In-Depth Topic Review

American Journal of Nephrology

Am J Nephrol 2018;48:96–107
DOI: 10.1159/000492033

Received: May 16, 2018
Accepted: July 4, 2018
Published online: August 15, 2018

When to Stop Eculizumab in Complement-Mediated Thrombotic Microangiopathies

Sven R. Olson[a] Eric Lu[b] Emilio Sulpizio[b] Joseph J. Shatzel[a] Jose F. Rueda[c] Thomas G. DeLoughery[a]

[a]Division of Hematology and Medical Oncology, Oregon Health and Science University, Knight Cancer Institute, Portland, OR, USA; [b]Department of Internal Medicine, Oregon Health and Science University, Portland, OR, USA; [c]Division of Nephrology and Hypertension, Oregon Health and Science University, Portland, OR, USA

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

Keywords
Thrombotic microangiopathy · Complement · Eculizumab · Thrombotic thrombocytopenic purpura · Hemolytic uremic syndrome · Atypical hemolytic uremic syndrome · Secondary hemolytic uremic syndrome · Transplant-associated-thrombotic microangiopathies · Drug-induced

Abstract
The terminal complement-inhibitor eculizumab has dramatically changed the management of patients with atypical hemolytic uremic syndrome (aHUS), and has also shown promise for treating certain forms of secondary HUS (sHUS), including that caused by drugs and solid-organ/hematopoietic stem cell transplant. While effective, eculizumab is costly and inconvenient. In this review, we evaluate the literature on eculizumab cessation in these diseases to better inform clinicians who consider stopping therapy. Reported relapse rates in aHUS after stopping eculizumab are as high as 30%, suggesting indefinite therapy is reasonable and that patients who choose to stop should be closely monitored. In sHUS, relapse is rare, justifying short courses of eculizumab.
© 2018 S. Karger AG, Basel

Introduction

Thrombotic microangiopathies (TMA) are a group of disorders characterized by the combination of intravascular microangiopathic hemolytic anemia, thrombocytopenia, and micro- and macrovascular thrombosis. The latter pathologic findings can manifest as varying degrees of end-organ damage, most commonly renal failure or neurologic deficits. TMAs can be further subdivided into 3 categories: thrombotic thrombocytopenic purpura (TTP), typical hemolytic uremic syndrome (typical hemolytic uremic syndrome [HUS]), and the group of disorders known as complement-mediated TMAs (Table 1) [1–3].

TTP is caused by a congenital or acquired deficiency in the metalloprotease ADAMTS13, resulting in impaired

KARGER

© 2018 S. Karger AG, Basel

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

Sven R. Olson, MD
Division of Hematology and Medical Oncology
Oregon Health and Science University
3181 SW Sam Jackson Park Road, Portland, OR 97239 (USA)
E-Mail olsosv@ohsu.edu

Table 1. Categories of thrombotic microangiopathies

Disease	TTP [4]	Typical HUS [2]	Atypical HUS [2, 3]	Secondary HUS [3]
Prevalence/incidence	– 1 case/million annually – Usual onset: adulthood (acquired)	– 2 cases/100,000 annually – Typically, children <5 years	– 2 cases/million annually – Onset at any age	Variable: dependent on underlying illness
Mechanism	– Deficiency in ADAMTS13 metalloproteinase – Inherited: 10% of cases – Acquired (auto-antibody mediated): 90% of cases – Impaired cleavage of large vWF multimers – Platelet activation and aggregation	– Enteric infections with *E. coli* or *Shigella* – Shiga-toxin-mediated endothelial, platelet, RBC damage	– Inherited mutation in alternative complement factor (90%), or acquired auto-antibody to complement factor (10%) – Uncontrolled formation of terminal complement pathway MAC – Endothelial, platelet, RBC damage – Frequently triggered by acute infection	– Associated conditions – Drug-induced – Post-HSCT or solid organ transplant – Autoimmune disease – Malignancy – Sepsis – Pregnancy – Variable proposed mechanisms
Thrombocytopenia	Severe: typically <30,000	Mild: typically >40,000	Mild: typically >40,000	Variable
Renal dysfunction, severity	Mild: serum creatinine typically <2.0 at presentation	May be severe: 50% require RRT in acute phase	May be severe	Variable
Extra-renal manifestations	Frequent – Neurologic: 60% (headache, confusion, seizures, stroke)	Frequent – Neurologic: 40% – Gastrointestinal: diarrhea, abdominal pain	Uncommon – 20%, mostly neurologic – Hypertension	Variable: dependent on underlying illness
Complement involvement	–	+	+++	++
Key diagnostic test	ADAMTS13: <10% activity	+ Stool Shiga toxin or stool culture for *E. coli, Shigella* organisms	Mutation/auto-antibody to complement proteins CFH, CFI, CFB, CD46, C3, DGKE	Variable, depending on underlying illness
Treatment	Plasma exchange Immune suppression – Corticosteroids ± Rituximab – ± maintenance Rituximab	Supportive care – Plasma exchange – Complement inhibition	Complement inhibition	Supportive care – Complement inhibition
Natural history	Prognosis: 10–20% mortality (with early treatment initiation) Up to 50% of acquired cases will relapse; reduced with maintenance rituximab	Prognosis: <5% mortality Spontaneous resolution in up to 85% within 1–2 weeks 30% with long-term renal dysfunction	Prognosis: may depend on underlying mutation, if present; absence of any detectable mutation does not necessarily indicate lower risk. CFH: unfavorable MCP: favorable. Up to 77% with long-term renal dysfunction	Variable: depending on underlying illness

RBC, red blood cell; CFH, complement factor H; CFI, complement factor I; CFB, complement factor B; DGKE, diacylglycerol kinase epsilon.

Am J Nephrol 2018;48:96–107
DOI: 10.1159/000492033

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

cleavage of circulating large von Willebrand factor multimers, excessive platelet adhesion, activation and aggregation, and finally microthrombi formation. The majority of adult cases of TTP are acquired via the production of anti-ADAMTS13 antibodies, and thus this disease can be effectively treated with therapeutic plasma exchange (PEX) and immune suppression [4].

