Letter to the Editor

Acta Hæmatologica

Acta Haematol 2017;138:194–197
DOI: 10.1159/000481724

Received: September 20, 2017
Accepted: September 22, 2017
Published online: November 15, 2017

No Relapse of Calcineurin Inhibitor-Associated Thrombotic Microangiopathy after Discontinuation of Eculizumab

Thomas Neumann[a] Andrzej Plis[a] Martin Weigel[a] Sylvia Stracke[b] Sigrun Friesecke[c] Stephanie-Susanne Stecher[c] Laila Schneidewind[a] Christoph Busemann[a] Christian Andreas Schmidt[a] William H. Krüger[a]

Departments of [a]Internal Medicine C (Haematology and Oncology, Stem Cell Transplantation, Palliative Care), [b]Internal Medicine A, and [c]Internal Medicine B, University Hospital Greifswald, Ernst-Moritz-Arndt University, Greifswald, Germany

Calcineurin inhibitor (CNI)-associated thrombotic microangiopathy (TMA) is a severe and often fatal complication after allogeneic stem cell transplantation (alloSCT) [1–3]. Administration of the CNIs cyclosporine-A and tacrolimus as well as sirolimus has been described as a risk factor [4]. Thrombocytopenia, the occurrence of schistocytes, and progredient anemia in conjunction with an increase in lactate dehydrogenase in the absence of antierythrocyte antibodies leads to diagnosis. Progredient renal failure and involvement of the CNS as described for TTP may occur. Diagnosis may be difficult since a variety of other problems may cause the addressed symptoms (except the occurrence of schistocytes): cytopenia may be caused by infections or related to graft-versus-host disease (GvHD), and drugs like cyclosporine-A can induce an increase in creatinine. Treatment of TMA is difficult and a therapeutic standard for therapy of CNI-associated TMA has not been established so far [5]. The discontinuation of CNIs is common practice and most patients undergo plasma exchange despite the activity of ADAMTS-13 being commonly normal. In consequence, this approach has an unsatisfying response rate between 20 and 50%.

Eculizumab is a humanized monoclonal antibody blocking complement activation. It is directed against C5 [6]. The major indication for eculizumab is paroxysmal nocturnal hemoglobinuria (PNH). However, it has been used with success in atypical hemolytic uremic syndrome (HUS), even after alloSCT [7, 8]. Eculizumab has been recommended as a lifelong therapy since PNH clones will not be eliminated and genetic alterations leading to atypical HUS persist. Since eculizumab inhibits the complement pathway, this therapy can be associated with severe infections as side effects [6, 9]. The approach to withdraw eculizumab after successful therapy of atypical HUS is under discussion [10–12]. Therefore, it would be desirable and could be possible to limit the administration of eculizumab in nongenetically determined TMA, especially in highly immunosuppressed patients after alloSCT with or without GvHD.

We here report our experience with discontinuation of eculizumab for transplant-associated TMA in 2 patients. In both patients, ADAMTS-13 deficiency was excluded prior to eculizumab therapy. Furthermore, a molecular analysis of the genes CFH, CFI, C3, CFB, ADAMTS-13, CFHR1, and CLU revealed no evidence for genetically determined HUS, either in samples from recipients or from stem cell donors.

Patient 1 was a 36-year-old CMV+ male suffering from a lymphocytic lymphoma carrying a p53 deletion. A partial remission could be induced by treatment with ibrutinib. He was conditioned myeloablatively with busulfan$_{16\ mg/kg}$/cyclophosphamide$_{120\ mg/kg}$ and low-dose alemtuzumab and allografted with nonmanipulated peripheral stem cells (8.48×10^6 CD34+ cells/kg) from a CMV+ male donor. Cyclosporine-A and short-course methotrexate were given for GvHD prophylaxis. Thrombocytes engrafted on day +8 and leucocytes on day +11. Ibrutinib was given for lymphoma relapse and GvHD prophylaxis was stopped to enhance graft-versus-leukemia effects. Cutaneous GvHD stage 3 (2° overall) was treated with cyclosporine-A and methylprednisolone. The lymphoma re-

A.P. and M.W. contributed equally to this work.

