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Independent adjudicator assessments of platelet refractoriness and rFVIIa efficacy in bleeding episodes and surgeries from the multinational Glanzmann's thrombasthenia registry

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Abstract

Glanzmann's thrombasthenia (GT) is a rare congenital bleeding disorder associated with decreased platelet aggregation due to qualitative/quantitative deficiencies of the fibrinogen receptor. Severe bleeding episodes and perioperative bleeding are typically managed with platelet transfusions, although patients can develop anti-platelet antibodies or experience clinical refractoriness. The GT Registry (GTR) was established to collect efficacy/safety data on hemostatic treatments for GT, including recombinant factor VIIa (rFVIIa). At the request of the United States Food and Drug Administration, three hematology experts evaluated platelet refractoriness, antibody status, and rFVIIa efficacy data on a case-by-case basis to support a potential indication for rFVIIa in GT. Adjudication included 195 patients with 810 events (619 severe bleeding episodes, 192 surgeries), and a consensus algorithm was developed to describe adjudicators' coding of refractoriness and antibody status based on treatment patterns over time. Most rFVIIa-treated events were in patients without refractoriness or antibodies. Adjudicators rated most rFVIIa-treated bleeding episodes as successful (251/266, 94.4%; rFVIIa only, 101/109, 92.7%; rFVIIa ± platelets ± other agents, 150/157, 95.5%); efficacy was consistent in patients with platelet refractoriness ± antibodies (75/79, 94.9%), antibodies only (10/10, 100.0%), and neither/unknown (166/177, 93.8%). Adjudicators also rated most rFVIIa-treated surgeries as successful (159/160, 99.4%; rFVIIa only, 65/66, 98.5%; rFVIIa ± platelets ± other agents, 94/94, 100.0%); efficacy was consistent in patients with platelet refractoriness ± antibodies (69/70, 98.6%), antibodies only (24/24, 100.0%), and neither/unknown (66/66, 100.0%). Unblinding the adjudicators to investigator efficacy ratings changed few assessments. Doses of rFVIIa were narrowly distributed, regardless of other hemostatic agents used.

1 | INTRODUCTION

Glanzmann's thrombasthenia (GT) is a rare autosomal recessive bleeding disorder caused by a deficiency of, or an abnormality in, the platelet membrane glycoproteins IIb or IIIa (GPIIb/IIIa).[1] These glycoproteins bind fibrinogen to mediate platelet cross-linking, and therefore patients with GT exhibit reduced platelet aggregation responses and clinical bleeding. The severity of bleeding episodes in patients with GT varies and manifestation typically begins in childhood, with symptoms including primarily mucocutaneous bleeding, such as purpura, epistaxis, gingival bleeding, easy bruising, and ecchymoses.[2,3] Three classifications of GT have been established based on differences in GPIIb/IIIa levels; Type I, Type II, and Type III GT indicate GPIIb/IIIa levels of less than 5% of normal, 5-20% of normal, and with a qualitative defect in GPIIb/IIIa function, respectively.

Treatment approaches towards managing bleeding in patients with GT generally vary with bleeding tendency.[2,4] Whereas mild and moderate episodes can typically be controlled with compression, local hemostatic agents, and antifibrinolytic therapy, standard treatment for more severe bleeding events and for surgical interventions most often consists of platelet transfusions. However, platelet transfusions are associated with certain risks, including the potential transmission of blood-borne agents and occurrence of immunologic transfusion reactions.[5] The use of platelet therapy may also be limited by a short platelet shelf-life (5-7 days) and potentially low availability in some hospitals or blood banks. Additionally, performing platelet transfusions requires

patient evaluation in a health care facility, and therefore early administration of platelets in the home setting is not feasible. Furthermore, following repeated platelet transfusions, patients with GT may develop alloantibodies targeting GPIIb/IIIa or human lymphocyte antigen (HLA), and may experience clinical refractoriness to subsequent platelet treatment.[2–4]

An additional therapeutic option for managing severe bleeding in patients with GT is recombinant factor VIIa (rFVIIa), which has been used successfully to control bleeding episodes and peri-operative bleeding in patients with GT, often in combination with antifibrinolytic therapy.[6–8] The precise mechanism by which rFVIIa promotes hemostasis is unknown, but is thought to include an increased activation of platelets, increased generation of thrombin, and increased deposition of fibrin, resulting in a stable and effective clot.[9–11]