Typical HUS is associated with diarrheal illnesses caused by gastrointestinal *Escherichia coli* or *Shigella* infections. Bacterial Shiga toxin causes direct cytotoxic damage to vascular endothelial, renal mesangial and epithelial cells, as well as platelets and red blood cells. The complement pathway is activated in typical HUS to varying degrees due to stimulation by infectious pathogens [3, 5]. Treatment is generally supportive, as more aggressive interventions have not been shown to improve outcomes [6].

In contrast to TTP and typical HUS, complement-mediated TMAs comprise a more heterogeneous group of disorders with a variety of risk factors and instigating triggers, though all are characterized by the dysregulated terminal complement pathway activation. These disorders are further subdivided into atypical HUS (aHUS) and secondary HUS (sHUS). aHUS is caused by congenital or acquired defects in alternative complement pathway regulatory proteins [1–3]. sHUS is the least well-defined group of complement-mediated TMAs, with a list of precipitating causes including drugs, solid-organ or stem cell transplant, and systemic illnesses such as sepsis, auto-immune disorders, and malignancy. Complement dysregulation likely plays a role in these underlying conditions, though this has not been clearly defined in all cases.

While PEX was historically utilized for all TMAs, this therapy was sub-optimal given the high rates of morbidity and mortality in patients with aHUS; indeed, the incidence of end-stage renal disease (ESRD) or death approached 40% at initial diagnosis, and 65% within 1 year [7]. In 2007, the monoclonal antibody eculizumab, targeting the terminal complement protein C5, was approved for the treatment of paroxysmal nocturnal hemoglobinuria; it was subsequently examined in several phase 2 trials for the treatment of aHUS and showed favorable efficacy in both acute and chronic settings in terms of normalization of hematologic parameters and improvement in glomerular filtration rate (GFR) [7, 8]. These studies led to the Food and Drug Administration (FDA) approval of eculizumab for the treatment of aHUS in 2011.

Complement inhibition with eculizumab has since gained favor in the treatment of other complement-mediated TMAs. While dysregulated complement activity is not the primary driver of typical HUS, infectious pathogens do activate complement to varying degrees [3, 5, 9], and several case series have shown favorable outcomes with early use of eculizumab, particularly in patients with severe neurologic symptoms [10, 11]. Eculizumab has also been increasingly explored for the treatment of sHUS, including in cases associated with drugs, solid organ, and stem cell transplant [12–15]. An important question that has been raised in all cases of complement-mediated TMAs is if and when eculizumab can safely be stopped. This concern is primarily driven by cost, as high as $700,000 USD per patient per year [16, 17]. The opposing argument to continue eculizumab indefinitely is a relatively high rate of TMA relapse after therapy discontinuation, outlined in this review [18]. The ability to identify patients with a low risk of TMA relapse following eculizumab discontinuation is an attractive prospect in these diseases. Here, we describe the frequency and outcomes of eculizumab discontinuation and suggest scenarios in which discontinuation would be appropriate.

Atypical HUS

About 5–10% of HUS cases appear to occur de novo. This entity, aHUS, is caused by the unregulated activation of the complement system due to inherited (genetic) or acquired (autoimmune) disruption of the alternate complement pathway [2, 18]. Under normal conditions, the alternate complement pathway is constitutively active leading to spontaneous hydrolysis of C3 and deposition of the product C3b on multiple host cells in contact with plasma. Further progression of complement activation downstream of this process is normally inhibited by several complement proteins including factor H, factor I, and membrane cofactor protein. Mutations in, or auto-antibodies against, these and other regulatory proteins can be identified in approximately 50% of aHUS cases [3], the end result of which is uncontrolled complement activity including formation of the membrane attack complex on endothelial cells, red blood cells, and platelets [2, 8]. Even in cases of heritable mutations in complement regulatory proteins, aHUS can manifest at any age; a second "hit" such as infection, pregnancy or immunization is typically required for the disease process to manifest [1]. Morbidity and mortality of untreated aHUS can vary depending on the underlying complement defect; Factor H mutations are most common and have been associated with rates of ESRD or death as high as 80% [1, 3].

For years, standard therapy for aHUS consisted of PEX, with duration of therapy guided by clinical response.

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

Long-term benefits of this therapy, however, were relatively poor, with two-thirds of patients progressing to ESRD or death within 3 years [8]. The FDA approval of eculizumab in 2011 heralded a new standard of care, and has proven effective in all ages and in both native and transplanted kidneys [1, 2]. Legendre et al. [7] examined 37 patients in 2 prospective, phase 2 clinical trials and found that eculizumab led to statistically significant increases in platelet counts, GFR and quality of life, and a TMA-free rate of 80%. In a 2-year follow-up of the same patient cohorts, 88% of patients reached hematologic normalization, with 95% of patients free from recurrent TMA. The development of neutralizing antibodies to eculizumab after prolonged therapy has been a theoretical concern, though after extended (2 year) follow up of the original cohorts of patients from landmark trials of eculizumab in aHUS, no patients developed neutralizing antibodies to the drug. Similarly, in a study of 75 patients with PNH treated with eculizumab for a median of 7.5 years, no patients developed neutralizing antibodies [8, 19]. The primary adverse effect of concern with long-term use of eculizumab is meningococcal infection, protection against which is reliant on intact terminal complement pathway activity. In the aforementioned trials, however, no meningococcal infections were observed after 2 years of follow up. The overall rates of meningococcal infection are currently cited at 0.5% annually, with only 16 cases reported by the CDC among all patients treated with eculizumab from 2008 to 2016. This suggests an overall favorable risk profile for the drug [7, 8, 16].