E-Mail karger@karger.com
www.karger.com/aha

William H. Krüger
Department of Internal Medicine C (Haematology and Oncology, Stem Cell Transplantation, Palliative Care), University Hospital Greifswald, Ernst-Moritz-Arndt University, Ferdinand-Sauerbruch-Strasse, DE–17475 Greifswald (Germany)
E-Mail william.krueger@uni-greifswald.de

Table 1. Characteristics, therapy, and course of thrombotic microangiopathy (TMA)

Parameter	Patient 1	Patient 2
Age at alloSCT, gender	36 years, male	59 years, female
Diagnosis	Small cell lymphocytic lymphoma, 17p-deletion	Multiple myeloma IgGκ, del17p + other aberrations
Conditioning	Busulfan/cyclophosphamide/ alemtuzumab	Melphalan, fludarabine, ATG
Donor type, HLA match	Matched-unrelated (10/10)	Matched-related (sister) (10/10)
Active GvHD at onset of TMA	Acute GvHD, skin 3° (2° overall)	Chronic GvHD, extensive disease, skin, lung
Interval alloSCT > TMA	37 days	18 months
Parameters at diagnosis of TMA		
Hemoglobin	4.3 mmol/L	5.4 mmol/L
Reticulocytes	5.94%	9.38%
Platelet count	13/nL	32/nL
Schistocytes at onset/maximum	38/1,000 (at onset = maximum)	17/1,000 erythrocytes (at onset = maximum)
LDH	13.9 μkat/L	12.2 μkat/L
Haptoglobin	n.d.	<0.08 g/L
Bilirubin	57.3 μmol/L	25.7 μmol/L
Serum creatinine/clearance	145 μmol/L	53 μmol/L
CNS involvement	No	Yes
Primary therapy of TMA		
Plasmapheresis	5 sessions over 6 days	5 sessions over 5 days
Result	No response	Minor response
Salvage therapy of TMA		
Start	6 days after onset of TMA	8 days after onset of TMA
Modality	Eculizumab, 16 infusions	Eculizumab, 7 infusions
Stop	6 months after onset of TMA	2 months after onset of TMA
Improvement of symptoms and laboratory parameters (days after start of eculizumab)		
Decrease in schistocytes	After 1 day	After 1 day
Increase in platelets	3 days	2 days
Decrease in LDH	6 days	Not evaluable
Clinical improvement	n.a.	Within a few days (CNS)
Parameters at last laboratory follow-up		
Interval from eculizumab discontinuation	13 weeks	18 weeks
Schistocytes	0	0 (8.5 months after eculizumab discontinuation)
Reticulocytes	1.23%	0.88%
Haptoglobin	1.4 g/L	1.6 g/L

Normal values: hemoglobin: 7.4–10 mmol/L (female), 8.6–11.2 mmol/L (male); thrombocytes: 140–440/nL; reticulocytes: 0.5–2.6%; schistocytes: <5/1,000 erythrocytes; LDH (lactate dehydrogenase): 0–4.22 μkat/L; bilirubin: 0–17 μmol/L; haptoglobin: 0.3–2.0 g/L; creatinine: 42–80 μmol/L (female), 49–97 μmol/L (male). n.d., not done; n.a., not applicable.

gressed into a continuous complete remission. The patient developed hemolytic anemia in conjunction with renal failure, a decrease in platelets, and the occurrence of schistocytes of maximal 38/1,000 (Table 1). ADAMTS-13 activity was normal. CNI was discontinued and treatment of GvHD was switched to methylprednisolone in conjunction with mycophenolate. Five sessions of plasmapheresis did not improve any parameter of TMA and treatment with eculizumab was initiated. Therapy with eculizumab and prophylaxis of infections were performed according the manufacturer's instructions. A total of 16 infusions were given over 6 months. Parameters of TMA normalized rapidly (Table 1; Fig. 1). In addition, common anti-infectious prophylaxes after alloSCT were given. Steroid-induced myopathy occurred, methylprednisolone was discontinued, and ruxolitinib (2 × 5–10 mg) was initiated for therapy of chronic GvHD (extensive disease) [13]. Repeated episodes of CMV and HHV6 reactivations were treated virustatically. Due to the high infection rate, eculizumab was discontinued after 6 months and controls of

