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ORIGINAL ARTICLE

Prophylactic and therapeutic recombinant factor VIIa administration to patients with Glanzmann's thrombasthenia: results of an international survey

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Summary. *Background*: Antibodies to glycoprotein (GP) IIb-IIIa and/or HLA may render platelet transfusions ineffective to stop bleeding or to cover surgery in patients with Glanzmann's thrombasthenia (GT). Anecdotal reports suggest recombinant factor (rF)VIIa might be a therapeutic alternative in these situations. *Objectives*: An international survey was conducted to evaluate further the efficacy and safety of rFVIIa in GT patients. *Patients*: We analyzed the use of rFVIIa during 34 surgical/invasive procedures and 108 bleeding episodes in 59 GT patients including 29 with current or previous antiplatelet antibodies, and 23 with a history of refractoriness to platelet transfusion. *Results*: rFVIIa was effective in 29 of the 31 evaluable procedures, and in 77 of the 103 evaluable bleeding episodes of which eight had a recurrence. A significantly higher success rate was observed in severe bleeding episodes when an arbitrarily defined 'optimal regimen' derived from the Canadian pilot study results (≥ 80 μg kg^{-1} rFVIIa/injection, dosing interval ≤ 2.5 h, three or more doses before failure declaration) was used compared with other regimens (77%; 24/31 vs. 48%, 19/40; χ^2, $P = 0.010$). Patients given maintenance doses had significantly fewer recurrences within 48 h of bleed cessation compared with those not given any (Fisher's exact test, $P = 0.022$). One thromboembolic event and one blood clot in the ureter occurring in surgical patients following prolonged continuous infusion of high-dose rFVIIa and antifibrinolytic drug use have been previously reported. *Conclusion*: rFVIIa seems a potential alternative to platelet transfusion in GT patients, particularly in those with antiplatelet antibodies and/or platelet refractoriness.

Keywords: antibodies to glycoprotein IIb-IIIa, Glanzmann's thrombasthenia, platelet transfusion, recombinant factor VIIa.

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Introduction

Glanzmann's thrombasthenia (GT) is a rare inherited disorder of platelet function caused by a quantitative or qualitative defects of the platelet membrane glycoprotein (GP) IIb-IIIa ($\alpha_{IIb}\beta_3$) complex [1,2] Clinical manifestations include easy bruising, purpura, epistaxis, gingival bleeding, menorrhagia and, less frequently, gastrointestinal bleeding, hematuria, hemarthrosis, muscle hematoma and central nervous system bleeding. Bleeding complications are also frequent after dental extraction, surgery and delivery. In a series of 112 GT patients [1], 77% had a history of red cell transfusion, reflecting the severity of bleeding episodes. When bleeding does not respond to local measures and/or antifibrinolytic drugs, platelet transfusion is currently the standard treatment. However, repeated platelet transfusions may result in GP IIb-IIIa and/or HLA immunization, and development of platelet refractoriness [1,3]. Blood products also carry other risks, including infections [4].

Finally, platelet concentrates, especially those prepared from single-donor apheresis and/or HLA-compatible, may not always be readily available.

Recombinant factor (rF)VIIa is currently approved for the treatment of hemophilia patients with inhibitors [5–7]. In 1996 Tengborn and Petruson [8] reported successful treatment with rFVIIa of a 2-year-old child with GT who had not responded to conservative treatment for severe epistaxis. There have since been a Canadian pilot study [9] performed on four GT children, a British study of five GT patients [10] and some additional case studies [11–18]. While the Canadian study [9] showed effectiveness on 23 of 24 bleeding episodes and one surgical prophylaxis, the British report [10] showed more variable results, with good/excellent results in only 12 of 25 bleeding episodes, although all three surgical procedures were successfully covered. Randomized trials would have been helpful to evaluate the effectiveness and risk–benefit of rFVIIa in GT. However, such studies are hindered by the rarity of GT; moreover, most bleeds in GT can be treated with local measures and/or antifibrinolytic drugs and only rarely do bleeds require the use of systemic hemostatic treatments such as platelet transfusion.