While these data are certainly encouraging, several critical issues remain. First, eculizumab is an intravenous infusion and requires twice-monthly dosing even during the maintenance phase. This can be a substantial inconvenience for patients committed to lifelong therapy. Second, frequent discussion still revolves around the drug's significant cost [8, 17]. Both of these treatment issues have spurred interest in less aggressive dosing schedules or complete discontinuation of eculizumab. A recent review by Macia et al. [18] summarized data on patient outcomes with eculizumab discontinuation, including evidence from case reports, unpublished cases, and national registries. Of the unpublished cases and case reports, 20 of 58 patients (34%), experienced a recurrence in TMA after therapy cessation. Among 5 clinical trials of eculizumab (4 prospective single-arm, 1 retrospective) published between 2008 and 2015, 61 of 130 patients discontinued therapy. Of those 61, after median follow up of 24 weeks, 12 (20%) had relapsed, with a small number developing serious adverse outcomes including a requirement for renal replacement therapy [18]. Relapse following cessation of therapy occurred after a median of 13 weeks, though this was highly variable (4–127 weeks). The French aHUS registry was examined between 2010 and 2014, with 38 of 109 patients discontinuing eculizumab therapy after a median duration of 17.5 months. Twelve of these patients (31%) suffered disease relapse [20]. This high rate was also reflected in an observational study of 16 patients conducted by Ardissino et al. [23], in which 5 of 16 (31%) patients had a relapse after drug discontinuation [21]. A complete review of published literature on dose alteration or discontinuation is outlined in Figure 1.

In summary, the current evidence suggests an aHUS relapse rate of approximately 30% after discontinuation of eculizumab therapy. In addition, aggregate data from clinical trials examining eculizumab discontinuation show a rate of organ failure after TMA relapse of 5% [18]. Several scenarios have been proposed as having a higher risk of relapse, including pregnant and pediatric patients, post-renal transplant patients, and patients with GFR <20 mL/min/1.73 m^2 [16, 18]. Certain complement gene mutations confer a higher risk for earlier and more severe disease phenotypes, and these same mutations may also increase the relapse risk. A review of the French aHUS registry found that in patients with identified mutations, 8 of 11 (72%) patients with factor H variants and 4 of 8 (50%) patients with membrane cofactor protein variants relapsed, while none of the 16 patients without detectable mutations relapsed. Aggregate data from prospective trials of eculizumab including 61 patients, however, showed that among cohorts of patients who did or did not relapse after discontinuation of therapy, frequency of identifiable complement mutations were essentially equal (58 and 49%, respectively) [18]. Without incorporation into a validated risk model, the prognostic value of genetic mutation and all other risk factors remains uncertain [18, 20]. A final consideration is that in those who discontinue eculizumab and suffer a relapse, limited evidence suggests resuming eculizumab reliably induces a second remission [20, 21]. While these data need further corroboration, it may help during discussions between providers and patients when considering treatment discontinuation.

If choosing to alter dosing schedules or discontinue eculizumab, a crucial consideration is how to monitor for signs of TMA relapse. Besides close monitoring of hemoglobin, platelets, and renal function, methods that have been explored include eculizumab drug levels (available only in very select centers), or various complement activity assays including CH50, AH50, and soluble terminal complement activity (sC5b-9). Serum C3,

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

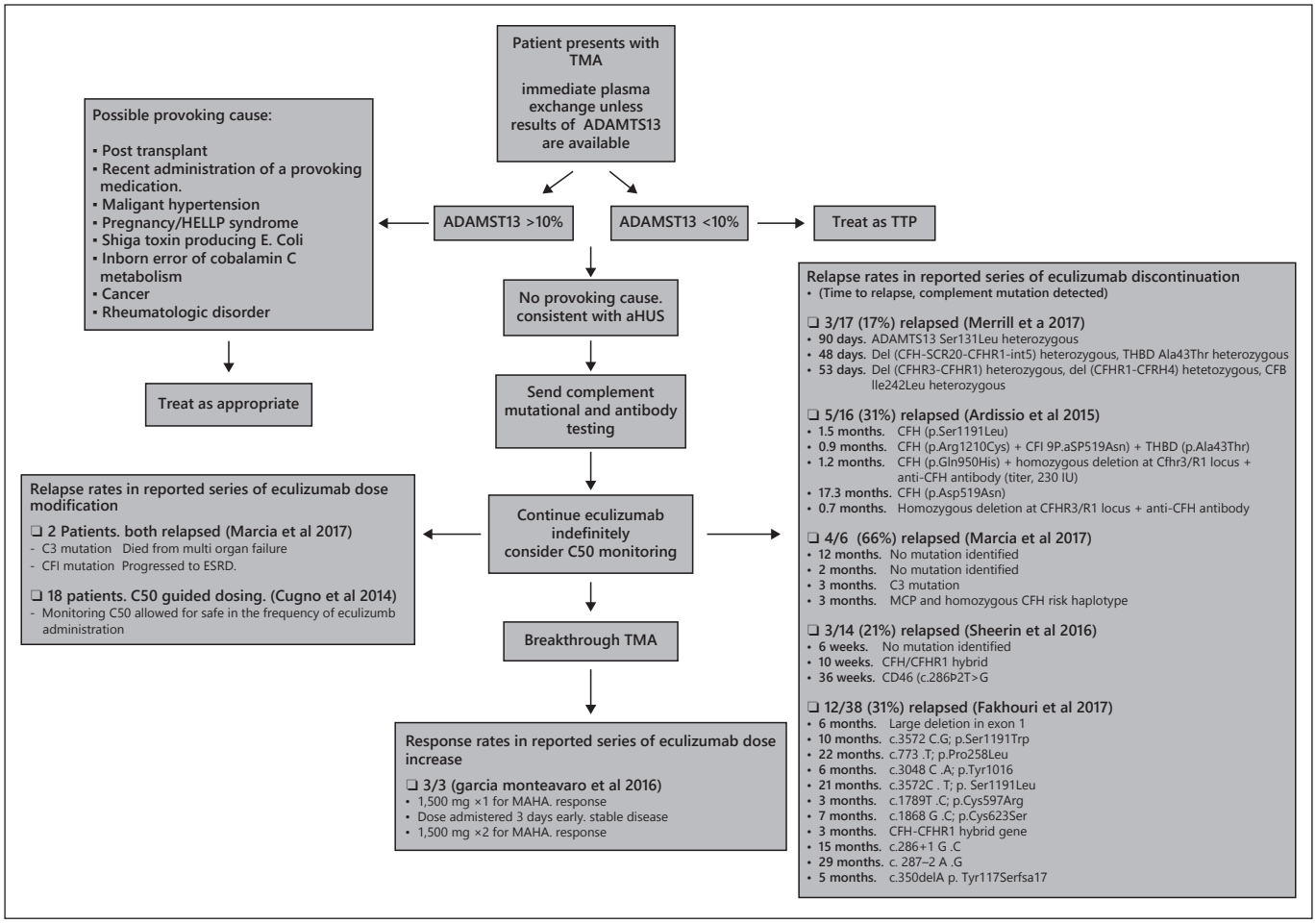

Fig. 1. Workup of acute TMA and the reported rates of relapse with eculizumab dose adjustment of cessation [16–18, 20, 21, 24, 41].