Because of the rarity of GT and difficulties in enrolling sufficient numbers of patients for a randomized controlled trial, a prospective multinational GT Registry (GTR) was established to collect data regarding the efficacy and safety of hemostatic treatments for GT, including rFVIIa. The registry was initiated as a postmarketing surveillance commitment to the European Union's Committee for Medicinal Products for Human Use, following approval by the European Medicines Agency of rFVIIa for the treatment of GT.[12] An external expert group monitored the registry and provided ongoing support of recruitment and analysis, including publication of primary data on the efficacy and safety of rFVIIa associated with specific patient events (bleeding episodes and surgeries).[13,14] Investigators found rFVIIa used alone to be effective in a majority of bleeding episodes (111 of 122; 91.0%) and surgical procedures (59 of 62; 95.2%).

Following discussion with the United States Food and Drug Administration (FDA) regarding a potential new indication of GT for rFVIIa, an objective adjudication committee of US hematologists unaffiliated with the registry was assembled to evaluate rFVIIa efficacy, platelet refractoriness, and anti-platelet antibody (anti-GPIIb/IIIa and anti-HLA) data from the GTR. Patient data were reviewed independently by the three adjudicators on a case-by-case basis in the context of all available information, including data from multiple events that occurred in each specific patient. Here we present a detailed methodology of the adjudication process and results. These data were used to support the FDA approval in July 2014 of rFVIIa for patients with GT with refractoriness to platelet transfusions, with or without antibodies to platelets.[15]

2 | METHODS

2.1 | Study population

A detailed description of the GTR data collection process has been presented elsewhere.[13,14] Briefly, the registry was a prospective, observational, multinational, Web-based platform that collected safety and efficacy data regarding the use of systemic hemostatic treatments in patients with GT (see Supporting Information appendix for a list of data fields). Patients were eligible for participation in the GTR if they had a diagnosis of congenital GT and exhibited a normal platelet count and morphology.[13,14] Congenital GT was defined by having a lifelong bleeding tendency characterized by impaired or absent platelet aggregation, impaired clot retraction and prolonged bleeding time, or prolonged platelet function analyzer closure time; optional diagnostic criteria were quantitative or qualitative evaluation of GPIIb/IIIa receptors, including flow cytometry and identification of gene defects.[13,14] Those with acquired platelet disorders, caused either by autoimmune disorders or medications, were excluded. All treatment decisions were based on local clinical practice. Patients were recruited between May 2007 and December 2011, and were enrolled from a total of 45 sites representing 15 countries.

The study was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Pharmacoepidemiology Practices. Before data entry, each site obtained approval by any necessary Independent Ethics Committee of Institutional Review Board, and by any local regulatory authorities. Informed consent was obtained from all patients, or from parents or other legal guardians for patients not of age to provide informed consent.

2.2 | Investigator reports

The case report forms completed by investigators collected patient information specific to single hemostatic events (bleeding episodes and surgical procedures), including patient histories, treatment reports, and assessments of treatment effectiveness, platelet refractoriness, and the presence of anti-platelet antibodies (HLA and/or anti-GPIIb/IIIa). Investigators entered information on refractoriness and antibody status at the time of each patient's enrollment and whenever either status changed. Effectiveness was evaluated on a 4-point scale of effective (hemostasis achieved for 6 hours or more or bleeding stopped), partially effective (bleeding was mild or decreased substantially), ineffective (bleeding was excessive or unchanged/worsened), or not possible to evaluate. Case report forms allowed for but did not require the inclusion of narratives to support case descriptions, treatment, and results, which were completed variably by the participating sites. Queries were sent to sites in cases of missing, inconsistent, or ambiguous information, and responses were added to the case report forms as necessary.

2.3 | Adjudication

An in-person adjudication meeting was held on January 16-18, 2013, in which three adjudicators gathered to review data from each patient within the GTR on a case-by-case basis. Members of the adjudication committee were chosen from a list of six US experts proposed by Novo Nordisk and approved by the FDA based upon availability. The adjudicators individually performed two independent evaluations of platelet refractoriness, anti-platelet antibody status, and rFVIIa effectiveness for each treatment event; an initial assessment was performed without information regarding investigator evaluations (blinded review), and a subsequent assessment was performed following case report unblinding. For each patient being assessed for a particular bleeding or surgical treatment, data initially provided to the adjudicators included treatment regimen and outcome entered (ie, whether bleeding stopped

and in what time frame); these were in addition to a summary list of patient demographics, initial platelet antibody/refractoriness status, and previous GT treatments. Investigator narratives on overall efficacy assessment for the particular episode were blinded initially and revealed only on the second fully unblinded review of the individual episodes. Each patient and their bleeding events were discussed twice by the committee, once following individual review of blinded data and once following review of unblinded data. Final assessments were considered the opinion of the adjudication committee if the same response was coded by two or three of the adjudicators; otherwise, opinions were considered indeterminate ("no consensus"). During the blinded review only, adjudicators could after discussion come to a determination of insufficient information.