We began an international survey in 1999 to better assess the efficacy and safety of rFVIIa in GT patients [19]. We report here the results of this survey.

Methods

International survey design

The international survey designed to obtain information on experience with the off-label use of rFVIIa in patients with GT was promoted through presentations in congresses, publications [19], and the Hemostasis Forum website (http://www.haemophilia-forum.org/). Completed forms that include data on the type of GT, history of antiplatelet or anti-HLA antibodies, previous responses to platelet transfusion, and details for each treatment episode (type, severity, treatment before rFVIIa, reason to use rFVIIa, rFVIIa treatment regimen, concurrent treatments, efficacy, and adverse events) were returned to the two coordinators (M-C.P., R.d'O.) with anonymous patient code. This survey was not a study protocol and each caregiver used rFVIIa according to their own treatment regimen. Patient consent was obtained according to local Ethics Committee requirements.

Definitions derived from the Canadian pilot study [9] were used. Bleeding was considered severe if it was intracranial, resulted from severe trauma, compressed a vital organ, or led to a fall in hemoglobin level of ≥ 20 g L^{-1} within 4 days. Bleeds that required systemic hemostatic treatment other than antifibrinolytic drugs, but did not fit at least one of these criteria, were considered moderate. Treatment with rFVIIa was considered successful if the bleeding stopped and did not recur within 48 h of bleed cessation. The time between the initiation of rFVIIa treatment and time bleeding stopped was recorded as follows: ≤ 6 h, > 6–≤ 12 h, > 12–≤ 24 h or > 24–≤ 48 h. Recurrences were defined as bleeding from the same site less than 48 h after a successful treatment. Treatment was considered ineffective if the bleeding stopped more than 48 h after the initiation of rFVIIa treatment and/or if another treatment (apart from antifibrinolytic drugs) was needed. Efficacy was considered not evaluable if platelets were administered concurrently with rFVIIa. The database includes some published cases [8–13,16].

Anti-platelet antibody assessment

Antibodies to GP IIb-IIIa and to HLA were tested locally, using monoclonal antibody-specific immobilization of platelet antigens (MAIPA), other immunological methods, or methods based on inhibition of normal platelet aggregation by the patient's plasma.

Recombinant factor VIIa (rFVIIa; NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) is manufactured by biotechnology, and no human derivatives are used during the manufacturing or formulation processes [20].

Analysis of rFVIIa regimens

As rFVIIa treatments were heterogeneous with respect to the dose per injection, dosing interval, number of doses used before declaration of failure, we compared an arbitrarily defined 'optimal regimen' derived from the Canadian pilot study [9] (rFVIIa ≥ 80 μg kg^{-1} per injection, dosing interval ≤ 2.5 h, at least three doses before declaration of inefficacy) with other rFVIIa regimens.

Statistical analysis

Because the numbers of GT patients and bleeding episodes requiring systemic hemostatic treatment are small the required sample size was not calculated prospectively, and the statistical analysis is therefore descriptive. Non-parametric tests appropriate for small samples were used. To compare qualitative data, we used the χ^2 test or Fisher's exact test, as appropriate. Quantitative variables were compared using the Wilcoxon non-parametric test. All tests were two-tailed, and the level of statistical significance was set at 5%. Statistical analysis was performed by the Clinica & Statistica Department of Biostatistics (Issy les Moulineaux, France) on a PC running SAS software (version 8.01; SAS Institute Inc., Cary, NC, USA).

Results

Patients

Data on 59 consecutive reported patients with GT treated with rFVIIa received from 37 hospitals in 14 countries in Europe, North America, Australia and Asia were included in the analysis. There were 24 males and 35 females, age 1–72 years (median 22 years) with 27 being ≤ 15 years. Disease severity