C4, and sC5b-9, however, have demonstrated limited sensitivity and specificity and correlate poorly with disease activity, and thus have limited diagnostic or prognostic significance [22]. Several small studies have published favorable outcomes of patients with aHUS who have eculizumab doses administered with progressively longer intervals based on CH50, or classical complement activity, testing [21, 23]. Ardissino et al. [23] used a cutoff classical complement activity <10% to justify increasing the dose interval up to 28 days, and activity of >30% to justify decreasing dosing intervals. Of the 38 patients to which these dose adjustments were applied, none relapsed. These findings were corroborated by another cohort of 18 patients using similar dose adjustment criteria [21]. Unmonitored dose reduction was examined in 2 patients, with both relapsing [18]. There are also reports of potential breakthrough of the traditional dosing schedule, but which responded to dose increase [24]. Finally, a low cost and low risk method utilized in some studies is home urine dipstick testing for evidence of hemoglobinuria; this method merits further exploration in those at high risk for relapse, and could be measured by patients between scheduled in-office follow up with physicians. Fakhouri et al. [20] proposed a strategy for considering eculizumab discontinuation in aHUS, which notably recommends at least 6 months of therapy.

Bottom Lines

- In aHUS, the risk of relapse after eculizumab discontinuation is high (30%) with unpredictable timing; available data suggests indefinite therapy remains the most reasonable recommendation.
- For patients who wish to stop therapy, careful discussion of the risks outlined in this section should be held with the patient.

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

- Prospective data is lacking to adequately stratify risk of relapse after eculizumab discontinuation; risk may be increased by certain complement protein mutations.
- Small series and in vitro data suggest that prolonging intervals between doses of eculizumab based on CH50 results may be safe.
- No standard approach exists to monitor for relapse after eculizumab discontinuation; a reasonable strategy is to follow hemoglobin, platelets, serum creatinine, and lactate dehydrogenase (LDH) in the following schedule after stopping drug: at 2 and 4 weeks, then monthly for 6 months, then every 3–4 months.

Drug-Induced TMA

Multiple case reports, series and systematic reviews have highlighted an association between certain drugs and the development of TMA. Historically, quinine was the most frequently implicated; contemporary drugs include anti-neoplastic agents gemcitabine, oxaliplatin and mitomycin, bevacizumab, tacrolimus, cyclosporine, and sirolimus [25]. Proposed mechanisms for drug-induced TMA (dTMA) include direct cytotoxic or immune-mediated damage to host tissues, the latter mechanism via formation of drug-dependent auto-antibodies Both of these mechanisms have been suggested to cause damage to endothelial and renal mesangial cells, platelets, and neutrophils [2, 25]. The natural history of dTMA typically reflects the underlying mechanism; cases of immune-mediated disease show acute onset within 2–3 weeks of drug initiation or upon re-initiation of an intermittently administered drug, in a pattern typical for hypersensitivity reactions [25]. Cytotoxic damage can present with variable patterns but tend to manifest as either acute TMA following initial exposure to a drug, or slowly progressive TMA with cumulative drug exposure, commonly detected as progressive CKD and hypertension [25].

Treatment of dTMA consists primarily of stopping the offending drug and supportive care. The involvement of the complement system, however, has been suggested based on published experience using eculizumab in this setting (Table 2), most with the use of gemcitabine. The largest, multi-center case series by Grall et al. [26] reviewed 8 patients with gemcitabine-induced TMA. Eculizumab was initiated within a median of 19.5 days of dTMA diagnosis, with a median of 4.5 doses given. About 6 of 8 (75%) patients showed hematologic recovery after a single dose. Similarly, renal function partially or completely resolved in 6 of 8 (75%) patients, though time to renal recovery was not reported. Five of the patients eventually died from other complications of progressive malignancies, while 3 patients remained alive after eculizumab cessation (time not reported).

The second largest series published by Weitz and Deloughery et al. [27] included 7 patients, 4 of who were treated with gemcitabine; others received dasatinib, bevacizumab, and bleomycin. All cases had refractory TMA despite discontinuation of the culprit drug for at least 8 weeks. All 7 cases showed improvement in hematologic parameters and/or renal function over a median treatment period of 14 weeks. After cessation of eculizumab and over a follow-up period of 120 weeks, no patients experienced recurrent TMA.

Other case reports have shown similar outcomes with eculizumab use. In some of these cases, eculizumab was stopped after as few as 2 doses, though some were treated for as long as 15 months [28]. As with aHUS, all published cases of dTMA treated with eculizumab found that hematologic recovery occurred rapidly (within weeks), while renal recovery often took months [28]. The criteria for stopping eculizumab in these cases are not consistently listed, but therapy was typically continued until substantial improvement in thrombocytopenia and anemia and diminished signs of hemolysis.

Similar to other forms of TMA, identifying risk factors for dTMA recurrence is crucial. Mutations in complement proteins may predispose patients to dTMA, with the drug serving as the second "hit" for development of overt disease, though data on this association are currently lacking and can only be inferred from studies on other forms of sHUS such as the post-transplant setting. Currently, given the paucity of data on outcomes of dTMA treated with eculizumab in any setting other than gemcitabine, universal recommendations on risk-stratification to guide dose alterations cannot be made. In cases of gemcitabine-induced dTMA, however, we feel it is reasonable to utilize eculizumab for refractory cases and that eculizumab discontinuation can be safely accomplished once hematologic remission has been achieved, as suggested in the following recommendations.

Bottom lines

- In select cases of refractory dTMA unresponsive to culprit-drug discontinuation, a trial of eculizumab should be attempted.
- Eculizumab should be administered in doses typically used for aHUS (Induction: 900 mg IV weekly for 4 weeks. Maintenance: 1,200 mg IV every 2 weeks).

