–6 hours until haemostasis is achieved, with dose and frequency of injections adapted to each individual [8].

3.2. The Seven Treatment Evaluation Registry

In 1999, the IF7 was established with the aim of improving our knowledge and understanding of FVII CD. In 2004, the IF7 Study Group created the STER to conduct rFVIIa pharmacovigilance. The STER completed enrolment in 2012, and data were merged with the IF7 registry to form one large, homogeneous database [42].

The STER was a large, international, prospective, observational, web-based registry created to collect and describe data on the treatment and outcomes of patients with FVII CD (including therapy-related adverse events). Its aim was to evaluate the efficacy and safety of the different therapeutic options for spontaneous bleeds, prophylaxis and surgical coverage in patients with FVII CD [6,7]. The information gathered on the treatment of patients with FVII CD should help clinicians to make treatment decisions based on consolidated clinical evidence as well as their personal clinical experience. The primary objectives of STER were to: describe the available treatments for bleeds in a large international cohort of well-defined patients with FVII CD; investigate the occurrence of inhibitors to FVII, and thrombotic complications; describe short-term prophylaxis and how this relates to surgical procedures; describe long-term prophylaxis; and assess efficacy and safety of treatment modalities in a real-life clinical setting.

Investigators followed strictly controlled data collection procedures established by the IF7 Study Group. Data for patients with FVII CD from 18 countries worldwide were collected online and stored in a custom-designed, Microsoft SQL Server 2000 database, which contained electronic case-report forms (with no components installed on the centre computers). At treatment initiation, various demographics were recorded, including: age; weight; gender; presenting symptoms and bleeding type; subsequent symptoms and bleeding type; date of diagnosis; and previous treatment. As patients with FVII CD are at known risk of developing inhibitors, testing was conducted in a central laboratory, using a method specifically developed for measuring antibodies to FVII [43]. Investigators accessed the system when a patient required treatment for acute bleeding episodes, prophylaxis or surgical intervention. To date, the STER online registry has collated information from more than 600 patient cases [42].

3.2.1. Prediction of ensuing bleeding

In other inherited bleeding disorders, attempts have been made to assess the predictive power of patient bleeding history, to enable identification of patients who may have a more severe phenotype. In this respect, a quantitative bleeding score, related to the number and severity of bleeding symptoms and to the association between patterns of bleeding symptoms and laboratory characteristics of patients, has been employed to validate the clinical criteria for the diagnosis of type 1 von Willebrand disease [44,45]. Because of the clinical and genetic specificity of FVII CD, it was felt that a similar approach should be pursued in FVII deficiency, so that treatments can be tailored in accordance with the predicted disease severity and specific clinical needs.

Data from the STER have been used to investigate which factors upon disease presentation may be useful in predicting the ensuing bleeding phenotype [42]. In 626 patients with FVII CD (325 females), it was revealed that the first major bleeding symptom was an independent predictor of the risk of subsequent major bleeds. At disease presentation/diagnosis,

Table 5
Treatment outcomes for acute bleeding episodes treated with recombinant activated factor VII in congenital FVII deficiency: data from the Seven Treatment Evaluation Registry [6]

	n	Days of treatment, median (range)	No. of doses, median (range)	Total dose (μg/kg)		Treatment outcome[a]				
				Median	Range	Excellent	Effective	Partially effective	Ineffective	Not evaluable
Total	79	1 (1–14)	1 (1–87)	60	10–3600	38	35	3	NR	3
Haemarthrosis	27	1 (1–3)	1 (1–7)	60	10–300	15	10	2	NR	NR
Menorrhagia	14	1 (1–6)	2 (1–8)	50	20–270	6	8	NR	NR	NR
Epistaxis and gum bleeding	19	1 (1–1)	1 (1–8)	52	27–480	12	5	NR	NR	2
CNS bleeds	8	1 (1–14)	8 (3–87)	160	90–2610	1	6	1	NR	NR
Haematomas (muscle and subcutaneous)	9	1 (1–1)	1 (1–3)	60	26–100	5	4	NR	NR	NR
Other	2	1 (1–12)	4 (4–75)	120	100–3600	NR	2	NR	NR	1