Adjudicated refractoriness to platelet transfusions was determined by the three adjudicators with consideration of multiple criteria: (1) investigator-reported refractoriness at any time in the registry and/or the historical report of antibodies (GPIIb/IIIa or HLA if reported), (2) patterns of treatment consistent with unresponsiveness (eg, a switch in treatment regimen), and (3) perceived treatment responses, based on the timing and extent of treatment compared to those of comparable episodes. Classification of patient refractoriness and antibody status was represented by four possible categories: refractory with antibodies, refractory with no antibodies, antibodies only, and none/unknown. All adjudicator assessments of refractoriness and antibody status presented here reflect final (unblinded) evaluations.

As requested by the FDA, effectiveness assessments made by the adjudicators were classified on a 2-point scale of hemostasis achieved (success) or hemostasis not achieved (failure).

2.4 | Statistical analysis

Data were summarized using descriptive statistics. Categorical variables are presented as numbers and percentages, and numerical variables as mean, median, and 5th, 25th, 75th, and 95th percentiles.

3 | RESULTS

The GTR contained data collected from 218 patients with GT who experienced a total of 1073 events (870 bleeding episodes and 204 surgeries; one event was reported as both a bleeding episode and a surgery) (Figure 1). Numbers of events considered in this FDA-requested adjudication plan differ slightly from those reported in previous analyses conducted by the GTR External Expert Panel because of differences in handling bleeding episodes; previous analyses had recategorized two episodes as surgeries, excluded six episodes as not appropriate for assessment, and excluded or collapsed 64 episodes as linked events.[13,14] The adjudication analysis of platelet refractoriness and anti-platelet antibody status was performed on patients who experienced severe bleeding episodes or surgical procedures (excluding events characterized as easy bruising or subcutaneous bleeding), resulting in an adjudication population of 195 patients with 810 treatment events (619 severe bleeding episodes and 192 surgical procedures). The adjudicated rFVIIa efficacy analysis was performed on patients in the adjudication population who received rFVIIa, resulting in a rFVIIa-treatment population of 131 patients who experienced a total of 266 bleeding episodes (41% rFVIIa only; 59% rFVIIa + other hemostatic agents) and 160 surgical procedures (41% rFVIIa only; 59% rFVIIa + other hemostatic agents) including one surgical procedure where rFVIIa was mentioned only in the free text narrative. Of the total of 10 emergency surgical procedures, seven were treated with rFVIIa (four of which were in patients with adjudicator-categorized antibodies or refractoriness), and three were treated with platelets (one of which was in a patient with adjudicator-categorized antibodies or refractoriness). Examples of rFVIIa-treated emergency procedures included endoscopy for upper GI bleeding, exploratory laparotomy and/or oophorectomy for ruptured ovarian cyst with bleeding (two cases), interventions related to epistaxis (two cases), and dilation and curettage following vaginal delivery for retained placental fragments.

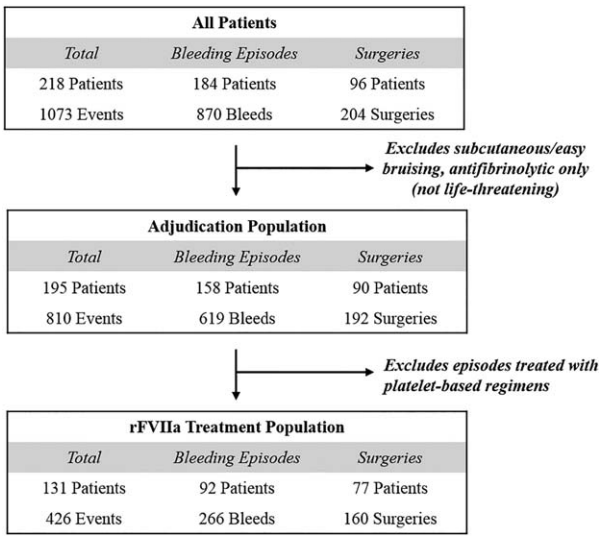

FIGURE 1 The adjudication and rFVIIa treatment populations

3.1 | Adjudicated platelet refractoriness and history of anti-platelet antibody status