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

Am J Nephrol 2018;48:96–107
DOI: 10.1159/000492033

Table 2. Studies of drug-induced thrombotic microangiopathy treated with eculizumab

Study	Number of patients and age (median)	Drug	Median doses of eculizumab	Median follow-up in weeks (range)	Response to eculizumab (hematologic)	Outcome at follow-up time	Criteria for stopping eculizumab
Starck and Wendtner [44], 2013	1 (45)	Gemcitibine	4	23	Response after 1 dose	No recurrent TMA	Resolution of TMA
Krishnappa et al. [45], 2018	1 (64)	Gemcitibine	20	32	Response after 2 doses	No recurrent TMA	Patient passed from cancer
Rogier et al. [46], 2016	1 (68)	Gemcitibine	7	–	–	–	Resolution of TMA
Turner et al. [28], 2017	2 (75+59)	Gemcitibine Gemcitibine	– 16 weeks – 15 months Doses not described	–	Responded after 1 dose	No recurrent TMA 1 patient was rechallanged with gemcitabine without recurrence	1. Death at 16 weeks from cancer 2. "Uncertain need for continuation"
Lopez Rubio et al. [47], 2017	1 (74)	Gemcitibine	7	–	–	Off dialysis. No recurrent TMA reported	Resolution of TMA
Grall et al. [26], 2016	8 (not described)	Gemcitibine	Not described	–	75%	No recurrent TMA reported. All had at least partial renal recovery	Not reported 5/8 died within one year
Gosain et al. [48], 2017	2 (54+61)	Gemcitibine Carfilzomib	5.5	(33–52)		No recurrent TMA OS 100%	Resolution of TMA
Weitz and Deloughery [27], 2017	7 (48)	Gemcitibine × 4 Dasatinib Bevacizumab Belomycin	14 weeks (2–24) 1 ongoing through chemo	78 (36–120)	100%	No recurrent TMA	Resolution of TMA or completion of chemotherapy
Zanchelli et al. [49], 2017	1	Oxaliplatin	–	–	–	No recurrent TMA	–
Facchini et al. [50], 2017	1 (3)	gemcitabine and oxaliplatin	7	6 months	–	Complete response. Five months later, presented with respiratory failure and cytopenias suggestive of TMA. Eculizumab restarted 2 doses, but patient died from cardiac event	Resolution of TMA
AL Ustwani et al. [51], 2014	4 (71)	Gemcitibine × 4	4.5	–	100%	No recurrent TMA	Not described
Faguer et al. [52], 2013	1	Mitomycin-C	8	18 months	Response after 1 dose	No recurrent TMA	Resolution of TMA

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

- Eculizumab should be continued at least until hematologic recovery; renal function may take months to recover.
- Similar to aHUS, close monitoring of hemoglobin, platelets, serum creatinine, and LDH after eculizumab discontinuation should be employed.

Transplant-Associated TMA

Another form of sHUS encountered with increasing frequency is transplant-associated TMA (TA-TMA). Due to discrepancies in diagnostic criteria, the incidence of TA-TMA after hematopoietic stem cell transplant (HSCT) and solid-organ transplant is variable, at 6–76% and 1–15%, respectively [29]. The pathophysiology of solid organ and HSCT TMA remains poorly understood, but is suspected to involve a similar constellation of endothelial damage, hemolysis, and platelet activation. However, in TA-TMA, as with many other forms of sHUS, the disease process is often initiated by phenomena distinct from, or only indirectly related to, complement activation [3]. Nonetheless, recent studies have implicated complement activation via both the classic and alternative pathways, which have subsequently led to the off-label use of eculizumab in this setting [13, 14].

Risk factors for the development of TA-TMA include chemotherapy and radiation components of the conditioning regimen in patients receiving HSCT, exposure to calcineurin inhibitors (CNI) used for immune suppression, unrelated organ donors, human leukocyte antigen mismatch, graft-versus-host disease (GVHD), and viral infections [14]. In addition, complement protein mutations and auto-antibodies have been implicated in TA-TMA, both as a risk for initial and recurrent TMA. Jodele et al. [13] reported a series of 6 pediatric cases of HSCT TMA, all of which had heterozygous deletions in CFHR3-CFHR1, as well as some having anti-factor H antibodies. A prospective study of 77 pediatric patients undergoing HSCT similarly demonstrated a high rate (65%) of complement gene variants in those developing TMA, compared to only 9% seen in those who did not develop TA-TMA [30]. Mutations in CFH and CFB [31] have been found to confer the highest risk of aHUS recurrence in solid-organ allografts, and for this reason, guidelines from the "Kidney Disease: Improving Global Outcomes (KDIGO)" group recommend genetic testing prior to considering the discontinuation of eculizumab for aHUS [31].

Given the complexity of transplant physiology, it can be difficult to establish which of these risk factors are most significant. Overlap of pathophysiologic mechanisms with other forms of complement-mediated TMAs are entirely possible, particularly when drugs such as CNIs are implicated. This makes diagnostic criteria for TA-TMA challenging; besides the typical features of thrombocytopenia, microangiopathic hemolytic anemia, renal failure, and neurologic impairment, no widely endorsed diagnostic criteria have been established, and what criteria do exist have not yet been validated in clinical practice [32–34].

Prognosis of TA-TMA is historically poor, with a reported overall survival after HSCT of 50–75% [35]. In solid-organ transplant, outcomes can be similarly severe, with a reported rate of renal allograft failure of 60–100% with conservative measures alone [29]. The first step in treatment involves prompt discontinuation of culprit drugs, particularly CNIs [32, 35]. Plasma exchange was historically used for refractory cases, though as with aHUS, the efficacy of this practice has been questioned [36]. Other options include intensification of immunosuppression with alternative agents, or complement inhibition via eculizumab [37].

Large, prospective studies examining eculizumab in this setting are lacking. Existing case reports, series, and cohort studies of eculizumab use in the transplant setting are summarized in Table 3. Several of these studies have reported encouraging response rates, but these results should be tempered with the poor overall survival, particularly after HSCT, of patients who often succumb to other transplant complications despite sustained eculizumab response. A retrospective cohort study by Bohl et al. [38] of patients with TA-TMA after HSCT treated with eculizumab vs. conventional therapy illustrates this well; despite an initial response (defined as transfusion-independence and improvement in renal function) of 93% (13/15) after a median of 9 doses of eculizumab, the overall survival at 30 weeks was only 33% (5/15). Non-meningococcal infections accounted for 70% of the deaths, and progressive TA-TMA accounted for only 20% of the deaths. One TMA relapse after eculizumab cessation was reported.