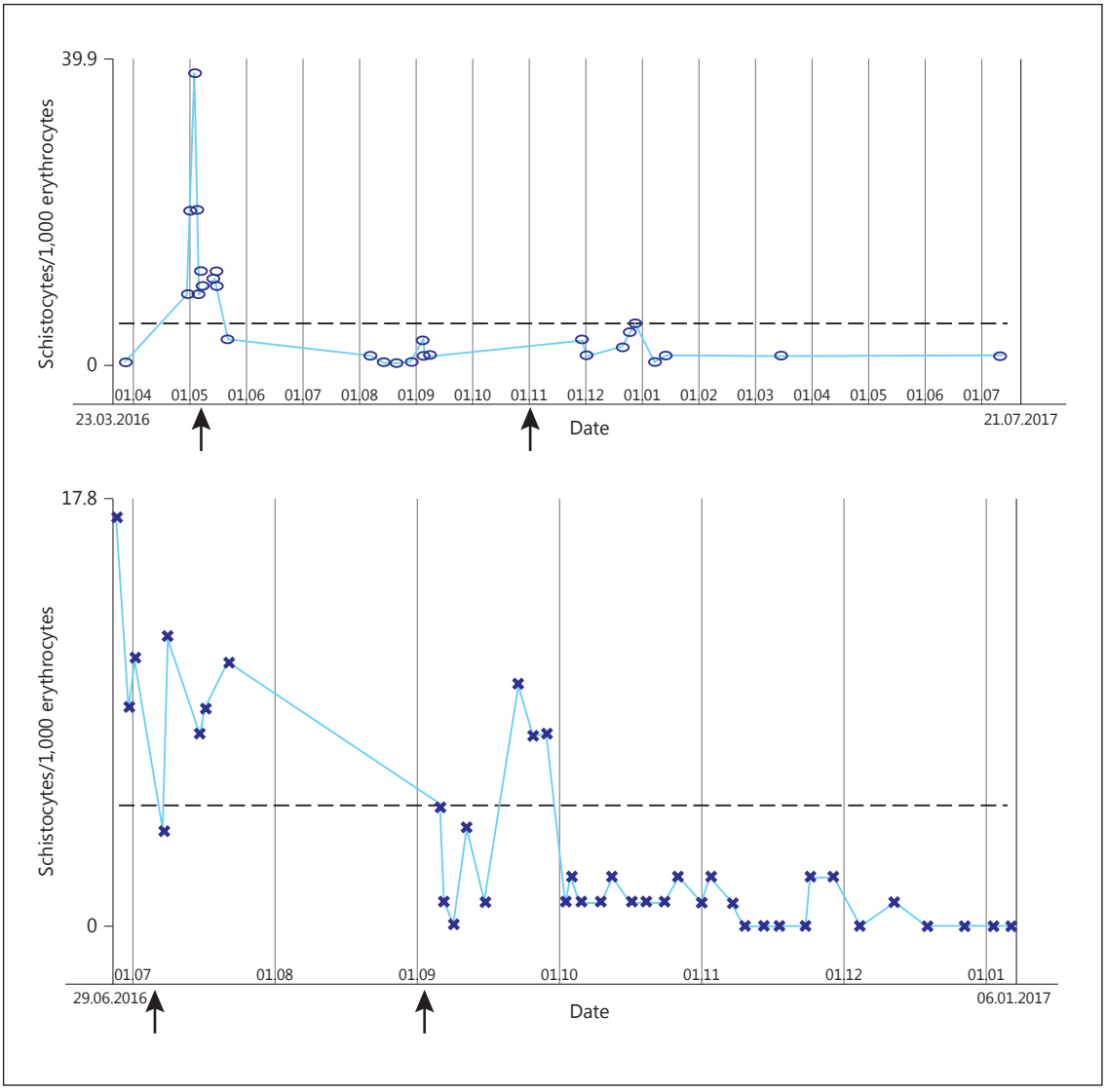

Fig. 1. Course of schistocytes (fragmentocytes)/1,000 red cells. **a** Patient 1. **b** Patient 2. The vertical lines indicate the months and the broken horizontal line the upper normal value. The arrows indicate the beginning and end of therapy with eculizumab. Patient 2: the second peak after the discontinuation of eculizumab is due to a period of hemodialysis.

TMA parameters gave no hint for relapse of atypical HUS after a further follow-up of 2.5 months (Table 1). Chronic GvHD is currently excellently controlled by ruxolitinib 2 × 10 mg. The patient has a Karnofsky score of 80%, and has no signs of active GvHD, infectious complications, or TMA 4.5 months after the discontinuation of eculizumab.

Patient 2 was a 59-year-old female, who was allografted from her HLA-identical sister for myeloma relapse after high-dose melphalan and autologous SCT. She was transferred from a local hospital to our unit 18 months after alloSCT with thrombocytopenia, progredient anemia, headache, and anisocoria, highly suggestive for TMA. Furthermore, she suffered from extensive chronic GvHD with cutaneous, mucosal, hepatic, and pulmonary manifestation. CNS infection or bleeding were excluded by CT scan and peripheral blood smear showed 17/1,000 schistocytes. LDH, bilirubin, and reticulocytes were increased, and haptoglobin was reduced. The kidneys were not involved (Table 1; Fig. 1). Tacrolimus had been terminated by telephonic advice prior to admission. Initial treatments of TMA were 5 sessions of plasmapheresis. Since plasmapheresis led only to minor improvement of CNS symptoms and ADAMTS-13 level was normal, the treatment was switched to eculizumab. Therapy with eculizumab and prophylaxis of infections were performed according the manufacturer's instructions. A total of 7 in-