Adjudicator assessments of platelet refractoriness and history of antibody status were reported for each individual treatment event, and incorporated a consideration of all available patient information, including data from any previous events included in the registry. Following the case-by-case review of refractoriness and antibody status, the adjudicators consolidated their assessment approaches into a consensus algorithm (Supporting Information Figure S1). This algorithm incorporates data regarding investigator assessments of refractoriness and antibody status, treatment approaches, and clinical responses, and describes the overall methodology developed to code refractoriness and antibody status.

The adjudicator classifications of platelet refractoriness and anti-platelet antibody status were mostly consistent with those reported by the investigators (Table 1). Adjudicator reclassifications included 58 out of 59 platelet-treated bleeding episodes (98.3%) and three out of four platelet-treated surgeries (75.0%) that were coded by the investigators

TABLE 1 Comparison of investigator-reported and adjudicator-categorized refractoriness and antibody status in bleeding episodes and surgical procedures

		Adjudicator-categorized refractory/antibody status, n (%)				
		Refractory + antibodies	Refractory - antibodies	Antibodies only[a]	None/ unknown	Total
Bleeding Episodes						
		Any rFVIIa-treated bleeding episode (n = 266)				
Investigator-reported status	Refractory + antibodies	18 (78.3)	-	4 (17.4)	1 (4.3)	23
	Refractory - antibodies	-	33 (82.5)	-	7 (17.5)	40
	Antibodies only[a]	24 (58.5)	-	6 (14.6)	11 (26.8)	41
	None/unknown	4 (2.5)	-	-	158 (97.5)	162
		Any platelet-treated bleeding episode (n = 298)				
Investigator-reported status	Refractory + antibodies	1 (1.7)	-	58 (98.3)	-	59
	Refractory - antibodies	-	-	1 (14.3)	6 (85.7)	7
	Antibodies only[a]	-	-	27 (58.7)	19 (41.3)	46
	None/unknown	-	-	-	186 (100.0)	186
Surgical Procedures						
		Any rFVIIa-treated surgical procedure (n = 160)				
Investigator-reported status	Refractory + antibodies	28 (71.8)	-	11 (28.2)	-	39
	Refractory - antibodies	-	12 (92.3)	-	1 (7.7)	13
	Antibodies only[a]	30 (66.7)	-	13 (28.9)	2 (4.4)	45
	None/unknown	-	-	-	63 (100.0)	63
		Any platelet-treated surgical procedure (n = 32)				
Investigator-reported status	Refractory + antibodies	1 (25.0)	-	3 (75.0)	-	4
	Refractory - antibodies	-	-	-	-	0
	Antibodies only[a]	1 (9.1)	-	8 (72.7)	2 (18.2)	11
	None/unknown	-	-	-	17 (100.0)	17

[a]Refers to antibody status specified and refractory none or unknown.
Shaded boxes reflect identical investigator and adjudicator ratings.

as "refractory with antibodies" but reclassified by the adjudicators as "antibodies only." This reclassification reflects a perceived inconsistency between the administration of platelets and a reported history of platelet refractory status, and modifies what appeared to be a different determination of platelet refractoriness by the investigators. The majority of these reclassified platelet-treated bleeding episodes (55 of 58) occurred in two children and were coded for effectiveness by the investigators as "effective" or "partially effective." Adjudication also resulted in a reclassification of 24 out of 41 rFVIIa-treated bleeding episodes (58.5%) and 30 out of 45 rFVIIa-treated surgical procedures (66.7%) that were coded by the investigators as "antibodies only" to "refractory with antibodies," based on analysis of treatment patterns for similar bleed types over time. A majority of rFVIIa-treated bleeding episodes (177 of 266; 66.5%) and 66 of 160 (41.3%) of rFVIIa-treated surgical procedures occurred in patients without adjudicator-determined platelet refractoriness or anti-platelet antibodies.