Other series have shown less favorable outcomes with eculizumab; one study published in abstract form by Vaughn et al. [39] reported outcomes of 20 adults with TA-TMA after HSCT treated with eculizumab, with a response rate of only 55% (defined as transfusion-independence and creatinine improvement). Responders received a median of 6.5 doses of eculizumab. No comment on recurrent TMA was made. This study did, however, report a significantly reduced median cost of inpatient care and

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

Am J Nephrol 2018;48:96–107
DOI: 10.1159/000492033

Table 3. Studies of transplant-associated thrombotic microangiopathy treated with eculizumab

Study	Number of patients and age (median)	Transplant type	Median days from diagnosis to eculizumab treatment (range)	Median doses of eculizumab given (range)	Median duration of follow-up in weeks (range)	Response to eculizumab (hematologic), % (*n*)	Outcome at follow-up time
Dhakal and Bhatt [14], 2015*	26 (33)	HSCT (*n* = 9) Solid-organ transplant (*n* = 17)	82 (NR)	5.5 (2–21)	52 (3–113)	92 (24/26)	No recurrent TMA OS 92%
Fernández et al. [53], 2015	1 (30)	HSCT	0	5	4	Yes	No recurrent TMA OS 0%
Morales et al. [54], 2015	1 (42)	Solid-organ transplant	7	6	12	Yes	No recurrent TMA
De Fontbrune et al. [55], 2015	12 (39)	HSCT	31 (3–154)	6 (1–31)	62 (10–187)	50 (6/12)	No recurrent TMA OS 33% (4 patients died from of TA-TMA)
Sevindik et al. [56], 2015	1 (43)	HSCT	4	2	2	Yes	No recurrent TMA OS 0%
Vasu et al. [57], 2016	5 (38)	HSCT	65 (35–103)	7 (3–52)	12 (4–74)	80 (4/5)	No recurrent TMA OS 60% (two died from sepsis)
Ikeda et al. [58], 2016	2 (47)	Solid-organ transplant	4 (2–5)	6.5 (5–8)	44 (35–52)	100 (2/2)	No recurrent TMA OS 100%
Jodele et al. [13], 2016	30 (5)	HSCT	NR	14 (2–38)**	NR	NR	No recurrent TMA OS 62% at 1 year
Abusin et al. [59], 2017	2 (5)	HSCT	19 (7–30)	16 (13–19)***	78 (36–120)	100 (2/2)	No recurrent TMA OS 50%
Nozawa et al. [60], 2017	1 (1)	HSCT	7	5	104	Yes	No recurrent TMA OS 0%
Vaughn et al. [39], 2017	20 (43 for responders; 60 for non-responders)	HSCT	2 (0–272)	6.5 (2–17) for responders 3 (1–7) for non-responders	NR	55 (11/20)	NR
Epperla et al. [40], 2017	5 (NR)	HSCT (*n* = 3) Solid-organ transplant (*n* = 2)	12 (4–57)	5 (1–6)	NR	60 (3/5)	No recurrent TMA
Cavero et al. [12], 2017	15 (52)	HSCT (*n* = 2) Solid-organ transplant (*n* = 13)	10 (4–53)	5 (2–17)	29 (7–76)	80 (12/15)	No recurrent TMA
Bohl et al. [38], 2017	15 (48)	HSCT	10 (1–49)	9 (1–23)	30	93 (13/15)	No recurrent TMA OS 33%

* Retrospective analysis of 12 case reports/series up through November 2014. ** Dosing based on CH50 levels, rather than aHUS dosing. ***Eculizumab taper used. NR, not reported.

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

length of stay when comparing eculizumab responders and non-responders (USD 259,734 vs. USD 1,525,758, and 9 vs. 61 days, respectively). Factors conferring a significantly higher chance of eculizumab refractoriness included older age, active GVHD, and number of comorbidities.

TA-TMA following solid-organ transplant has been reported in a wide spectrum of donor organ types including renal, small bowel, lung, liver, heart, and pancreas [12, 14, 40]. In existing case series, better outcomes have been observed in TA-TMA associated with solid organs. Dhakal et al. [14] summarized case series showing an eculizumab response rate of 100% (17/17) in solid-organ transplants, but only 78% (7/9) of HSCT patients. In this series, a median of 5 doses of eculizumab were given, and at a median follow-up of 21 weeks, all survivors were without recurrent TMA. In a more recent series including 15 cases of TA-TMA (13 of which were solid-organ transplants), responses to eculizumab were seen in 12/15 (80%) cases, with treatment duration lasting anywhere from 2 to 30 weeks [12]. The follow-up duration varied for each patient, though no recurrences of TMA were reported after a maximum of 17.5 months follow-up [12]. Similarly, in a recent smaller case series, responses were observed in 100% of those with solid-organ transplants [40].

It should be emphasized again that many cases of TA-TMA may actually be related to other factors including CNI use. Also, TA-TMA in the setting of hematological malignancy may actually be driven by infection, late conditioning toxicities or GVHD. This is reflected by outcomes of TA-TMA treated with eculizumab stratified by underlying reason for organ transplant. In solid-organ TMA series previously described, renal transplants were carried out for reasons other than previous TMA; outcomes of subsequent TMA were universally favorable with few, if any relapses. In contrast, TMA relapse tends to occur more frequently after renal transplant performed because of aHUS-mediated renal damage. Major clinical trials of eculizumab for aHUS included patients who had received prior renal transplants; of the 61 patients reported in these trials, 16 (26%) had previous renal transplants, and 25% of these (3/16) suffered TMA relapse after eculizumab cessation, a similar rate to all-comers who stop therapy [18]. This is an important distinction, as cessation of eculizumab may only be a safe consideration in those without a prior diagnosis of de novo aHUS.