NR, not reported; n, number of bleeding episodes; CNS, central nervous system.
[a] Treatment outcome was defined as:
- Excellent: Single administration leading to cessation of overt bleeding and related symptoms; prompt (within a few hours) relief of pain; disappearance of swelling and return to the previous range of joint or limb mobility. Bleed cessation also evaluated by imaging if appropriate.
- Effective: More than one administration needed to obtain the same results as above.
- Partially effective: More than one administration needed, but symptoms subsided slowly and the return of limb and joint mobility was partial.
- Ineffective: No changes.
- Not evaluable: No elements for evaluation available.

Table 6
Recombinant activated factor VII use for surgical procedures in congenital FVII deficiency: data from the Seven Treatment Evaluation Registry

Surgery	Number of procedures	Number of treatment days	Total number of doses	Total dose (μg/kg)	Mean daily dose (μg/kg)	Mean dose (μg/kg)	Range of doses (μg/kg)	Efficacy rate[a]
Minor [34]	29	1–10	1–16	7.2–510	4.8–300	3.6–300	NR	100%
Major [48]	24	1–18	1–37[b]	12–1571[c]	10–90	NR	4.2–87[b]	87.5%

NR, not reported.
[a] Defined as 'no bleeding occurred', based on evaluation by treating physician and/or blood loss during the intervention as well as the number of red blood cell units given.
[b] Based on 22 procedures; two procedures were performed using continuous infusion rather than bolus doses.
[c] Includes two procedures covered with continuous infusion.

272 (43%) patients were non-bleeding, 277 (44%) had minor bleeds, and 77 (12%) major bleeds. During a median 9-year index period of observation, 88% of patients who were non-bleeding at presentation remained asymptomatic, while 75% of minor bleeders had new minor bleeds, and 83% of major bleeders had new major bleeds. The relative risk for ensuing bleeds during the index period was calculated, adjusting for FVII:C levels and other clinical/demographic variables. Relative risk was 6.02 in patients presenting with major bleeds, and 5.87 in those presenting with minor bleeds (both $P < 0.001$). Compared with non-bleeding individuals, the relative risk for major bleeds was 10.95 in patients who presented with minor bleeds, and 28.21 in those who presented with major bleeds (both $P \leq 0.001$) [42].

3.2.2. Recombinant FVIIa in acute bleeds

A total of 101 acute bleeding episodes in the STER were analysed in 75 patients with FVII CD in 23 haemophilia treatment centres from 15 countries (41 were females; age range 0.1–71 years; FVII:C <1–20%) [6]. Bleeds were grouped as follows: haemarthroses (n = 30); muscle/subcutaneous haematomas (n = 16); epistaxis (n = 12); gum bleeds (n = 13); menorrhagia (n = 16); CNS bleeds (n = 9); GI bleeds (n = 2); and other (n = 3).

Haemostatic treatment was rFVIIa in 79 (78%) of the acute bleeding episodes, and the median dose administered was 60 μg/kg (Table 5). Efficacy with rFVIIa was excellent in 38 bleeds (i.e., one day/one dose) and effective in 35 bleeds, yielding an overall efficacy of 92% [6]. Excellent/effective efficacy rates were high across the different bleed types: haemarthroses (93%); menorrhagia (100%); epistaxis and gum bleeding (89%); CNS bleeds (88%); and haematomas (100%; Table 5).