3.2 | Adjudicated rFVIIa efficacy

The mean (median) age of the rFVIIa-treated population at first recorded event was 24.2 (21.5) years. Whereas the majority of rFVIIa-treated bleeding episodes occurred in patients aged 0 to 16 years (65%), most rFVIIa-treated surgical procedures occurred in patients older than 16 years (86%). A majority of patients were female (57%), and most were Caucasian (54%). The most common disease type was Type 1 (47%); 10% were Type II, 2% were Type III, and 41% were unknown.

3.2.1 | Bleeding episodes

The most frequently reported bleeding locations were epistaxis (44%), gum bleeding (18%), menorrhagia (14%), and oral bleeding associated with tooth or dental extraction (11%). The doses of rFVIIa administered per infusion were narrowly distributed (median [Q1, Q3], 90 [90, 95]

TABLE 2 Adjudicator evaluation of efficacy – bleeding episodes

	No. of Patients[e]	No. of Episodes	Success n (%)	Failure n (%)	Insufficient Data n (%)	No Consensus n (%)
All rFVIIa[a]	92	266	251 (94.4)	4 (1.5)	6 (2.3)	5 (1.9)
By treatment regimen						
rFVIIa only	44	109	101 (92.7)	2 (1.8)	4 (3.7)	2 (1.8)
rFVIIa ± platelets ± other hemostatic agents	69	157	150 (95.5)	2 (1.3)	2 (1.3)	3 (1.9)
By antibody/refractory group						
Refractoriness ± platelet-specific antibodies[b,c]	31	79	75 (94.9)	2 (2.5)	2 (2.5)	0
Platelet-specific antibodies[b,c]	8	10	10 (100.0)	0	0	NA
Neither or unknown[c,d]	57	177	166 (93.8)	2 (1.1)	4 (2.3)	5 (2.8)

[a]All treatment regimens that included treatment with rFVIIa.
[b]Includes GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies.
[c]Treatment was rFVIIa only for 26/79 episodes with refractoriness with or without antibodies, 2/10 episodes with platelet-specific antibodies only, and 81/177 episodes with neither or unknown. The remainder received rFVIIa with platelets and/or antifibrinolytic agents.
[d]Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractory status unknown.
[e]Patient numbers are not additive. Patients may have episodes with different treatment regimens and have more than one antibody/refractory status.

μg/kg), and were similar between bleeding episodes treated with rFVIIa only (median [Q1, Q3], 90 [90, 90] μg/kg) and those treated with rFVIIa + other hemostatic agents (median [Q1, Q3], 90 [90, 100] μg/kg) (Supporting Information Figure S2A). The time interval between doses was also similar between bleeding episodes treated with rFVIIa only (median [Q1, Q3], 3.0 [2.0, 4.0] hours) and those treated with rFVIIa + other hemostatic agents (median [Q1, Q3], 3.0 [2.0, 6.0] hours) (Supporting Information Figure S2B), although the number of doses administered per event was greater for episodes treated with rFVIIa + other hemostatic agents (median [Q1, Q3], 3.0 [1.0, 6.0]) than for those treated with rFVIIa only (median [Q1, Q3], 2.0 [1.0, 3.0]) (Supporting Information Figure S2C). These dosing data served as the basis for the indicated dosing for GT in the United States.

Overall, adjudicators rated most rFVIIa-treated bleeding episodes as successful (94.4%); few episodes were reported as a treatment failure (1.5%) (Table 2). Rates of treatment success were similar between bleeding episodes treated with rFVIIa only (92.7%) and those treated with rFVIIa + other hemostatic agents (95.5%), and were similar between all adjudicator-assessed antibody/refractoriness categories (93.8% to 100.0%). Detailed information regarding dosing and efficacy by type of bleeding episode is shown in Supporting Information Table S1.

3.2.2 | Surgical procedures

A majority of the surgical procedures were reported as elective (92%); 4% were reported as emergencies and 4% were unspecified. The most frequent types of surgical procedures were dental (66%), endoscopy (8%), and nasal (5%). The doses of rFVIIa administered per infusion were similar between surgical procedures treated with rFVIIa only (median [Q1, Q3], 90 [90, 115] μg/kg) and those treated with rFVIIa + other hemostatic agents (median [Q1, Q3], 92 [90, 135] μg/kg) (Supporting Information Figure S3A); the time interval between doses was also similar between these surgical groups (median [Q1, Q3], 2.0 [2.0, 3.0] hours and 3.0 [2.0, 5.0] hours, respectively) (Supporting Information Figure S3B). Numbers of doses per admission were greater for episodes treated with rFVIIa + other hemostatic agents (median [Q1, Q3], 3.0 [2.0, 5.0]) than for those treated with rFVIIa only (median [Q1, Q3], 2.5 [2.0, 3.0]) (Supporting Information Figure S3C), and were greater for major surgeries than for minor surgeries (median [Q1, Q3], 11.0 [3.0, 21.0] and 2.5 [2.0, 3.0], respectively). These dosing data served as the basis for the indicated dosing for GT in the United States.

