Imlifidase Utilization in Glanzmann Thrombasthenia with Anti-GPIIb/IIIa and Anti-HLA Alloimmunization and Severe Platelet Refractoriness following Hematopoietic Stem Cell Transplant.

Mohammad AlNajjar¹, Ryan Rochat², Amanda Grimes³, Amir Navaei⁴, Todd Eagar⁵, Caridad Martinez¹, Khalid Yassine¹, Robert Krance¹, and Saleh Bhar¹

¹Baylor College of Medicine Center for Cell and Gene Therapy  
²Baylor College of Medicine Division of Pediatric Infectious Diseases  
³Texas Children’s Cancer Center and Hematology Centers  
⁴Baylor College of Medicine Texas Children’s Hospital  
⁵Methodist Hospital

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Abstract

Glanzmann Thrombasthenia (GT) is an inherited bleeding disorder of poor platelet function secondary to a defect in platelet membrane glycoprotein IIb/IIIa (GPIIb/IIIa). Patients with GT may develop anti-platelet antibodies including anti-GPIIb/IIIa which can lead to severe refractory thrombocytopenia and life-threatening bleeding, management of which is challenging. We report successful use of imlifidase, a novel IgG protease enzyme, as part of a multimodal approach for management of severe platelet refractoriness and alloimmunization in a child with GT and primary graft failure following hematopoietic stem cell transplant (HSCT). The patient had no detectable anti-platelet alloantibodies following imlifidase, and underwent a second HSCT.

INTRODUCTION

Glanzmann Thrombasthenia (GT) is an inherited bleeding disorder characterized by the lack of platelet aggregation due to a defect in platelet membrane glycoprotein GPIIb/IIIa receptor (1). Patients with GT are at risk of alloimmunization and the development of anti-platelet alloantibodies including anti-Human-Leukocyte-Antigen (HLA) and/or anti-GPIIb/IIIa antibodies (2-5). The prevalence of alloimmunization in GT is estimated at 30% with anti-GPIIb/IIIa antibodies being the most common type of antibodies (6). Alloimmunized patients can become refractory to platelet transfusions making bleeding management difficult (3). Hematopoietic Stem Cell Transplant (HSCT) is a curative option in alloimmunized patients and those with severe bleeding (7-10).

Management strategies for severe bleeding in alloimmunized patients with platelet refractoriness can be divided into bleeding-control strategies and antibody-management strategies (6). While there is no standardized antibody-management therapy in GT, the approach is typically immunosuppressive or immunomodulatory (7, 11), and may be extrapolated from experiences managing other antibody-mediated disorders.

Imlifidase is a novel protease enzyme that cleaves IgG molecules, leading to a rapid decline in circulating IgG-antibody titers (12-16). The medication demonstrated efficacy in managing sensitized kidney transplant recipients with anti-HLA antibodies (12-16). Here, we present a child with GT and anti-GPIIb/IIIa and
anti-HLA alloimmunization and severe platelet-refractoriness following HSCT. We describe our management approach and outcome following the use of imlifidase.

CASE REPORT

Our patient was diagnosed with GT at 4 months of age. She had a de novo homozygous deletion in the ITGB3 gene with a variant designated c. 1788del that was not previously described in the literature. Due to her increased bleeding frequency with a condensed MCMDM-1 bleeding score of 15, she was referred for HSCT at 4 years of age.

Pre-transplant evaluation revealed normal platelet count and the presence of anti-HLA alloantibodies. Planned donor cells did not have the corresponding antigen to the identified anti-HLA antibodies, and the patient therefore proceeded with HSCT utilizing mismatched-umbilical cord donor. No screening for Anti-GPIIb/IIIa antibodies was done pre-HSCT as the patient had no prior history of platelet transfusions. The patient received myeloablative conditioning regimen and graft vs host disease (GvHD) prophylaxis. (Figure 1) The patient received her first platelet transfusion on Day +4 and also developed E. coli bacteremia on the same day. By Day +9, the patient had an undetectable platelet count and was refractory to transfusions. Qualitative testing on Day +12 confirmed the presence of anti-GPIIb/IIIa antibodies. By day +28, our patient was in primary graft failure, and had high-titer alloantibodies including anti-HLA-A2 antibodies, which was the locus where the patient had a mismatch.

By the second week post-transplant, patient developed grade 3 bleeding defined as significant bleeding requiring transfusion support (18). Specifically, as part of the bleeding-control strategy, she received thrombopoietin receptor agonist, romiplostim, in addition to low-rate continuous platelet transfusion. More intensive management strategies were employed when active bleeding was encountered which included faster-rate platelet transfusion (10 ml/kg over 1 hour) and recombinant factor 7 concentrate (rFVII) every two to four hours until hemostasis was achieved. Systemic tranexamic acid infusion was used as an adjunct in the absence of contraindications. Octreotide infusion was used to manage GI bleeding.

Antibody-management strategy was carried out in a stepwise fashion. Initially, she received two courses of high-dose intravenous immunoglobulin (IVIG), but this was unsuccessful. The patient then received therapeutic plasma exchange (TPE) for a total of seven sessions concurrently with high-dose corticosteroids, but her platelet refractoriness did not improve. Thereafter, targeted immunotherapies with Daratumumab, Bortezomib, and Rituximab were used. This led to a decrease in anti-HLA-A2 antibody level, but without a platelet response. Given the urgency to control life-threatening bleeds and the need to undergo a second HSCT, we considered the use of imlifidase. (19) After regulatory approvals, compassionate doses of the drug were provided by the manufacturer. The patient received two doses of imlifidase on Days +82 and +84 from first HSCT, which corresponded to Days -1 and +1 of the second HSCT. The patient received reduced-toxicity myeloablative regimen for her second HSCT using mismatched-cord at a different HLA locus from the first transplant.