fusions were given over 2 months. Headache and anisocoria disappeared rapidly and schistocytes and reticulocytes decreased. Further therapy of chronic GvHD was mycophenolate in combination with methylprednisolone and ruxolitinib (2 × 5–10 mg) [13]. Severe pulmonary GvHD in conjunction with an abdominal compartment syndrome after massive gastrointestinal bleeding required artificial respiration and hemodialysis, leading to a transient increase in schistocytes. Due to infectious problems, eculizumab was terminated after 2 months. The patient was under weaning from artificial respiration with moderately controlled chronic GvHD under ruxolitinib/mycophenolate/methylprednisolone. She died from severe GvHD without clinical or laboratory signs of TMA 8.5 months after onset (Table 1; Fig. 1).

The excellent response of atypical TMA after alloSCT to eculizumab in 2 of 2 patients as well as the association of TMA with other severe complications after alloSCT is in accordance with other reports. It has been not clarified so far whether atypical HUS after alloSCT requires lifelong therapy with eculizumab like patients suffering from PNH. In their series, de Fontbrune et al. [7] terminated eculizumab only in nonresponders or in the case of other severe problems such as refractory GvHD or relapsing malignancy. Termination of eculizumab would be desirable after alloSCT with or without GvHD, since it leads to additional immunosuppression by blocking complement activation. In both of the reported patients, eculizumab was terminated after exclusion of evidence for genetically determined HUS 6 and 2 months after treatment began, respectively, due to severe infections under monitoring of parameters indicating active TMA. No patient developed relapse of TMA: one could be discharged with a Karnofsky score of 80%, and the other was under weaning from artificial respiration. The authors conclude cessation of eculizumab therapy in these patients should be attempted to avoid long-term complement block in highly immunosuppressed patients. Monitoring of TMA parameters is mandatory. Further follow-up and confirmation or rebuttal of our results in additional patients with this rare complication after alloSCT is necessary.

Disclosure Statement

The authors declare no conflicts of interest.

