HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2017 November 28.

Published in final edited form as:

Biol Blood Marrow Transplant. 2016 July ; 22(7): 1337–1340. doi:10.1016/j.bbmt.2016.03.032.

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

Sonata Jodele[1,*], **Christopher E. Dandoy**[1], **Lara Danziger-Isakov**[2], **Kasiani C. Myers**[1], **Javier El-Bietar**[1], **Adam Nelson**[1], **Gregory Wallace**[1], **Ashley Teusink-Cross**[3], and **Stella M. Davies**[1]

[1]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[2]Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[3]Department of Pharmacy, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Abstract

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.

[*]Correspondence and reprint requests: Sonata Jodele, MD, Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 11027, Cincinnati, OH 45229. sonata.jodele@cchmc.org (S. Jodele).

Financial disclosure: The authors have no financial disclosures to report.

Conflict of interest statement: S.J. and S.M.D. have a US Provisional patent application for methods and compositions related to transplant-associated thrombotic microangiopathy. Other authors have no disclosures to report.

Keywords

Hematopoietic stem cell; transplant associated; thrombotic microangiopathy; TA-TMA; Complement blockade; Eculizumab; Meningococcal infection; Meningococcal vaccine

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 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 pathogens and received antiviral, antifungal, and pneumocystis jirovecii pneumonia (PJP) prophylaxis. All febrile patients received broad-spectrum antibiotics and underwent infectious disease evaluations as clinically indicated.

There was no incidence of meningococcal infection in any study subject. Ten of 30 subjects (33%) had 1 documented bloodstream infection while receiving eculizumab therapy. Three patients had 2 bloodstream infections with different pathogens during the therapy time. Identified pathogens were *Staphylococcus epidermidis* (n = 5), *Enterococcus faecium* (n = 4), *Steptococcus mitis* (n = 1), *Streptococcus sanguinis* (n = 1), *Klebsiella pneumonia* (n = 1), and *Staphylococcus aureus* (n = 1). Two patients had candidemia. Cytomegalovirus viremia was documented in 7 subjects (23%) and Epstein-Barr virus viremia in 11 (36.6%). The incidence of grades II to IV acute GVHD was 60% (15/25) in this high-risk cohort. The median time to GVHD diagnosis was 32 days after HSCT (range, 15 to 94). All patients with documented bacterial or fungal infections had acute GVHD and were on immunosuppressive therapy.

Eleven eculizumab-treated patients died. Median time to death after TMA diagnosis was 135 days (range, 21 to 268). Four patients were receiving eculizumab at the time of death, and 7 were off eculizumab therapy for 4 weeks to 4 months before death after resolving TMA. There were no deaths due to bacteremia. Causes of death were GVHD (n = 5), GVHD/TMA (n = 4), pulmonary hemorrhage (n = 1), and invasive fungal disease (n = 1). Overall infection rates were similar in HSCT recipients treated with eculizumab for high-risk TMA as compared with HSCT recipients with TMA from our prospective observational study who did not receive any complement blocking therapy (Table 1) [13].

DISCUSSION

We treated 30 HSCT recipients with high-risk TMA using the terminal complement blocker eculizumab without administering a meningococcal vaccine because of the severely immunocompromised status in the early post-transplant period. All patients received antimicrobial prophylaxis with adequate coverage against meningococcus until complement function recovery was documented after eculizumab therapy discontinuation. There were no documented events of meningococcal infections in patients receiving eculizumab. The incidence of bacterial bloodstream infections (33%) documented during the time of terminal complement blockade was similar to the incidence in HSCT recipients with TMA who did not receive any complement blocking agents (28%, P=.79). The pathogens reported were organisms that are commonly seen in immunocompromised HSCT recipients, especially those with active GVHD and receiving additional immunosuppressants. Candidemia was

documented in 2 patients, and both infections occurred in severely immunocompromised individuals receiving multiple immunosuppressive medications for steroid-refractory acute GVHD.

Concern for meningococcal meningitis and the requirement for timely vaccination is clearly appropriate in patients with paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome who are immune competent before therapy, receive life-long therapy with eculizumab, and are at risk for exposure to *N. meningitides* while attending school or public places. HSCT recipients require a limited course of eculizumab, generally early post-transplant when severely immunocompromised, and are usually treated on the inpatient unit under strict infectious disease precautions and often receive broad-spectrum antibiotics adequate to prevent or treat meningococcus. In addition, they receive antifungal and antiviral prophylaxis and very close monitoring for infections.