was known in 49 patients, of whom 39 had type I GT (< 5% GP IIb-IIIa), seven type II (5–15% GP IIb-IIIa) and three variant-type (dysfunctional GP IIb-IIIa complexes). The status of platelet antibodies (to GPIIb-IIIa and/or HLA) was known in 54 patients. Twenty-nine (49%) were positive for anti-GPIIb-IIIa ($N = 16$), anti-HLA ($N = 8$) or both ($N = 5$), in the recent past or immediately before the use of rFVIIa. Twenty-three patients were refractory to platelets, 17 with platelet antibodies, and five without. Overall, platelet refractoriness correlated with the presence of platelet antibodies (Fisher's exact test, $P = 0.002$). The one or more reasons for using rFVIIa given for each of the 142 surgical and bleeding episodes treated include platelet inefficacy for the current bleed ($N = 20$, 14%) or previous bleeds ($N = 49$, 35%), history (past or present) of antiplatelet immunization ($N = 59$, 42%), and prevention of antiplatelet immunization ($N = 61$, 43%) or blood-borne pathogen transmission ($N = 53$, 37%).

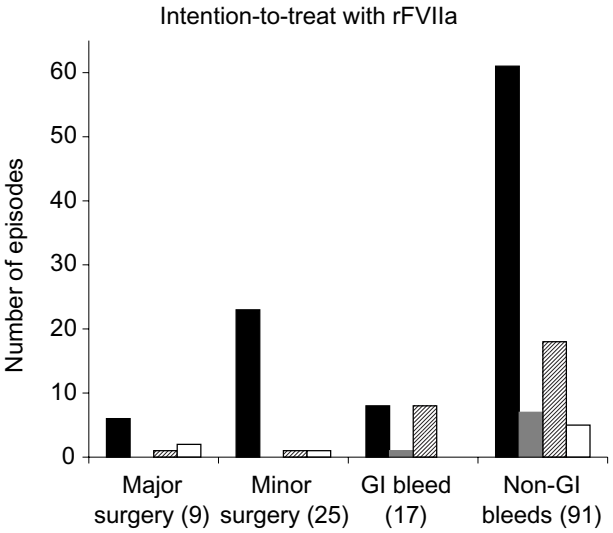

Fig. 1. Intention-to-treat analysis of recombinant factor (rF)VIIa therapy/prophylaxis in 34 invasive procedures and 108 bleeding episodes (■, success; ■, recurrence; ▨, failure; □, not evaluable).

rFVIIa surgical prophylaxis

rFVIIa was used to cover 34 invasive procedures (nine major, 25 minor), the majority ($N = 27$) in adults.

Of the nine major procedures covered, rFVIIa prophylaxis was successful in six, by bolus injections in three (laparotomy, laparoscopic bilateral oopherectomy, hysterectomy) and by continuous infusion (CI) in three (colostomy, colostomy revision, intestinal resection) (Fig. 1, Table 1). The single failure was in a 22-year-old woman undergoing endoscopic uterine myomectomy who required platelet transfusion and 3 units of red cell transfusions for persistent oozing after receiving 16 doses of rFVIIa (91 μg kg^{-1} every 2 h) over 30 h, concurrently with antifibrinolytic drugs. rFVIIa efficacy could not be evaluated owing to concurrent platelet transfusion in the remaining two procedures (pyelolithotomy and skin grafting) that was carried out without excessive bleeding.

The 25 minor procedures comprised nine dental extractions, four other dental procedures, and 12 miscellaneous procedures [three colonoscopy with polypectomy, two cystoscopy with ureteric stent insertion, and one each of ureteric stent removal, central catheter (Port-a-Cath™) insertion, central catheter removal, hernia repair, tracheotomy, knee injection and otolaryngological cryosurgery]. rFVIIa prophylaxis was successful in 23 procedures, by bolus in 20 and CI in three (Fig. 1, Table 1). There was one failure: recurrent hematuria following ureteric stent removal required 95 doses of rFVIIa (average 113 μg kg^{-1}) over 8 days in a 23-year-old platelet-refractory woman. rFVIIa efficacy could not be evaluated for one Port-a-Cath™ insertion carried out without excessive bleeding as platelets were given concurrently with rFVIIa.

rFVIIa treatment of bleeding episodes

Recombinant FVIIa was used to treat 108 bleeding episodes (76 severe, 32 moderate), from the gastrointestinal (GI) tract ($N = 17$; 16 severe, one moderate), nose ($N = 45$; 32 severe,

