The Glanzmann Thrombasthenia Registry: safety of platelet therapy in patients with Glanzmann thrombasthenia and changes in alloimmunization status

Glanzmann thrombasthenia (GT) is a rare, inherited, autosomal-recessive platelet disorder resulting in absent, reduced or defective glycoprotein (GP) IIb/IIIa (also known as integrin $\alpha_{IIb}\beta_3$).[1] As GPIIb/IIIa is a receptor required for platelet aggregation, patients with GT are unable or have reduced ability to form clots and are at risk of spontaneous and increased bleeding following trauma and surgery, with potentially serious consequences.[1] Standard-of-care GT treatment involves platelet transfusion,[1] ideally human leukocyte antigen (HLA)-matched single-donor and leukocyte-reduced apheresis platelets; however, this therapy may be associated with alloimmunization leading to refractoriness to future platelet transfusion and/or allergic reactions.[1] This report describes the safety of platelet-based therapy in patients with GT included in the Glanzmann Thrombasthenia Registry (GTR) (*clinicaltrials gov. Identifier: NCT01476423*).

Platelet-refractoriness is a variable term generally referring to the failure of platelets to increase after transfusion or platelet functional ineffectiveness to control bleeding.[1] Anti-platelet antibodies against HLA and/or GPIIb/IIIa may cause platelet ineffectiveness.[1] The presence of anti-platelet antibodies does not always lead to platelet-refractoriness, whilst the absence of antibodies may occur in patients experiencing platelet-refractoriness.[1]

Recombinant activated factor VII (rFVIIa, NovoSeven®, Novo Nordisk A/S, Bagsværd, Denmark)[2] is an alternative therapy in patients with GT with refractoriness to platelet transfusions and/or platelet antibodies, or where platelets are not readily available.[1] The GTR was a prospective, observational, international registry, which assessed effectiveness and safety of available treatment options in patients with GT.[3,4] Treatment was administered as per local practices and included rFVIIa (F7), platelets (P) and antifibrinolytics/other hemostatic treatments (OH) alone or in combination. Treatment data were recorded for 218 patients of all ages with a diagnosis of congenital GT enrolled from 45 sites in 15 countries between May 10, 2007 and December 16, 2011.[3,4] Following a protocol amendment (January 10, 2008), cases generated from 2004 could be registered retrospectively.[5] Patients with acquired thrombasthenia due to medication or autoimmune disease were excluded.

A complementary study from the GTR was performed to identify patients with a recorded change in platelet-refractoriness and/or anti-platelet antibody status during the follow-up period, confirmed either as an adverse event (AE) during hospital admission, or through data collected at the next admission. Clinical criteria for platelet-refractoriness have been defined[3,4] and include bleeding during surgery and/or persistence of bleeding and/or rebleeding within 24 hours (despite adequate platelet infusion).[4] The GTR captured data which was entered at patient inclusion and, where available, relevant historical treatment and platelet-refractoriness/antibody status data was added. Effectiveness was assessed using a previously defined three-point scale.[3,4] Statistical analyses were descriptive.

Overall, 218 patients were included in this sub-analysis, of whom 34 (16%) had ≥1 instance of platelet-refractoriness recorded and 65 (30%) had anti-platelet antibodies. GPIIb/IIIa antibodies were recorded in 47 (22%) patients, HLA antibodies in 21 (10%) patients and 13 patients (6%) had both GPIIb/IIIa and HLA antibodies.

During the GTR study period, a change in platelet refractoriness and/or antibody status was recorded in five (2%) registered patients (referred to as patients 1–5) (*Online Supplementary Table S1*). In these patients, platelet-based regimens had been used before the beginning of the study and were used in 64 of 77 (83%) of study admissions.

Patient 1 was an adult male with a negative-to-positive change in antibody status for HLA antibodies over three admissions in 10 months. At the first admission, treatment with F7POH was evaluated as effective, with a negative follow-up test for HLA antibodies approximately 5 months later. At the following two admissions, treated with POH and P, the patient tested positive for HLA antibodies. Both treatments were recorded as effective.

Patient 2 was a male pediatric patient with five admissions over 1 year. At admissions 1 and 2, the patient received F7OH and F7POH, respectively. Both treatments were effective, and the patient was negative for platelet-refractoriness. All subsequent admissions were treated with F7OH effectively but were declared positive for platelet-refractory status by the investigator. Antibody status was negative at admission 2; however, 5 months after the fourth admission the patient was declared GPIIb/IIIa antibody-positive.