We report the largest cohort of HSCT recipients treated with eculizumab, and our data indicate that terminal complement blockade in the early post-transplant period was not associated with meningococcal infections, while using appropriate antimicrobial prophylaxis and precautions against infection exposures until complement function is restored after therapy completion. This observation is important not only for immunocompromised patient care but also for clinical study planning, where in some cases meningococcal vaccines are mandated before starting complement blocking therapy. There are no expectations that HSCT recipients will generate protective antibodies and have an adequate response to meningococcal vaccine during the early post-transplant period, making requirement for meningococcal vaccine clinically unindicated. Mahler et al. [14] from Memorial Sloan Kettering Hospital were the first to evaluate the response to the meningococcal conjugate vaccine (MCV4) after allogeneic HSCT in children and young adults, offering vaccination in a cohort of patients who were 2.3 years post-transplant. This study found no response to vaccination in 51% of patients or response to only 1 antigen, generally type A, an uncommon cause of disease in the United States. Response to serogroup C, a common cause of meningococcal disease worldwide, was particularly poor, despite the children being more than 2 years beyond transplant [14]. Despite this, it is very important that clinicians acknowledge the increased risk of infections with encapsulated bacteria in patients receiving complement blocking therapy. Appropriate antibiotic prophylaxis should be used in HSCT recipients while complement is blocked, regardless of vaccination status, even in patients receiving complement blockers as late as 2 years post-transplant or until adequate response to vaccines can be documented.

References

1. Reiss UM, Schwartz J, Sakamoto KM, et al. Efficacy and safety of eculizumab in children and adolescents with paroxysmal nocturnal hemoglobinuria. Pediatr Blood Cancer. 2014; 61:1544–1550. [PubMed: 24777716]
2. Greenbaum LA, Fila M, Ardissino G, et al. Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. Kidney Int. 2016; 89:701–711. [PubMed: 26880462]
3. Soliris [package insert]. Cheshire, CT: Alexion Pharmaceuticals Inc.; 2014.

4. Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP) 2013. Morbid Mortal Wkly Rep. 2013; 62(RR02):1–28.

5. Cullinan N, Gorman KM, Riordan M, et al. Case report: benefits and challenges of long-term eculizumab in atypical hemolytic uremic syndrome. Pediatrics. 2015; 135:e1506–e1509. [PubMed: 25941307]

6. Struijk GH, Bouts AH, Rijkers GT, et al. Meningococcal sepsis complicating eculizumab treatment despite prior vaccination. Am J Transplant. 2013; 13:819–820. [PubMed: 23289494]

7. Bouts A, Monnens L, Davin JC, et al. Insufficient protection by Neisseria meningitidis vaccination alone during eculizumab therapy. Pediatr Nephrol. 2011; 26:1919–1920. [PubMed: 21643943]

8. Jodele S, Fukuda T, Mizuno K, et al. Variable eculizumab clearance requires pharmacodynamic monitoring to optimize therapy for thrombotic microangiopathy after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2016; 22:307–315. [PubMed: 26456258]

9. de Fontbrune FS, Galambrun C, Sirvent A, et al. Use of eculizumab in patients with allogeneic stem cell transplant-associated thrombotic microangiopathy: a study from the SFGM-TC. Transplantation. 2015; 99:1953–1959. [PubMed: 25651309]

10. Kim SS, Patel M, Yum K, Keyzner A. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: review of pharmacologic treatment options. Transfusion. 2015; 55:452–458. [PubMed: 25209960]

11. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009; 15:1143–1238. [PubMed: 19747629]

12. Parkkali T, Kayhty H, Lehtonen H, et al. Tetravalent meningococcal polysaccharide vaccine is immunogenic in adult allogeneic BMT recipients. Bone Marrow Transplant. 2001; 27:79–84. [PubMed: 11244441]

13. Jodele S, Davies SM, Lane A, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. Blood. 2014; 124:645–653. [PubMed: 24876561]

14. Mahler MB, Taur Y, Jean R, et al. Safety and immunogenicity of the tetravalent protein-conjugated meningococcal vaccine (MCV4) in recipients of related and unrelated allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2012; 18:145–149. [PubMed: 21820392]

Table 1

Demographics and Disease Characteristics for HSCT Recipients with TMA

	Treated with Eculizumab (n = 39)	Not Treated (n = 30)	*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.