Table 1 Invasive procedures ($N = 29$) successfully treated with recombinant factor (rF)VIIa as first-line therapy (three non-evaluable episodes and two that failed rFVIIa not included)

Bolus injection (3 episodes)	Median (range)	Continuous infusion (3 episodes)	Median (range)
Major surgery			
Dosage (μg kg^{-1} per injection)	92 (80–92)	Initial bolus dosage (μg kg^{-1})	49 (28–70)*
Doses used (N)	14 (4–33)	CI dosage (μg kg^{-1} h^{-1})	5 (5–30)
Total dosage (μg kg^{-1}) used	1288 (368–2640)	Total dosage (μg kg^{-1}) used	1779 (1182–10080)
Length of treatment (h)	47 (11–141)	Length of treatment (h)	285 (225–336)
Bolus injection (20 episodes)		Continuous infusion (3 episodes)	
Minor surgery			
Dosage (μg kg^{-1} per injection)	109 (74–150)	Initial bolus dosage (μg kg^{-1})	88 (72–110)
Doses used (N)	3 (1–19)	CI dosage (μg kg^{-1} h^{-1})	12 (9–20)
Total dosage (μg kg^{-1}) used	300 (112–2042)	Total dosage (μg kg^{-1}) used	948 (715–2376)
Length of treatment (h)	7 (0.1–152)	Length of treatment (h)	67 (60–267)

*Not included in calculation: a 72-year-old woman was already on contiuous infusion at 30 μg kg^{-1} for 2 days for treatment of GI bleed before intestinal resection (no initial bolus dose given).

13 moderate), oropharynx ($N = 29$; 19 severe, 10 moderate) and miscellaneous sites ($N = 17$; nine severe, eight moderate, see below). Nose bleeds and oropharyngeal bleeds were more frequent in children (84% and 86%, respectively), while bleeding from the GI tract and miscellaneous sites was more frequent in adults (65% and 59%, respectively). Immediately before rFVIIa use, platelet transfusions were ineffective in 15 episodes, and antifibrinolytic drugs together with local measures were ineffective in 68. rFVIIa was used as first-line therapy in 25 episodes (23%).

rFVIIa treatment regimens varied according to local medical decisions. An intention-to-treat analysis is shown in Fig. 1: bleeding stopped in 77 episodes (71%) but eight (i.e. 10%) recurred, so that the overall success rate with recurrence excluded was 64% (69/108). The duration of bleeding was known in 62 episodes that stopped without a recurrence, and of these, 36 (58%) received maintenance doses (median 2, range 1–45 for 35, extended CI infusion for one). In contrast, of the eight episodes that stopped but had a recurrence, only one (13%) received a maintenance dose (Fisher's exact test, $P = 0.022$). Of the remaining 31 episodes, 26 (24%) persisted (ineffective), five could not be evaluated due to concurrent platelet transfusion, four of which stopped and one diminished. No significant difference in efficacy was observed between patients with and without platelet antibodies and/or platelet refractoriness (data not shown).

Evaluable bleeds were also analyzed according to the rFVIIa treatment regimen. The overall success rate (with recurrences excluded) in the 41 severe and moderate bleeds treated with the arbitrarily defined 'optimal regimen' was 78% (32/41), compared with 60% (37/62) with other rFVIIa regimens (χ^2, $P = 0.052$). The success rate for the 'optimal' bolus regimen compared with 'non-optimal' bolus regimen was significantly higher for the severe bleeds (24/31 or 77% vs. 18/33 or 55%; χ^2, $P = 0.010$) (Fig. 2), but not for the moderate bleeds (8/10 or 80% vs. 18/22 or 82%).

Analysis of the responses of different types of bleeding to rFVIIa suggests a difference between GI bleeds and non-GI bleeds, with the success rate lower for GI bleeds. The success rate for episodes treated by CI was lower than that by bolus injections.

