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Terminal Complement Blockade after Hematopoietic Stem Cell Transplantation Is Safe without Meningococcal Vaccination

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A B S T R A C T

Eculizumab inhibits terminal complement-mediated intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria and complement-mediated thrombotic microangiopathy (TMA) in patients with atypical hemolytic uremic syndrome and is now used as a first-line therapy in these diseases. Eculizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of an increased risk of meningococcal infections in persons without adequate functional complement. Administration of meningococcal vaccine is required at least 2 weeks before administering the first dose of eculizumab, and this advice is included in the product label. Eculizumab use for treatment of TMA in hematopoietic stem cell transplantation (HSCT) recipients brings a significant dilemma regarding REMS required meningococcal vaccination. TMA after HSCT usually occurs within the first 100 days after transplantation when patients are severely immunocompromised and are not able to mount a response to vaccines. We evaluated 30 HSCT recipients treated with eculizumab for high-risk TMA without meningococcal vaccine. All patients received antimicrobial prophylaxis adequate for *Neisseria meningitides* during eculizumab therapy and for 8 weeks after discontinuation of the drug. Median time to TMA diagnosis was 28 days after transplant (range, 13.8 to 48.5). Study subjects received a median of 14 eculizumab doses (range, 2 to 38 doses) for HSCT-associated TMA therapy. There were no incidences of meningococcal infections. The incidences of bacterial and fungal bloodstream infections were similar in patients treated with eculizumab (n = 30) as compared with those with HSCT-associated TMA who did not receive any complement blocking therapy (n = 39). Our data indicate that terminal complement blockade in the early post-transplant period can be performed without meningococcal vaccination while using appropriate antimicrobial prophylaxis until complement function is restored after therapy completion.

INTRODUCTION

Eculizumab is a monoclonal antibody that specifically binds the complement protein C5, inhibiting cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Eculizumab inhibits terminal complement mediated intravascular hemolysis in paroxysmal nocturnal hemoglobinuria patients and complement-mediated thrombotic microangiopathy (TMA) in patients with atypical hemolytic uremic syndrome and is approved by the US Food and Drug Administration for treatment of these 2 diseases [1,2]. Eculizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy, or REMS (reference ID 3642341) because of the increased risk of meningococcal infections in persons lacking functional complement [3]. Administration of a polyvalent meningococcal vaccine is required at least 2 weeks before administering the first dose of eculizumab according to Advisory Committee on Immunization Practices recommendations for patients with complement deficiencies, unless the risks of delaying eculizumab therapy outweigh the risk of developing a meningococcal infection [4]. This advice is included in the product label (reference ID 3855296). Vaccination reduces but does not eliminate the risk of meningococcal infections, and serious meningococcal infections have been reported in several patients with

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paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome treated with eculizumab after receiving timely vaccination [5-7].

Eculizumab use for treatment of TMA in hematopoietic stem cell transplantation (HSCT) recipients brings a significant dilemma regarding REMS required meningococcal vaccination [8-10]. TMA after HSCT usually occurs within first 100 days after transplantation when patients are severely immunocompromised and are usually receiving immunosuppressive therapy for graft-versus-host disease (GVHD) prophylaxis. Adaptive (T and B cell) immunity post-transplant must be at least partially reconstituted for patients to mount a clinically relevant response to a vaccine (ie, an increase of specific antibody levels to a level considered protective). B cell counts are typically zero or near-zero in the first 1 to 3 months after HSCT and gradually return to normal by 12 months post-transplant. Both B and T cell function can be impaired for a prolonged period of time because of immunosuppressive medications used for GVHD prophylaxis or therapy. The known tempo of immune function recovery after HSCT led to the current Centers for Disease Control and Prevention recommendations for revaccination starting no sooner than 6 to 24 months in HSCT recipients who are no longer receiving immunosuppression and show no signs of GVHD [11,12]. However, it is important to realize that many HSCT recipients remain immunocompromised far beyond 2 years after transplant, especially individuals with chronic GVHD or receiving rituximab. For at least 1 year after transplantation, essentially all HSCT recipients remain predisposed to infections from encapsulated bacteria, fungi, and viruses and many or most are unlikely to mount an adequate response to vaccines. Vaccines are not used in the first 3 months after transplantation because there is no expectation that a protective level of antibody will be produced. Here we present our institutional experience of infections in children receiving eculizumab therapy early after HSCT for high-risk TMA without receiving meningococcal vaccine.