Overall, adjudicators rated most rFVIIa-treated surgical procedures as successful (99.4%) (Table 3). Rates of treatment success were similar between bleeding episodes treated with rFVIIa only (98.5%) and those treated with rFVIIa + other hemostatic agents (100.0%), and were similar between all adjudicator-assessed antibody/refractoriness categories (98.6% to 100.0%). Detailed information regarding dosing and efficacy by type of surgical procedure is shown in Supporting Information Table S1.

3.2.3 | Investigator-reported vs. adjudicator-assessed effectiveness

Blinded adjudicator assessments of efficacy were largely consistent with investigator effectiveness ratings (Supporting Information Table S2). Of the 255 bleeding episodes and 155 surgical procedures that were rated by investigators as effective or partially effective, 240 bleeding episodes (94.1%) and 154 surgeries (99.4%) were rated by the adjudicators as successful. Twelve bleeding episodes and one surgical procedure that were rated by the investigators as effective or partially effective were classified by the adjudicators as insufficient data. Of the five bleeding episodes and three surgical procedures that were rated by the investigators as ineffective, four bleeding episodes (80.0%) and three surgical procedures (100.0%) were classified by the adjudicators as successful; all eight of these events were in cases where rFVIIa was used in conjunction with other hemostatic agents and/or platelets.

The unblinding of adjudicators to investigator effectiveness ratings had minimal effect on adjudicator assessments. Seven bleeding episodes that were rated as insufficient data in adjudicators' blinded

TABLE 3 Adjudicator evaluation of efficacy – surgical procedures

	No. of Patients[e]	No. of Procedures	Success n (%)	Insufficient Data[f] n (%)
All rFVIIa[a]	77	160	159 (99.4)	1 (0.6)
By treatment regimen				
rFVIIa only	35	66	65 (98.5)	1 (1.5)
rFVIIa ± platelets ± other hemostatic agents	57	94	94 (100.0)	0
By antibody/refractory group				
Refractoriness ± platelet-specific antibodies[b,c]	33	70	69 (98.6)	1 (1.4)
Platelet-specific antibodies[b,c]	11	24	24 (100.0)	0
Neither or unknown[b,d]	36	66	66 (100.0)	0

[a]All treatment regimens that included treatment with rFVIIa.
[b]Includes GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies.
[c]Treatment was rFVIIa only for 22/70 episodes with refractoriness with or without antibodies, 13/24 episodes with platelet-specific antibodies only, and 31/66 episodes with neither or unknown. The remainder received rFVIIa with platelets and/or antifibrinolytic agents.
[d]Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractory status unknown.
[e]Patient numbers are not additive. Patients may have episodes with different treatment regimens and have more than one antibody/refractory status.
[f]No reports of failure or lack of consensus was reported.

assessments were reclassified after un-blinding; one episode was reclassified to treatment success, one bleeding episode was reclassified to treatment failure, and five episodes were reclassified with no consensus. No surgical procedures were reclassified following unblinded review.

4 | DISCUSSION

Expert adjudication of the GTR data provided an objective assessment of individual patient case reports and a consistent approach towards determining platelet refractoriness, antibody status, and treatment effectiveness. An important goal of the adjudication process was to reduce biases caused by variability in investigator assessments and incompleteness of data; adjudicators benefitted from an objective perspective in which patient data could be reviewed in the context of any additional events included in the registry, and assessments were based on patterns of treatment over time. These methods provide a unique way to examine observational data beyond descriptive statistics to learn more about the underlying disease state and treatment variability, and may provide a model for independent review of similar data sets.