3.2.3. Recombinant FVIIa – prophylaxis to prevent bleeding

Data were collected on 24 prophylactic regimens in 21 patients with severe FVII CD in the STER [7]. Excluding two cases of severe, refractory menorrhagia, rFVIIa administration was 'frequent' (three times weekly) in 18 courses, and 'infrequent' (up to twice weekly) in four courses. The outcome with rFVIIa prophylaxis was excellent in 14/22 courses (13 frequent and one infrequent administration), effective in five courses (four frequent, one infrequent) and partly effective in two (both frequent); this meant overall efficacy was 86%. The total weekly rFVIIa dose was similar for courses with excellent (mean 85.7 μg/kg; median 90 μg/kg) and effective (mean 106.8 μg/kg; median 132 μg/kg) outcomes. The patient with a partly effective outcome received a low dose of rFVIIa (42 μg/kg) [7]. The median dose for long-term prophylaxis was 30 μg/kg (range 16.5–57 μg/kg), and the median frequency was three doses per week [7].

For paediatric patients (n = 22, <12 years old), the median dose for long-term prophylaxis was 30 μg/kg (range 17–200 μg/kg; the dose most often used was 30 μg/kg in 10 patients), with a median frequency of three doses per week (range 1–7; the dose frequency most often reported was three per week in 13 patients) [8]. There were no reports of TEs or new inhibitors associated with prophylaxis in the STER [7]. Inhibitors against FVII were detected in children who received fresh frozen plasma (FFP) before prophylactic rFVIIa was instituted for life-threatening CNS or GI bleeds, and in one patient who had a history of repeated treatments with FFP, prothrombin complex concentrate, plasma-derived FVII and rFVIIa because of severe gynaecological bleeds. Considering treatment histories, it is impossible to assert which replacement triggered the immune response. FVII inhibitors

in patients with FVII deficiency represent a rare complication (approximately 1–3% of treated patients). Knowledge of the occurrence and characteristics of inhibitors to FVII is of interest because this is a rare event in a rare disorder, and an understanding of inhibitor development may improve patient management [46]. Further safety data on the use of rFVIIa in FVII CD can be found in the accompanying article by Neufeld et al. in this supplement [47].

3.2.4. Recombinant FVIIa in surgical procedures

Patients with FVII CD are at risk of bleeding for several days following surgery, meaning that replacement therapy to prevent such bleeding is required. The STER collected data on 24 major [48] and 29 minor [34] surgical procedures performed in patients with FVII CD under the coverage of rFVIIa (Table 6). Major surgeries were grouped as: obstetric/gynaecological/abdominal (n = 10); orthopaedic (n = 6); ear, nose and throat (ENT)/head/neck (n = 5); continuous infusion (n = 2); and cardiovascular (n = 1) [48]. Minor surgeries were grouped as: oral/dental (n = 13); endoscopic biopsies (n = 7); mixed surgical procedures (n = 5); and ENT/head/neck (n = 4) [34].

Haemostatic efficacy was observed in 21/24 (88%) major surgical procedures covered with rFVIIa (Table 6) [48]. Bleeding occurred during three major (orthopaedic) procedures; in all three, rFVIIa was given at low to very low doses. In the major surgeries overall, the total rFVIIa dose ranged from 12 μg/kg to 1571 μg/kg, and the mean daily dose from 10 μg/kg to 90 μg/kg (Table 6). The data indicated that rFVIIa provided effective haemostatic cover when suitable doses were used, which on the day of surgery was calculated (by Receiver Operated Characteristic analysis) as ≥13 μg/kg (first dose), with at least two additional doses [48]. In the 29 minor surgical procedures, haemostatic efficacy with rFVIIa coverage was 100% (i.e., no bleeding episodes were observed; Table 6) [34]. In contrast with the doses used for major surgeries, total rFVIIa dose for minor procedures ranged from 7.2 μg/kg to 510 μg/kg, and mean daily dose from 4.8 μg/kg to 300 μg/kg.

4. Conclusions

Considering the rarity of GT and FVII CD, the GTR and the STER have successfully managed to collect data for a substantial number of patients who have been treated for many acute bleeding episodes and surgical/invasive procedures. Data from both registries have expanded our knowledge of, and provided valuable insight into, these rare bleeding disorders and their treatment. Importantly, treatment with rFVIIa in the GTR and STER registries was well tolerated.