Patient 3 was a male pediatric patient with a previous history of platelet transfusion and 11 admissions over 7 years. Various treatments were administered throughout. Although POH was received at the first admission, the patient was not positive for refractoriness or antibodies until admission 7. The patient received platelets for admission 5 that were effective but was declared anti-platelet antibody-positive 5 months later. The nature of the platelet antibodies was

unavailable. F7POH was administered during admissions 8 (effective) and 9 (partially effective).

Patient 4 was a male pediatric patient with three admissions over <1 year, treated effectively with OH and POH at first and second admissions, respectively, without refractoriness. At the third admission, POH was administered but platelet transfusion was ineffective (platelet refractoriness positive) and the patient underwent surgical repair for hemostasis. The nature and status of the platelet antibodies were unavailable.

Patient 5 was a female pediatric patient with 55 admissions over 3 years and a history of platelet transfusion. Refractoriness status was recorded for 34 of 55 admissions and was positive at the first admission (POH treatment). Despite this, P and POH-based regimens were administered in 52 of 55 admissions; F7POH was administered during admission 12. At admission 50, the patient was negative for platelet-refractoriness. At admission 51, she was positive, switching to negative at admissions 52–54. Treatment effectiveness was recorded as ineffective on one occasion of platelet transfusion (admission 32) and only partially effective or effective in multiple admissions treated with P or POH. Antibody status was documented at admissions 5–21; the nature of platelet antibodies was unavailable, and a positive result was observed in all instances except admission 16, which was entered as negative.

Of 581 hospital admissions in 152 patients who received P or POH, 14 AE (13 minor) related to treatment for bleeding events were reported in seven patients. A single serious AE (generalized hives) occurred in a patient receiving POH (Table 1). The limited number of patients in this sub-study and the limited records on platelet refractoriness status after platelet transfusion means safety data must be interpreted with caution.

The development of anti-platelet antibodies after P or POH-based treatments may change the platelet refractoriness status and lead to the inefficacy of platelets to prevent or stop a bleed. This was observed in patient 4 at admission 3 where POH treatment failed to achieve hemostasis and surgical intervention was required. Additionally, anti-HLA antibodies may either decrease with time in the absence of a new P or POH treatment,[6] or may persist even without transfusion. Anti-HLA antibodies may result in serious post-transfusion complications including lung injury.[7] Therefore, to facilitate optimal treatment decisions from the available therapeutic tools, identifying platelet refractoriness/antibody status is crucial. Analogous to inhibitor assessment in hemophilia patients, baseline testing for antibodies to HLA and GPIIb/IIIa should be performed upon GT diagnosis, and periodically monitored following exposure to blood products containing platelets, which may include unwashed red-cell concentrates.[1,8] Thus, treatment choices can be adapted to minimize the risk of uncontrolled bleeding. The follow-up of anti-GPIIb/IIIa is also particularly important for women, as anti-platelet antibodies may lead to fetal/neonatal thrombocytopenia.

Despite limited data, several studies have reported anti-GPIIb/IIIa antibodies in patients with GT.[3,4,9-12] To date, the

Table 1. Adverse events occurring during hospital admissions of patients in the Glanzmann Thrombasthenia Registry receiving platelet-based hemostatic treatment not including recombinant activated factor VII either for a bleeding episode or for treatment related to surgery.

Adverse event	Events N	Patients N*	Admissions N†	Treatment		Platelet refractoriness‡		
				P, N	POH, N	Pos, N	Neg, N	NR, N
All events	14	7	10	4	6	0	3	4
Serious Generalized hives	1	1	1	0	1	0	0	1
Non-serious								
Urticaria	2	2	2	1	1	0	1	1
Itching	2	2	2	1	1	0	1	1
Intestinal infection	1	1	1	0	1	0	0	1
Febrile reaction	2	1	2	1	1	0	1	0
Post-transfusional allergy	1	1	1	0	1	0	0	1
Fever	1	1	1	0	1	0	1	0
Chills	2	2	2	1	1	0	1	1
Hyperthermia	1	1	1	1	0	0	0	1
Pneumonia	1	1	1	1	0	0	1	0

Multiple adverse events could be recorded for a patient during a single admission. Antibody status was not recorded for all patients experiencing an adverse event. *One patient experienced both a non-serious adverse event and a serious adverse event. †Related to treatment for a bleeding event. ‡Platelet refractoriness was defined as: bleeding during surgery despite an adequate amount (as determined by the treating clinician) of platelet infusion, and/or persistence of bleeding despite an adequate amount (as determined by the treating clinician) of platelet infusion, and/or rebleeding within 24 hours despite an adequate amount (as determined by the treating clinician) of platelet infusion.[3,4] OH: other hemostatic treatment (mostly antifibrinolytics); P: platelets; Pos: positive; Neg: negative; NR: not recorded; POH: platelets and other hemostatic treatments.