Dosing of eculizumab TA-TMA has not yet been established, and in most institutions, follows the FDA label for aHUS [37]. Jodele et al. [13, 30] have proposed titrating eculizumab dose and frequency based on CH50 levels, and suggest continuing eculizumab at least until resolution of hematologic abnormalities, followed by a minimum of 4 treatments at maintenance dosing. Based on available evidence, we feel discontinuing eculizumab in this manner is reasonable.

Bottom lines

- TA-TMA may benefit from complement inhibition with eculizumab in refractory cases despite discontinuation of suspected drugs and treatment of comorbid infections and GVHD.
- In cases of TA-TMA not associated with a prior diagnosis of *de novo* aHUS, we agree with guidelines [30] suggesting eculizumab treatment at least until resolution of hematologic abnormalities, followed by 4 additional maintenance doses, before considering discontinuation.
- In cases of TA-TMA with a prior diagnosis of de novo aHUS, available evidence suggests that indefinite complement inhibition with eculizumab is the most reasonable treatment.
- As with cases of aHUS and dTMA, close monitoring of hemoglobin, platelets, serum creatinine, and LDH after eculizumab discontinuation should be employed.

Future Directions

Relapse is a real concern for patients with complement-mediated HUS who choose to stop eculizumab. There is clearly a subset of patients who will remain free of relapse based on the currently available data [17, 18, 20, 21, 41], though how many of these patients will relapse after many more years of follow-up is unknown. Future work to better define the subset of patients who can safely stop therapy, ideally with the development of a prospectively validated scoring system, would be useful.

Several novel drugs targeting the terminal complement pathway are currently in development, driven both by the desire to overcome eculizumab resistance in PNH and aHUS, as well as to improve patient convenience and cost [42]. These include several second-generation anti-C5 monoclonal antibodies, C3 inhibitors, and small interfering RNAs (siRNA) engineered to inhibit transcription of complement proteins. Several of these have garnered attention for their subcutaneous route of administration and positive efficacy and safety results from phase II and III clinical trials [43]. If approved for complement-mediated TMAs, these drugs could ameliorate some of the concerns surrounding the prolonged use of eculizumab.

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

Conclusion

There is a substantial risk of TMA relapse when stopping eculizumab in patients with aHUS. In cases of sHUS, however, select groups of patients (dTMA, solid organ TMA, and HSCT TMA) appear to be able to discontinue eculizumab and remain relapse-free for several years. Stopping therapy in these patients after achievement of hematologic remission, but with close clinical and laboratory follow-up, seems reasonable. For cases of aHUS, the current data continue to argue in favor of indefinite eculizumab therapy. If patients or providers consider stopping therapy, a careful discussion of the risks and benefits as outlined here should be undertaken. Attractive future prospects for the treatment of complement-mediated TMAs include novel complement inhibition therapies that may reduce the cost and improve patient convenience.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Funding Source

The authors have no sources of funding to disclose. The research and writing of this manuscript was unfunded.

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023

References

1 Nester CM, Thomas CP: Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated? Hematology Am Soc Hematol Educ Program 2012;2012:617–625.
2 Shatzel JJ, Taylor JA: Syndromes of thrombotic microangiopathy. Med Clin North Am 2017;101:395–415.
3 Jokiranta TS: HUS and atypical HUS. Blood 2017;129:2847–2856.
4 Joly BS, Coppo P, Veyradier A: Thrombotic thrombocytopenic purpura. Blood 2017;129:2836–2846.
5 Orth D, et al: Shiga toxin activates complement and binds factor h: evidence for an active role of complement in hemolytic uremic syndrome. J Immunol 2009;182:6394–6400.
6 Menne J, et al: Validation of treatment strategies for enterohaemorrhagic *Escherichia coli* O104:H4 induced haemolytic uraemic syndrome: case-control study. BMJ 2012;345:e4565.
7 Legendre CM, et al: Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Eng J Med 2013;368:2169–2181.
8 Licht C, et al: Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int 2015;87:1061–1073.
9 Kielstein JT, et al: Best supportive care and therapeutic plasma exchange with or without eculizumab in Shiga-toxin-producing E. coli O104:H4 induced haemolytic-uraemic syndrome: an analysis of the German STEC-HUS registry. Nephrol Dial Transplant 2012;27:3807–3815.
10 Lapeyraque AL, et al: Eculizumab in severe shiga-toxin-associated HUS. N Engl J Med 2011;364:2561–2563.
11 Pape L, et al: Eculizumab in typical hemolytic uremic syndrome (HUS) with neurological involvement. Medicine (Baltimore) 2015;94:e1000.
12 Cavero T, et al: Eculizumab in secondary atypical haemolytic uraemic syndrome. Nephrol Dial Transplant 2017;32:466–474.
13 Jodele S, et al: Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Biol Blood Marrow Transplant 2014;20:518–525.
14 Dhakal P, et al: Eculizumab in transplant-associated thrombotic microangiopathy. Clin Appl Thromb Hemost 2017;23:175–180.
15 Vasu S, et al: Eculizumab therapy in adults with allogeneic hematopoietic cell transplant-associated thrombotic microangiopathy. Bone Marrow Transplant 2016;51:1241.
16 Ardissino G, et al: Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. Am J Kidney Dis 2014;64:633–637.
17 Merrill SA, et al: Eculizumab cessation in atypical hemolytic uremic syndrome. Blood 2017;130:368–372.
18 Macia M, et al: Current evidence on the discontinuation of eculizumab in patients with atypical haemolytic uraemic syndrome. Clin Kidney J 2017;10:310–319.
19 Hillmen P, et al: Assessment of human anti-human antibodies to eculizumab after long-term treatment in patients with paroxysmal nocturnal hemoglobinuria. Am J Hematol 2016;91:E16–E17.
20 Fakhouri F, et al: Pathogenic variants in complement genes and risk of atypical hemolytic uremic syndrome relapse after eculizumab discontinuation. Clin J Am Soc Nephrol 2017;12:50–59.
21 Cugno M, et al: Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome. J Thromb Haemost 2014;12:1440–1448.
22 Noris M, et al: Dynamics of complement activation in aHUS and how to monitor eculizumab therapy. Blood 2014;124:1715–1726.
23 Ardissino G, et al: Complement functional tests for monitoring eculizumab treatment in patients with atypical hemolytic uremic syndrome: an update. Pediatr Nephrol 2018;33:457–461.
24 Garcia Monteavaro C, Peralta Rosello C, Quiroga B, et al: Adjustment of eculizumab dosage pattern in patients with atypical hemolytic uremic syndrome with suboptimal response to standard treatment pattern. Case Rep Nephrol 2016;2016:7471082.
25 Al-Nouri ZL, et al: Drug-induced thrombotic microangiopathy: a systematic review of published reports. Blood 2015;125:616–618.
26 Grall M, et al: Efficacy of eculizumab in gemcitabine-induced thrombotic microangiopathy: experience of the French thrombotic microangiopathies reference centre. Blood 2016;128:136.
27 Weitz IC, Deloughery T: Effective treatment of chemotherapy induced atypical Haemolytic Uraemic Syndrome: a case series of 7 treated patients. Br J Haematol 2017, Epub ahead of print.
28 Turner JL, et al: Gemcitabine-associated thrombotic microangiopathy: response to complement inhibition and reinitiation of gemcitabine. Clin Colorectal Cancer 16:e119–e122.
29 Noris M, Remuzzi G: Thrombotic microangiopathy after kidney transplantation. Am J Transplant 2010;10:1517–1523.
30 Jodele S, et al: A new paradigm: diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial injury. Blood Rev 2015;29:191–204.
31 Goodship TH, et al: Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int 2017;91:539–551.