Conflict of interest statement

G Di Minno discloses the following financial relationships – speaker or a member of a speaker bureau for: Boehringer Ingelheim, Sanofi, Bayer, Novo Nordisk, Pfizer, Biotest and Grifols; consultant or ad hoc speaker/consultant for: Boehringer Ingelheim, Eli Lilly, Sanofi, Bayer, CSL Behring, Novo Nordisk, Pfizer, Biotest and Grifols.

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References

[1] Di Minno G, Coppola A, Di Minno MN, Poon MC. Glanzmann's thrombasthenia (defective platelet integrin alphaIIb-beta3): proposals for management between evidence and open issues. Thromb Haemost 2009;102:1157-64.
[2] Lapecorella M, Mariani G. Factor VII deficiency: defining the clinical picture and optimizing therapeutic options. Haemophilia 2008;14:1170-5.
[3] Di Minno G, d'Oiron R, Zotz R, Poon M-C. Treatment modalities and outcomes in 870 non-surgical bleeds in 184 Glanzmann's thrombasthenia patients: the International Prospective Glanzmann's Thrombasthenia Registry. http://www.eventure-online.com/eventure/public/publicAbstractView.form?id=217038&congressId=6839. [Accessed April 8, 2015].
[4] Poon M-C, d'Oiron R, Zotz R, Di Minno G. Treatment modalities and outcomes in 204 surgical procedures in 96 Glanzmann's thrombasthenia (GT) patients: the International Prospective Glanzmann's Thrombasthenia Registry (GTR). J Thromb Haemost 2013;11(Suppl. 2):161.
[5] Poon MC, Zotz R, Di Minno G, Abrams ZS, Knudsen JB, Laurian Y. Glanzmann's thrombasthenia treatment: a prospective observational registry on the use of recombinant human activated factor VII and other hemostatic agents. Semin Hematol 2006;43(1 Suppl. 1):S33-6.
[6] Mariani G, Napolitano M, Dolce A, Perez Garrido R, Batorova A, Karimi M, et al. Replacement therapy for bleeding episodes in factor VII deficiency. A prospective evaluation. Thromb Haemost 2013;109:238-47.
[7] Napolitano M, Giansily-Blaizot M, Dolce A, Schved JF, Auerswald G, Ingerslev J, et al. Prophylaxis in congenital factor VII deficiency: indications, efficacy and safety. Results from the Seven Treatment Evaluation Registry (STER). Haematologica 2013;98:538-44.
[8] NovoSeven® summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000074/WC500030873.pdf. [Accessed March 3, 2015].
[9] NovoSeven® RT Highlights of Prescribing Information. http://www.fda.gov/downloads/...ucm056954.pdf. [Accessed April 8, 2015].
[10] NiaStase RT® Product Monograph. http://webprod5.hc-sc.gc.ca/dpd-bdpp/. [Accessed April 8, 2015].