GI bleeds All 17 GI bleeds (16 severe, one moderate) treated with rFVIIa (12 with bolus and five with CI) were evaluable (Fig. 1, Table 2). The bleeding stopped in nine episodes (53%; bolus $N = 8$; CI $N = 1$), seven within 6 h of starting rFVIIa, eight within 12 h and all nine within 24 h. One episode recurred after 36 h, but was controlled with six additional doses of rFVIIa. Eight treatments failed, four following bolus injections (two angiodysplasia; two upper GI bleeding) and four following CI (one each of angiodysplasia; Mallory–Weiss syndrome; lower GI bleeding; postradiation colonic bleeding). Six failures were successfully rescued: one episode stopped with rFVIIa after > 48 h of treatment; two stopped with surgery, two with platelets and one with

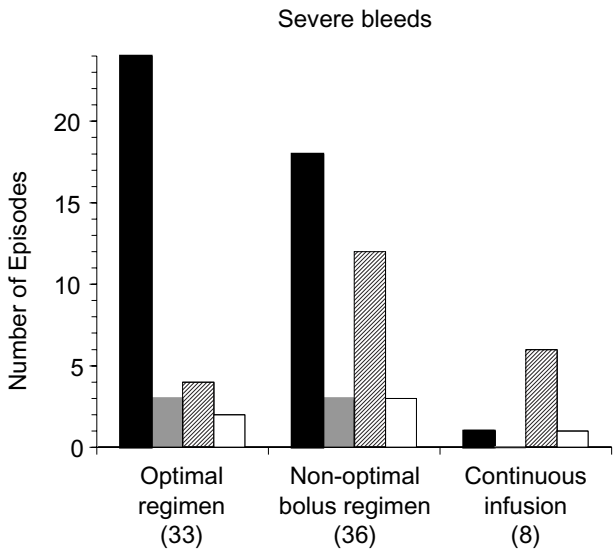

Fig. 2. Severe bleeding episodes: outcome of different recombinant factor (rF)VIIa regimens (■, success; ■, recurrence; ▨, failure; □, not evaluable). 'Optimal regimen' derived from a Canadian pilot study [9] and defined as rFVIIa boluses of at least 80 μg kg^{-1}, no more than 2.5 h apart; at least three doses before declaration of failure. 'Non-optimal bolus regimen': all other bolus regimens.

electrocoagulation. In the remaining two failures, one who received only a single dose (120 μg kg^{-1}) continued to bleed for 6 weeks, and another one continued to bleed after three doses of rFVIIa (100 μg kg^{-1} every 2 h) and died of septicemia 24 h later.

Non-GI bleeds A total of 91 non-GI bleeding episodes (45 nose, 29 oropharynx, 17 miscellaneous; 60 severe, 31 moderate) were treated with rFVIIa, 88 by bolus injection and three by CI (Fig. 1). Among the miscellaneous bleeds were nine severe bleeds (three postop, three menorrhagia, one postpartum, one intra-abdominal, one laryngopharyngeal bleed complicating nasotracheal intubation) and eight moderate episodes. Five treatments were not evaluable. Of the remaining 86 evaluable treatments (84 by bolus injections, two by CI), 68 (79%) treated by bolus injections stopped (Table 2). The response rate was not significantly different between nose (32 of 43, 74%), oropharyngeal (23 of 29, 79%) and miscellaneous (13 of 14; 93%) bleeds. Among those responding, seven episodes (10%, four nose and three miscellaneous bleeds) had a recurrence, all successfully rescued with Yag laser ($N = 1$), rFVIIa alone ($N = 2$), platelets alone ($N = 2$) or both ($N = 2$). There were 18 failures including the two episodes treated by CI and 16 by bolus injections (four declared after a single injection, five after two and the remaining seven after three to five). All were successfully rescued with platelet transfusion ($N = 12$), antifibrinolytic drug and 1-8-deamino-D-arginine vasopressin (DDAVP) ($N = 1$), addition of antifibrinolytic drug to the same CI regimen ($N = 1$), Yag laser ($N = 1$) or unknown ($N = 3$).