GTR has the largest GT cohort in which alloantibody proportion was assessed.[3,4] Nevertheless, as a change in antibody/platelet-refractoriness status was not an objective of the GTR, it was not recorded for every admission, making interpretation difficult.[3,4] Additionally, the GTR was not specifically designed to record platelet-related AE.

Not all centers participating in the GTR conducted platelet antibody studies due to the specialized nature, and potentially restricted availability, of testing. Indeed, in patients 3–5, the nature of the platelet antibodies (anti-HLA or GPIIb/IIIa) was unavailable. Thus, antibody status is likely underreported.[10] Additionally, as antibodies can be cleared if no further transfusions are received, delayed assessment may give misleading negative results.[12] Conversely, platelet transfusion may remain effective in previously alloimmunized GT patients as transfused platelets may not be removed immediately (potentially dependent on antibody isotype).[10,11] Non-neutralizing antibodies (detected by immunological assays) that do not inhibit platelet aggregation may explain some persistent clinical efficacy of transfused platelets.

Fluctuations in platelet refractoriness status, as observed in patient 5, suggest that some database entries may be inaccurate. Therefore, misinterpretation of the platelet refractoriness definition or incorrect data entry cannot be excluded.

Despite positive platelet refractoriness/antibody status, administration of platelet-based regimens continued in most admissions instead of transitioning to rFVIIa-based regimens. rFVIIa may not have been readily available during the timeframe of the GTR, either because of not yet being locally approved, or not being approved by the hospital or the patient's insurance. Notably, rFVIIa was administered in patients 3 and 5 when platelet antibodies were positive. On two of these occasions in patient 3 and once in patient 5, treatment with F7POH was effective/partially effective. Hence, rFVIIa could have contributed to the outcome.

Due to the real world nature of the database, admission records were often incomplete, making interpretation difficult. Importantly, bleeding event type and/or platelet refractoriness/antibody status can affect treatment efficacy and impact the patient treatment journey. This highlights the importance of comprehensively recording patient data, outcomes, platelet efficacy and antibody testing in patients with GT. Hence, there is an unmet need to initiate clinical practice changes to ensure routine antibody testing is performed within weeks of transfusion to improve patient management decisions.

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Disclosures

MCP was the chair of Novo Nordisk's expert panel on the Glanzmann Thrombasthenia Registry, has been an *ad hoc* speaker for Bayer, Novo Nordisk, and Pfizer, attended advisory board meetings of CSL Behring, KVR Pharmaceuticals, Novo Nordisk, Octapharma, Pfizer, Bayer, Roche, Sobi and Takeda, and received grant funding from Bayer and CSL Behring. RdO was a member of Novo Nordisk's expert panel on the Glanzmann Thrombasthenia Registry, has received research support for clinical trials or fees for advisory board honoraria or invitation as speaker in symposia from: Baxalta/Shire/Takeda, Biomarin, CSL Behring, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, Sobi and Spark Therapeutics. SB is an employee of Novo Nordisk. RBZ was a member of Novo Nordisk's expert panel on the Glanzmann Thrombasthenia Registry, has been a speaker in symposia for Aspen, AstraZeneca, Bayer, Biotest, Boehringer Ingelheim, CSL Behring, GlaxoSmithKline, LEO Pharma, MEDA, Novartis, Novo Nordisk, Octapharma, Pfizer, Sanofi-Aventis, has been a member of advisory boards at Bayer, BMS, Novo Nordisk, Pfizer and he has received research funding from CSL Behring. GDM was a member of Novo Nordisk's expert panel on the Glanzmann Thrombasthenia Registry.

Contributions

MCP, RdO, RBZ and GDM, as members of Novo Nordisk's expert panel on the Glanzmann Thrombasthenia Registry (GTR), participated in the planning and data monitoring of the GTR. All

authors participated in data analysis, with SB providing the statistical analytical expertise. All authors contributed equally to the revision, finalization and approval of the manuscript.

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Data-sharing statement

The subject level analysis data sets for the research presented in the publication are available from the corresponding author on reasonable request.

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