References

1 Kennedy GA, Bleakley S, Butler J, Mudie K, Kearey N, Durrant S: Posttransplant thrombotic microangiopathy: sensitivity of proposed new diagnostic criteria. Transfusion 2009;49:1884–1889.

2 Shimoni A, Yeshurun M, Hardan I, Avigdor A, Ben-Bassat I, Nagler A: Thrombotic microangiopathy after allogeneic stem cell transplantation in the era of reduced-intensity conditioning: the incidence is not reduced. Biol Blood Marrow Transplant 2004;10:484–493.

3 Oran B, Donato M, Aleman A, Hosing C, Korbling M, Detry MA, Wei C, Anderlini P, Popat U, Shpall E, Giralt S, Champlin RE: Transplant-associated microangiopathy in patients receiving tacrolimus following allogeneic stem cell transplantation: risk factors and response to treatment. Biol Blood Marrow Transplant 2007;13:469–477.

4 Rosenthal J, Pawlowska A, Bolotin E, Cervantes C, Maroongroge S, Thomas SH, Forman SJ: Transplant-associated thrombotic microangiopathy in pediatric patients treated with sirolimus and tacrolimus. Pediatr Blood Cancer 2011;57:142–146.

5 Laskin BL, Goebel J, Davies SM, Jodele S: Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Blood 2011;118:1452–1462.

6 Röth A, Dührsen U: Treatment of paroxysmal nocturnal hemoglobinuria in the era of eculizumab. Eur J Haematol 2011;87:473–479.

7 de Fontbrune FS, Galambrun C, Sirvent A, Huynh A, Faguer S, Nguyen S, Bay J-O, Neven B, Moussi J, Simon L, Xhaard A, Resche-Rigon M, O'Meara A, Fremeaux-Bacchi V, Veyradier A, Socié G, Coppo P, de Latour RP: Use of eculizumab in patients with allogeneic stem cell transplant-associated thrombotic microangiopathy: a study from the SFGM-TC. Transplantation 2015;99:1953–1959.

8 Peffault de Latour R, Xhaard A, Fremeaux-Bacchi V, Coppo P, Fischer AM, Helley D, Socié G: Successful use of eculizumab in a patient with post-transplant thrombotic microangiopathy. Br J Haematol 2013;161:279–280.

9 Schrezenmeier H, Höchsmann B: Eculizumab opens a new era of treatment for paroxysmal nocturnal hemoglobinuria. Expert Rev Hematol 2009;2:7–16.

10 Ardissino G, Possenti I, Tel F, Testa S, Salardi S, Ladisa V: Discontinuation of eculizumab treatment in atypical hemolytic uremic syndrome: an update. Am J Kidney Dis 2015;66:172–173.

11 Sahutoglu T, Basturk T, Sakaci T, Koc Y, Ahbap E, Sevinc M, Kara E, Akgol C, Caglayan FB, Unsal A, Daha MR: Can eculizumab be discontinued in aHUS? Case report and review of the literature. Medicine (Baltimore) 2016;95:e4330.

12 Wetzels JF, van de Kar NC: Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome. Am J Kidney Dis 2015;65:342.

13 Zeiser R, Burchert A, Lengerke C, Verbeek M, Maas-Bauer K, Metzelder SK, Spoerl S, Ditschkowski M, Ecsedi M, Sockel K, Ayuk F, Ajib S, de Fontbrune FS, Na IK, Penter L, Holtick U, Wolf D, Schuler E, Meyer E, Apostolova P, Bertz H, Marks R, Lübbert M, Wäsch R, Scheid C, Stölzel F, Ordemann R, Bug G, Kobbe G, Negrin R, Brune M, Spyridonidis A, Schmitt-Gräff A, van der Velden W, Huls G, Mielke S, Grigoleit GU, Kuball J, Flynn R, Ihorst G, Du J, Blazar BR, Arnold R, Kröger N, Passweg J, Halter J, Socié G, Beelen D, Peschel C, Neubauer A, Finke J, Duyster J, von Bubnoff N: Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia 2015;29:2062–2068.