[11] Bellucci S, Caen J. Molecular basis of Glanzmann's Thrombasthenia and current strategies in treatment. Blood Rev 2002;16:193-202.
[12] Nurden AT, Pillois X, Wilcox DA. Glanzmann thrombasthenia: state of the art and future directions. Semin Thromb Hemost 2013;39:642-55.
[13] Toogeh G, Sharifian R, Lak M, Safaee R, Artoni A, Peyvandi F. Presentation and pattern of symptoms in 382 patients with Glanzmann thrombasthenia in Iran. Am J Hematol 2004;77:198-9.
[14] George JN, Caen JP, Nurden AT. Glanzmann's thrombasthenia: the spectrum of clinical disease. Blood 1990;75:1383-95.
[15] Bolton-Maggs PH, Chalmers EA, Collins PW, Harrison P, Kitchen S, Liesner RJ, et al. A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. Br J Haematol 2006;135:603-33.
[16] Rajpurkar M, Chitlur M, Recht M, Cooper DL. Use of recombinant activated factor VII in patients with Glanzmann's thrombasthenia: a review of the literature. Haemophilia 2014;20:464-71.
[17] Spiess BD. Platelet transfusions: the science behind safety, risks and appropriate applications. Best Pract Res Clin Anaesthesiol 2010;24:65-83.
[18] MacLennan S, Williamson LM. Risks of fresh frozen plasma and platelets. J Trauma 2006;60(6 Suppl.):S46-50.
[19] Hedner U. Factor VIIa and its potential therapeutic use in bleeding-associated pathologies. Thromb Haemost 2008;100:557-62.
[20] Lisman T, Adelmeijer J, Heijnen HF, de Groot PG. Recombinant factor VIIa restores aggregation of alphaIIbbeta3-deficient platelets via tissue factor-independent fibrin generation. Blood 2004;103:1720-7.
[21] Poon MC, Demers C, Jobin F, Wu JW. Recombinant factor VIIa is effective for bleeding and surgery in patients with Glanzmann thrombasthenia. Blood 1999;94:3951-3.
[22] Poon MC, d'Oiron R, Von Depka M, Khair K, Négrier C, Karafoulidou A, et al. Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey. J Thromb Haemost 2004;2:1096-103.
[23] Study ID F7Haem-3521 F7GLANZ. Non-interventional study report: study abstract. http://novonordisk-trials.com/Website/pdf/registry/bin_20141031-012557-143.pdf. [Accessed March 30, 2015].
[24] Di Minno G, Zotz RB, d'Oiron R, Bindslev N, Di Minno MND, Poon M-C. The international prospective Glanzmann Thrombasthenia Registy: treatment modalities and outcomes in non-surgical bleeding episodes in Glanzmann thrombasthenia patients. Haematologica 2015;May 22. pii: haematol.2014.121475.
[25] Poon M-C, d'Oiron R, Zotz RB, Bindslev N, Di Minno MND, Di Minno G. The international prospective Glanzmann Throbasthenia Registry: treatment and outcomes in surgical intervention. Haematologica 2015;May 22. pii: haematol.2014.121384.