The GTR is the largest observational study on GT and few previous studies have investigated rFVIIa efficacy data in this patient population, although the adjudicated rFVIIa efficacy findings are consistent with reports from these previous studies. Results of an international survey demonstrated high rates of physician-reported rFVIIa efficacy in the treatment of bleeding episodes (77 of 103 [74.8%]; although eight bleeding episodes occurred within 48 hours after successful treatment, giving an overall efficacy rate of 69/103 [67.0%]) and in surgical/invasive procedures (29 of 31; 93.5%) in patients with GT.[7] Additionally, an open-label Iranian study in patients with GT reported a "good" or "partial" response to rFVIIa in 26 of 28 bleeding episodes (92.9%).[6] Results of multiple case reports in patients with GT also presented rFVIIa efficacy data, and demonstrated an overall rFVIIa response rate of 25 of 36 bleeding episodes (69.4%) and 27 of 28 surgeries (96.4%).[8]

A notable finding of this analysis was the high use of rFVIIa in patients classified by the investigators as having neither platelet refractoriness nor antibodies, despite the indication in the European label for patients with GT with antibodies to GPIIb/IIIa and/or HLA and with past or present refractoriness to platelet transfusions.[8] This pattern of use may reflect efforts by physicians to avoid platelet exposure and therefore reduce the potential for patients to develop refractoriness, or in some cases a potential unavailability of platelets as an immediate treatment option or a greater convenience of rFVIIa compared to platelet transfusions.

Safety data from the GTR have been previously reported, and indicate a favorable safety profile of rFVIIa in patients with GT.[13,14,16] The only serious adverse event probably or possibly related to rFVIIa was a deep vein thrombosis reported in a 25-year-old female receiving rFVIIa, platelets, and packed red blood cells eight days after an emergency laparotomy for an ovarian cyst with hematoma and ureteral compression.[14]

The GTR results have been presented in two previous reports of investigator-reported data based upon the analysis by the GTR External Expert Panel following reclassification of certain episodes,[13,14] in addition to the current report of adjudicated data based upon the FDA-approved adjudication plan. Minor differences in methodologies resulted in slightly different reports of patient numbers and treatment events between these two sets of analyses and the primary report of postmarketing surveillance data submitted to European Medicines Authority on an annual basis and following closure of the registry. Unlike previous published reports, the current analysis excluded events characterized by subcutaneous/easy bruising and those treated only with antifibrinolytics, which were considered to not meet criteria agreed upon for severe bleeds requiring systemic hemostatic therapy. Prior publications are also based on an independent analysis of raw data files, and reflect collapsing of linked admissions to index events, exclusion of nonbleeding events, and recategorization of two bleeding episodes as surgical events (see figure 1 in Di Minno et al.[13]). While the multiple records for single admissions were easily identified based

upon the "notes" provided in the CRFs reviewed and questioned by the adjudicators, the adjudication plan did not allow for consolidation of multiple records where each had an investigator-reported efficacy assessment; in contrast, the GTR External Expert Panel was able to consolidate those records with a single efficacy assessment.

An important limitation of the adjudication analysis presented here is the limited and variable amount of patient data provided by the investigators. The underlying raw data from EMA reporting was analyzed by the adjudicators, however, because the GTR had closed at the time of the analysis, adjudicators were limited to data and case narratives that had been submitted by the investigators, and had no opportunities to query the data. Additionally, although data on platelet refractoriness and antibody status could be reported by investigators during each event, these fields were not required in the registry. Adjudicators were also directed not to merge or consolidate treatment events, even if the case report forms clearly indicated that subsequent events had resulted from a single bleed, which contributed to some of the "insufficient data" or "no consensus" findings. Coding for treatment regimen could be modified based upon product mention in open text narratives (e.g., 1 of 160 rFVIIa-treated surgeries where rFVIIa was noted only in narrative), and post-bleed transfusions without hemostatic treatment could be excluded. Variable definitions and scales for the evaluation of efficacy, as well as variable time periods after bleeding for investigator assessments, relative to the entire treatment regimen documented, may also limit comparisons of investigator and adjudicator-coded efficacy. For example, adjudicators' consideration of the entire treatment, including rFVIIa dosing/pattern and treatment sequence (first-line vs. second-line or salvage rFVIIa, when platelets or other hemostatic agents were used relative to efficacy assessment), likely contributed to evaluation as successful 7 of 8 bleeding episodes/surgeries that investigators reported at the time of assessment to be ineffective. Another notable aspect of the adjudication analysis is the sponsorship by Novo Nordisk Inc.; adjudicators may therefore be perceived as lacking complete independence in their assessments.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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