Imlifidase was well tolerated with no side effects. Platelet refractoriness resolved immediately, and the continuous platelet drip was discontinued. (Figure 1) Testing at 4 hours and 30 days from the last dose of imlifidase confirmed the absence of anti-platelet antibodies. The patient engrafted following her second HSCT.

The patient later developed several transplant-related complications including severe transplant-associated thrombotic microangiopathy (TA-TMA), grade IV GvHD, and various infections, which collectively led to increased platelet consumption but without evidence of platelet-refractoriness or the development of anti-platelet antibodies. Management of the transplant-related complications necessitated ongoing use of immunosuppression. The patient unfortunately later succumbed to her transplant-related complications, namely severe TA-TMA and grade IV GvHD, and passed away 220 days following her first transplant.

DISCUSSION

Developing anti-platelet antibodies and severe refractoriness immediately following HSCT was unique about
our case. It is difficult to prevent alloimmunization in GT (2,20,21). The new mutation identified in our case may have contributed to the severity of alloimmunization. Published studies correlate some homozygous mutations with higher risk of antibody formation (22). Finding conclusive molecular and clinical phenotype correlation is difficult in rare disorders. Not only is HLA-A2 considered the most prevalent HLA allele and present on platelets, but there is also evidence that human hematopoietic stem cells express GPIIb/IIa antigen. (23,24,25) Developing anti-HLA-A2 and anti-GPIIb/IIa antibodies likely contributed to both primary graft failure, and platelet-refractoriness in our patient.

The efficacy of using continuous platelet drip in critically ill pediatric patients was highlighted again in our case (26). The persistence of severe platelet-refractoriness despite using IVIG, corticosteroids, and TPE highlighted the severity of the alloimmunization. This warranted targeting antibody-producing plasma cells as the next approach. There are reports of successful off-label use of Daratumumab and Bortezomib in immune thrombocytopenia (ITP) (27,28). Patients in these reports had higher platelet trough levels and required several courses of therapy over a prolonged period of time before showing any response (27-30). Meanwhile, our patient was actively bleeding with no detectable platelets making it justifiable to search for an alternative treatment option to help manage her bleeding and severe platelet-refractoriness.

Kidney transplantation literature reports on imlifidase and the management of pre-transplant HLA-sensitization and antibody-mediated kidney transplant rejections. The use of imlifidase in kidney transplant and other diseases has been with minimal side effects (13-15). Its remarkable efficacy stems primarily from its ability to rapidly deplete both plasma and extravascular pools of IgG (12-16). It is rapid-acting with a short half-life of 4.9 (±2.8) hours (13). Rebound increase in IgG levels may occur but our patient was already on immunosuppression for GvHD prophylaxis, minimizing the latter risk. The ultimate goal behind using imlifidase in our patient was to provide hemostasis and to create a time-window that would permit a successful second HSCT, which was ultimately achieved.

In conclusion, we report the novel and effective use of imlifidase in (a) pediatric case, (b) patient with Anti-GPIIb/IIa antibodies in GT with severe platelet-refractoriness and (c) Anti-HLA antibodies pre-HSCT. We acknowledge that our patient received several antibody-directed therapies prior to imlifidase including a second myeloablative conditioning regimen. However, the dramatic increase in platelet count following imlifidase administration following lack of platelet response to all other therapies proves its efficacy in IgG neutralization. This report supports the need for additional research into expanding the use of imlifidase to refractory ITP, HSCT, and pediatric population.

Conflicts of Interest:
The authors of this manuscript have no conflicts of interest to declare.

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Figure 1. Platelet count, Anti-GPIIb/IIIa, and Anti-HLA-A2 antibody response to various bleeding-control (red color) and antibody management (blue color) strategies over time, with marked platelet response demonstrated following imlifidase therapy at Days +82 and +84. Anti-GPIIb/IIIa antibodies were confirmed positive on Day +12 and were later undetectable on Day +84. Anti-HLA-A2 was first detected on Day +28 and became negative on Day +84. Bleeding-control strategies consisted of continuous platelet drip (Given as 5 ml/kg over 4hrs, continuously), recombinant factor 7 (rFVII) (100 μg/kg every two to four hours until hemostasis achieved), Romiplostim (two initial doses of 5μg/kg/dose and a third dose of 10 μg/kg/dose), Tranexamic acid infusion (1-2 mg/kg/hr), and Octreotide infusion (1-4 μg/kg/hr). Antibody management strategies included IVIG (first dose was 2 g/kg divided over 5 days, and the second dose was a single 1 g/kg). Therapeutic Plasma Exchange (TPE) (total of 7 sessions, with the first three sessions done manually due to ongoing bleeding before switching to automated TPE), corticosteroids (three days at 30mg/kg/day of Methylprednisolone), Bortezomib (5 doses of 1.3mg/m²), Daratumumab (single dose of 16mg/kg/dose), and Rituximab (375mg/m² x 3 weekly doses). Two doses of imlifidase (0.25 mg/kg) were given on days -1 and +1 with the second stem cell infusion occurring in between the two doses. Conditioning regimen for the 1st cord-HSCT was Busulfan, cyclophosphamide and Anti-Thymocyte Globulin (ATG). GvHD prophylaxis in the first HSCT was cyclosporine and mycophenolate. For the second cord-HSCT, the patient received Treosulfan, fludarabine and Thiopeta. GvHD prophylaxis in the second transplant included steroids and tacrolimus.