[26] Peyvandi F, Bolton-Maggs PH, Batorova A, De Moerloose P. Rare bleeding disorders. Haemophilia 2012;18(Suppl. 4):148-53.
[27] Perry DJ. Factor VII Deficiency. Br J Haematol 2002;118:689-700.
[28] World Federation of Hemophilia. Report on the Annual Global Survey. http://www1.wfh.org/publication/files/pdf-1427.pdf. [Accessed March 3, 2015].
[29] Borhany M, Pahore Z, Ul Qadr Z, Rehan M, Naz A, Khan A, et al. Bleeding disorders in the tribe: result of consanguineous in breeding. Orphanet J Rare Dis 2010;5:23.
[30] Mariani G, Herrmann FH, Dolce A, Batorova A, Etro D, Peyvandi F, et al. Clinical phenotypes and factor VII genotype in congenital factor VII deficiency. Thromb Haemost 2005;93:481-7.
[31] Di Minno MND, Batorova A, Napolitano M, Dolce A, Di Minno G, Bernardi F, et al. At disease presentation, severity of the bleeding symptoms predicts the following bleeds in patients with FVII deficiency. Blood 2011;118:543.
[32] Mariani G, Bernardi F. Factor VII Deficiency. Semin Thromb Hemost 2009;35:400-6.
[33] Giansily-Blaizot M, Biron-Andreani C, Aguilar-Martinez P, de Moeloose P, Briquel ME, Goudemand J, et al. Inherited factor VII deficiency and surgery: clinical data are the best criteria to predict the risk of bleeding. Br J Haematol 2002;117:172-5.
[34] Mariani G, Dolce A, Napolitano M, Ingerslev J, Giansily-Blaizot M, Di Minno MD, et al. Invasive procedures and minor surgery in factor VII deficiency. Haemophilia 2012;18:e63-5.
[35] Mariani G, Konkle BA, Ingerslev J. Congenital factor VII deficiency: therapy with recombinant activated factor VII – a critical appraisal. Haemophilia 2006;12:19-27.
[36] Berrettini M, Mariani G, Schiavoni M, Rocino A, Di Paolantonio T, Longo G, et al. Pharmacokinetic evaluation of recombinant, activated factor VII in patients with inherited factor VII deficiency. Haematologica 2001;86:640-5.
[37] Greenberg DL, Davie EW. Blood coagulation factors: Their complementary DNAs, genes and expression. In: Colman RW, Hirsh J, Marder VJ, Clowes AW, George JN, editors. Hemostasis and Thrombosis. Philadelphia: Lippincott Williams & Wilkins; 2001: p. 135-56.
[38] Gopalakrishnan R, Hedner U, Ghosh S, Nayak RC, Allen TC, Pendurthi UR, et al. Bio-distribution of pharmacologically administered recombinant factor VIIa (rFVIIa). J Thromb Haemost 2010;8:301-10.
[39] Lopez-Vilchez I, Hedner U, Altisent C, Diaz-Ricart M, Escolar G, Galan AM. Redistribution and hemostatic action of recombinant activated factor VII associated with platelets. Am J Pathol 2011;178:2938-48.
[40] Mathijssen NC, Masereeuw R, Holme PA, van Kraaij MG, Laros-van Gorkom BA, Peyvandi F, et al. Increased volume of distribution for recombinant activated factor VII and longer plasma-derived factor VII half-life may explain their long lasting prophylactic effect. Thromb Res 2013;132:256-62.
[41] Morfini M, Batorova A, Mariani G, Auerswald G, Bernardi F, Di Minno G, et al. Pharmacokinetic properties of recombinant FVIIa in inherited FVII deficiency account for a large volume of distribution at steady state and a prolonged pharmacodynamic effect. Thromb Haemost 2014;112:424-5.
[42] Di Minno MN, Dolce A, Mariani G. Bleeding symptoms at disease presentation and prediction of ensuing bleeding in inherited FVII deficiency. Thromb Haemost 2013;109:1051-9.
[43] Nicolaisen EM. Antigenicity of activated recombinant factor VII followed through nine years of clinical experience. Blood Coagul Fibrinolysis 1998;9(Suppl. 1):S119-23.
[44] Rodeghiero F, Castaman G, Tosetto A, Batlle J, Baudo F, Cappelletti A, et al. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: an international, multicenter study. J Thromb Haemost 2005;3:2619-26.
[45] Tosetto A, Rodeghiero F, Castaman G, Goodeve A, Federici AB, Batlle J, et al. A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: results from a multicenter European study (MCMDM-1 VWD). J Thromb Haemost 2006;4:766-73.
[46] Batorova A, Mariani G, Kavakli K, De Saez AR, Caliskan U, Karimi M, et al. Inhibitors to factor VII in congenital factor VII deficiency. Haemophilia 2014;20:e188-91.
[47] Neufeld EJ, Negrier C, Arkhammar P, Benchikh el Fegoun S, Simonsen MD, Rosholm A, et al. Safety update on the use of recombinant activated factor VII in approved indications. Blood Reviews 2015;29(Suppl. 1):S34-41.
[48] Mariani G, Dolce A, Batorova A, Auerswald G, Schved JF, Siragusa S, et al. Recombinant, activated factor VII for surgery in factor VII deficiency: a prospective evaluation – the surgical STER. Br J Haematol 2011;152:340-6.
[49] Monroe DM, Hoffman M, Oliver JA, Roberts HR. Platelet activity of high-dose factor VIIa is independent of tissue factor. Br J Haematol 1997;99:542-7.
[50] Weeterings C, de Groot PG, Adelmeijer J, Lisman T. The glycoprotein Ib-IX-V complex contributes to tissue factor-independent thrombin generation by recombinant factor VIIa on the activated platelet surface. Blood 2008;112:3227-33.
[51] Poon M-C. Factor VIIa. In: Michelson AD, editor. Platelets. New York: Academic Press; 2013: p. 1257-73.