METHODS

Study Population

All consecutive HSCT recipients who received eculizumab for high-risk TMA after HSCT at our center from January 2012 to December of 2015 were included in the analysis. All study subjects had high-risk TMA features, including terminal complement activation evidenced by plasma sC5b-9 concentrations above normal (>244 ng/mL) and nephrotic range proteinuria (random urine protein/creatinine ratio > 2 mg/mg) present at the time of TMA diagnosis, in addition to hematologic TMA markers (schistocytes, elevated lactate dehydrogenase, reduced haptoglobin, de novo anemia, and thrombocytopenia) as previously described in our prospective observational study [13]. Clinical and laboratory data were retrospectively summarized from the electronic medical record into HSCT databases. All bacterial, fungal, and viral infections were captured starting from eculizumab therapy initiation until the full complement system recovery was documented after eculizumab therapy completion or patient's death. Vaccination history was reviewed in all study subjects. Infections during eculizumab therapy were summarized and compared with HSCT recipients with TMA who were prospectively monitored but did not receive any complement blocking therapy on our prospective observational study evaluating TMA biomarkers as previously published. The institutional review board at our center approved the study.

Eculizumab Therapy and Prophylaxis for Infections

Eculizumab dosing for HSCT recipients with high-risk TMA was performed using total complement activity (CH50) and terminal complement activation (sC5b-9) monitoring as previously published by our group [8]. Meningococcal vaccine was not administered because of severe immunosuppression in the early post-transplant period. All patients were counseled for risk of meningococcal infection due to terminal complement blockade and were started on antimicrobial prophylaxis using ciprofloxacin or penicillin VK if not already receiving systemic antibiotics providing adequate coverage for *Neisseria meningitides* before starting the first dose of eculizumab. Antibiotic prophylaxis was continued at least 8 weeks after completing eculizumab therapy and until CH50 recovery to normal level indicating normalization of complement function in the blood.

RESULTS

Thirty consecutive HSCT recipients who completed eculizumab therapy for high-risk TMA and recovered normal complement system function after discontinuation of eculizumab or died during the transplantation process were included in our study analysis. Study patient demographics and disease characteristics are listed in the Table 1. Median time to TMA diagnosis in the treated group was 28 days after transplant (range, 13.8 to 48.5). The first 5 patients failed therapeutic plasma exchange before starting eculizumab therapy. Other patients received eculizumab as a first-line therapy for high-risk disease. No plasma products were administered during eculizumab therapy time. None of the study subjects received meningococcal vaccine before transplantation or before eculizumab therapy initiation. All patients received antimicrobial prophylaxis adequate for *N. meningitides* during the period of terminal complement blockade. Eighteen of 30 patients received eculizumab therapy exclusively during the inpatient stay after HSCT, and 12 patients completed maintenance eculizumab therapy after hospital discharge in the outpatient settings. Study subjects received a median of 14 eculizumab doses (range, 2 to 38). All patients had uniform monitoring for infectious

Table 1
Demographics and Disease Characteristics for HSCT Recipients with TMA

	Treated with Eculizumab (n = 30)	Not Treated (n = 39)	*P*
Median age, yr (IQR)	5.3 (3.6-11.1)	8.3 (3.3-13.8)	.56
Male	17 (56.7%)	26 (66.7%)	.46
Race			1.00
White	22 (73.3%)	29 (74.4%)	
Non-white	8 (26.7%)	10 (25.6%)	
Diagnosis			.41
Bone marrow failure	9 (30%)	15 (38.5%)	
Immune deficiency	13 (43.3%)	17 (43.5%)	
Malignancy	4 (13.3%)	6 (15.4%)	
Benign hematology, genetic/metabolic	4 (13.3%)	1 (2.6%)	
Donor type			.031
Related	5 (16.7%)	10 (25.6%)	
Unrelated	20 (66.7%)	29 (74.4%)	
Autologous	5 (16.7%)	0 (0%)	
Stem cell source			.52
Bone marrow	24 (80%)	26 (66.7%)	
Peripheral blood	5 (16.7%)	10 (25.6%)	
Cord blood	1 (3.3%)	3 (7.7%)	
HLA match			.59
Matched	16/25 (64%)	28 (72%)	
Mismatched	9/25 (36%)	11 (28%)	
Conditioning regimen			.63
Myeloablative	18 (60%)	20 (51.3%)	
Reduced intensity	12 (40%)	19 (48.7%)	
Calcineurin inhibitor for GVDH prophylaxis	25/25 (100%)	37/39 (95%)	.52
GVHD, grades III-IV	15/25 (60%)	10/39 (26%)	.1
TMA diagnosis, median days after HSCT (IQR)	28 (13.8-48.5)	32 (17-43)	.41
Meningococcal meningitis	0 (0%)	0 (0%)	1.00
Bacteremia	10 (33%)	11 (28%)	.79
Fungemia	2 (3.3%)	0 (0%)	.19
Cytomegalovirus viremia	7 (23%)	7 (18%)	.76
Epstein-Barr virus viremia	11 (36.6%)	4 (10.3%)	.02

IQR indicates interquartile range.