Table 2 Recombinant factor (rF)VIIa usage in the 96 evaluable bleeding episodes treated by bolus injection (five non-evaluable episodes and seven evaluable episodes treated by continuous infusion* not included)

	Success ($N = 7$)† Median (range)	Recurrence ($N = 1$)‡ Median (range)	Failure ($N = 4$) Median (range)
GI bleed			
Dosage (μg kg^{-1} per injection)	92 (75–238)	89	98 (80–120)
To stop bleeding			
Doses (N)	2 (1–6)	3	NA
Total μg kg^{-1} used	198 (87–594)	267	NA
Total usage (maintenance doses included)			
Doses (N)	5 (1–6)	3	13.5 (1–30)
Total μg kg^{-1} used	375 (87–594)	267	1290 (120–2400)
	Success ($N = 61$)†	Recurrence ($N = 7$)‡	Failure ($N = 16$)
Non-GI bleed			
Dosage (μg kg^{-1} injection)	100 (28–120)	105 (67–160)	96 (56–240)
To stop bleeding			
Doses (N)	2 (1–13)§	2 (1–3)	NA
Total μg kg^{-1} used	140 (56–1254)§	202 (106–480)	NA
Total usage (maintenance doses included)			
Doses (N)	3 (1–48)	2 (1–3)	2 (1–5)
Total μg kg^{-1} used	301 (56–5280)	202 (106–480)	236 (65–372)

*Of the seven evaluable rFVIIa treatments by continuous infusion, there was one success (GI bleed, 2440 μg kg^{-1} over 60 h) and six (four GI bleeds, two non-GI bleeds) failures (total usage: median 2293 μg kg^{-1}, range 352–7200 μg kg^{-1}; treatment period: median 150 h, range 41–528 h). †The dosage, number of doses and total μg kg^{-1} to stop bleeding and total number of doses and total μg kg^{-1} used (including maintenance doses) in the successful cases are not significantly different between the severe and the moderate episodes. ‡rFVIIa used for rescue not included in the table. §Data available only on 54 episodes. The exact timing of bleeding cessation is not well defined for one abdominal bleed (treated with 31 doses at 28 μg kg^{-1} every 3 h), for five hematoma and for one to prevent bleeding after a leg fracture. NA, Not applicable.

The exact time of bleeding cessation was difficult to assess in one severe and six moderate episodes. Fifty-one of the remaining 61 episodes (84%) stopped within 6 h, 56 (92%) within 12 h, 60 (98%) within 24 h and only one between 24 and 48 h.

Antifibrinolytic therapy concurrent with rFVIIa treatment

Antifibrinolytic drugs were given concurrently with rFVIIa in 27/34 invasive procedures, in 12/17 GI bleeds and in 70/91 non-GI bleeds. The success rates for those receiving antifibrinolytic drugs concurrently with rFVIIa were similar to those not receiving antifibrinolytic drugs, and were, respectively, 85% (23/27) vs. 71% (5/7) for invasive procedures and 63% (52/82) vs. 65% (17/26) for bleeding episodes.

Adverse events

Two serious adverse events (deep venous thrombosis with pulmonary embolism and clotting in one ureter) possibly related to rFVIIa were observed. In both cases, high-dose rFVIIa was administered by prolonged CI in combination with antifibrinolytic drugs in patients undergoing major surgery; these cases have recently been reported in detail [12,13]. Two other serious adverse events were reported in the survey, but were considered not related to rFVIIa: sepsis developed in two patients with persistent GI bleed, one of whom died 24 h after receiving three rFVIIa injections.

Discussion

Thrombin generation is impaired in GT patients [21]. The ability of high-dose rFVIIa to improve thrombin generation through direct binding to activated platelets [22,23] and/or overcoming the inhibitory effect of zymogen FVII [24] may contribute to its therapeutic efficacy in GT patients. It was recently shown *in vitro*, in a model of GT blood perfusion through an annular chamber containing damaged vascular segments, that high-concentration rFVIIa improved thrombin generation, increased fibrin deposition, and partially restored platelet aggregation [25]. Polymerized fibrin as mediated by thrombin generation is capable of inducing dose-dependent aggregation of platelets that lack $\alpha_{IIb}\beta_3$ [26], possibly through the involvement of platelet membrane GP Ib [27]. In another *in-vitro* perfusion model [28], where washed red cells and platelets deficient in $\alpha_{IIb}\beta_3$ (from GT patients, or normal platelets treated with anti-$\alpha_{IIb}\beta_3$) were perfused over a stimulated extracellular matrix of human umbilical vein endothelial cells, adhesion of these defective platelets to the matrix was significantly increased by high concentrations of rFVIIa in the presence of factors X and II. This improvement in adhesion was blocked by hirudin, anti-GP Ib and anti-von Willebrand factor antibodies.

This survey was successful in enrolling a large number of patients ($N = 59$) treated for a large number of invasive procedures ($N = 34$) and bleeding episodes ($N = 108$), considering the rarity of this disorder and the low frequency

of bleeding episodes requiring systemic hemostatic treatment. However, the design of such a survey has inherent limitations that need to be taken into account in the interpretation of the data. Although investigators were asked to report all positive and negative experiences, the possibility of under-reporting of negative experience still cannot be excluded. Other limitations include the heterogeneity of treatment regimens used, the different guidelines for the minimum rFVIIa doses to be used before failure was declared, and the lack of data on the time between bleeding onset and treatment initiation.

Despite these limitations, valuable information was obtained. We note a discrepancy between antiplatelet antibodies and platelet refractoriness, potentially due to insufficient sensitivity of some assays, the inability of some assays to distinguish between inhibitor and non-inhibitor antiplatelet antibodies, or the possible disappearance of antibodies before the next platelet transfusion. rFVIIa was particularly effective as prophylaxis for a wide variety of surgical and other invasive procedures (29/31 evaluable episodes). The overall success rate for bleeding episodes (64%) based on intention-to-treat analysis was lower than previously reported [9], presumably because of the heterogeneity of the treatment regimens. Of note is that at least five of the failures were declared after a single bolus dose of rFVIIa, and five after only two, so that the treatment may not be sufficient. The success rate using the arbitrarily defined 'optimal' treatment regimen was higher, and significantly so for the severe episodes (77%) compared with the use of 'non-optimal' bolus regimens (55%) or CI (14%) (χ^2, $P = 0.010$), underscoring the importance of adequate rFVIIa use. Additional doses of rFVIIa after bleeding stops may be beneficial, as the proportion of bleeding episodes given maintenance dose(s) was higher in those that stopped without recurrence than in those with recurrences (36/62 vs. 1/8, $P = 0.022$). We also observed that a high proportion (58/80, 83%) of the successfully treated bleeds stopped within 6 h after the first rFVIIa injection, suggesting that rFVIIa could be used as first-line therapy while waiting for the availability of adequate apheresis platelet concentrates. Recently, Almeida *et al.* [10] reported their experience of treating 25 non-GI bleeding episodes and three surgical procedures in five GT children (age $\leq$11 years) by bolus rFVIIa injections. In agreement with our survey, rFVIIa was effective for the three minor surgical procedures. However, only 12 of the 25 bleeding episodes (48%) had good/excellent results. The authors raised the question of whether the high failure rate may be related to nose bleeds in children, which tend to be more difficult to manage than in adults, as only seven of their 18 nose bleeds had good/excellent response (39%), three of which had recurrence. This suspicion is not borne out in our survey, where 27 of 35 (77%) evaluable nose bleeds occurring in children 1–14 years age (median three, mean 3.4) stopped bleeding after bolus rFVIIa with two recurrences. The poor result, as also suggested by the authors, was likely to be related to delayed treatment, as good/excellent responses were observed in 10 of their 14 episodes (71%) treated within 12 h of bleeding onset, but in only two of 11 (18%) treated after 12 h, confirming the importance of early treatment. Of note also in Almeida's series [10] is that five of nine good/excellent responses without recurrence also received platelet transfusions, but it is not clear if the platelets were given even after the bleeding had stopped because platelets became available, or were given concurrently with rFVIIa; the latter would have rendered the efficacy not evaluable in our survey. In our survey, bleeding also stopped in all five non-evaluable bleeding episodes given rFVIIa and platelets concurrently.

In our survey, GI bleeds appeared as particularly difficult to stop by rFVIIa. Possibilities include ineffectiveness of CI (used in four episodes), inadequate number of doses used (two episodes), and the severe nature of the bleeding lesion (four angiodysplasia and one Mallory–Weiss tear). In this study, CI was unsuccessful in six of the seven evaluable bleeds treated, even though the total usage was high relative to that by bolus injection (Table 1). CI appears effective in preventing bleeding in all six invasive/surgical procedures managed, but without reducing the total amount of rFVIIa used relative to that by bolus administration (Table 1). Furthermore, two serious thrombotic adverse events [12,13] appeared after prolonged CI of high-dose rFVIIa in combination with antifibrinolytic drugs.

In summary, rFVIIa given as bolus injections appears to be a safe and mostly effective alternative to platelet transfusion for the treatment and prevention of bleeding in patients with GT, particularly for those with antiplatelet antibodies and/or refractoriness to platelet transfusions. Until more data become available, the following treatment regimen for moderate to severe bleeds is suggested: bolus injections of $\sim$90 μg kg^{-1} per injection every 2 h until bleeding stops. One or more 'maintenance' dose(s) may be used to prevent recurrences. On general principle, we also recommend the use of antifibrinolytic agents in conjunction with rFVIIa at least for mucosal bleeds, although the current study was unable to prove additional benefit in all bleeds. Recombinant FVIIa might also be used to avoid platelet transfusion, thereby reducing exposure to the associated risks of platelet immunization or blood-borne infection. Avoidance of platelet immunization may be crucial for future treatment of life-threatening bleeds, or for prevention of neonatal/fetal thrombocytopenia induced by platelet antibodies transferred into the fetal circulation from the immunized GT mother, that may lead to fetal death or central nervous system bleeding in neonate [29,30]. However, high-dose HLA-compatible platelet transfusions, with or without antibody removal therapy [31,32], should not be delayed in case of life-threatening bleeding or when rFVIIa therapy fails.

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Conflict of interest statements

R.d'O. and C.N. received occasional honoraria from Novo-Nordisk for expert consultancy within the last 3 years. M-C.P. received occasional honoraria from NovoNordisk for giving lectures at accredited symposium meetings. All other authors have declared no conflict of interest.

Appendix

Members of the International Data Collection on Recombinant Factor VIIa and Congenital Platelet Disorders Study Group participated in the provision of data and intellectual input that resulted in the completion of this manuscript:

Australia: Melbourne (A. Street).
Austria: Vienna (S. Kuhle).
Belgium: Leuven (C. Van Geet).
Canada: Calgary (M-C. Poon, J. Wu), Quebec (C. Demers), Winnipeg (D. S. Houston), Toronto (V. Blanchette).
France: Kremlin Bicêtre (R. d'Oiron, T. Lambert), Lyon (C. Négrier), Limoges (L. de Lumley), Nantes (E. Fressinaud), Clermont-Ferrand (A. Marquès-Verdier), Saint-Etienne (C. Berger), Angers (P. Beurrier), Paris-Cochin (P. Paugy), Amiens (B. Pautard), Paris-Necker (M-F. Torchet), Lille (N. Trillot), Brest (M. Vicariot), Marseille (H. Chambost), Bordeaux (V. Guérin), Toulouse (P. Sié).
Germany: Hannover (M. von Depka), Heidelberg (A. Huth-Kuehne), Ulm (C. Guethner), Munich (K. Kurnik).
Greece: Athens (A. Karafoulidou), Thessaloniki (P. E. Makris).
Israel: Tel-Hashomer (G. Kenet).
Italy: Florence (M. Morfini), Catania (R. Musso).
Spain: Valencia (J. Lorenzo).
Sweden: Stockholm (P. Petrini), Malmö (L. Tengborn, S. Lethagen).
The Netherlands: Den Haag (W. B. J. Gerrits).
Turkey: Istanbul (O. Devecioglu).
UK: London (K. Khair), Edinburgh (A. Thomas), Birmingham (J. Wilde), Canterbury (M. Winter).
USA: San Antonio (H. A. Britton), Atlanta (T. Abshire), Minneapolis (M. Heisel), Indianapolis (A. Shapiro), Detroit (I. Warrier). Los Angeles (W-Y. Wong)
Thailand: Bangkok (A. Chuansumrit).

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