32 Ho VT, et al: Blood and marrow transplant clinical trials network toxicity committee consensus summary: thrombotic microangiopathy after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2005;11:571–575.
33 Ruutu T, et al: Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group. Haematologica 2007;92:95–100.
34 Kennedy GA, et al: Posttransplant thrombotic microangiopathy: sensitivity of proposed new diagnostic criteria. Transfusion 2009;49: 1884–1889.
35 Gavriilaki E, et al: Transplant-associated thrombotic microangiopathy: opening Pandora's box. Bone Marrow Transplant 2017;52: 1355–1360.
36 Sarkodee-Adoo C, et al: Thrombotic microangiopathy in blood and marrow transplant patients receiving tacrolimus or cyclosporine A. Transfusion 2003;43:78–84.
37 Dhakal P, Bhatt VR: Is complement blockade an acceptable therapeutic strategy for hematopoietic cell transplant-associated thrombotic microangiopathy? Bone Marrow Transplant 2017;52:352–356.
38 Bohl SR, et al: Thrombotic microangiopathy after allogeneic stem cell transplantation: a comparison of eculizumab therapy and conventional therapy. Biol Blood Marrow Transplant 2017;23:2172–2177.
39 Vaughn JL, et al: Response rates, non-relapse mortality, and financial implications of transplant-associated thrombotic microangiopathy treated with eculizumab. Blood 2017; 130(suppl 1):1932.
40 Epperla N, et al: Impact of treatment and outcomes for patients with posttransplant drug-associated thrombotic microangiopathy. Transfusion 2017;57:2775–2781.
41 Sheerin NS, et al: A national specialized service in England for atypical haemolytic uraemic syndrome-the first year's experience. QJM 2016;109:27–33.
42 Mastellos DC, et al: Expanding complement therapeutics for the treatment of paroxysmal nocturnal hemoglobinuria. Semin Hematol 2018, in press.
43 Ricklin D, et al: The renaissance of complement therapeutics. Nat Rev Nephrol 2018;14: 26–47.
44 Starck M, Wendtner CM: Use of eculizumab in refractory gemcitabine-induced thrombotic microangiopathy. Br J Haematol 2014; 164:894–896.
45 Krishnappa V, Gupta M, Shah H, et al: The use of eculizumab in gemcitabine induced thrombotic microangiopathy. BMC Nephrol 2018;19:9.
46 Rogier T, Gerfaud-Valentin M, Pouteil-Noble C, et al: [Clinical efficacy of eculizumab as treatment of gemcitabine-induced thrombotic microangiopathy: a case report]. Rev Med Interne 2016;37:701–704.
47 Lopez Rubio ME, Rodado Martinez R, Illescas ML, et al: Gemcitabine-induced hemolytic-uremic syndrome treated with eculizumab or plasmapheresis: two case reports. Clin Nephrol 2017;87:100–106.
48 Gosain R, Gill A, Fuqua J, et al: Gemcitabine and carfilzomib induced thrombotic microangiopathy: eculizumab as a life-saving treatment. Clin Case Rep 2017;5:1926–1930.
49 Zanchelli F, Tampieri E, Gozzetti F, et al: [Atypical hemolytic uremic syndrome related to oxalyplatin cancer chemotherapy responsive to eculizumab]. G Ital Nefrol 2017; 34:pii:gin/34.1.5.
50 Facchini L, Lucchesi M, Stival A, et al: Role of eculizumab in a pediatric refractory gemcitabine-induced thrombotic microangiopathy: a case report. J Med Case Rep 2017;11: 209.
51 Al Ustwani O, Lohr J, Dy G, et al: Eculizumab therapy for gemcitabine induced hemolytic uremic syndrome: case series and concise review. J Gastrointest Oncol 2014;5:E30–E33.
52 Faguer S, Huart A, Frémeaux-Bacchi V, Ribes D, Chauveau D: Eculizumab and drug-induced haemolytic-uraemic syndrome. Clin Kidney J 2013;6:484–485.
53 Fernández C, Lario A, Forés R, Cabrera R: Eculizumab treatment in a patient with hematopoietic stem cell transplantation-associated thrombotic microangiopathy and steroid-refractory acute graft versus host disease. Hematol Rep 2015;7:6107.
54 Morales E, Rabasco C, Gutierrez E, Praga M: A case of thrombotic micro-angiopathy after heart transplantation successfully treated with eculizumab. Transpl Int 2015;28:878–880.
55 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.
56 Sevindik OG, Alacacioglu I, Katgi A, et al: Renal and neurological response with eculizumab in a patient with transplant associated thrombotic microangiopathy after allogeneic hematopoietic progenitor cell transplantation. Case Rep Hematol 2015;2015:425410.
57 Vasu S, Wu H, Satoskar A, et al: Eculizumab therapy in adults with allogeneic hematopoietic cell transplant-associated thrombotic microangiopathy. Bone Marrow Transplant 2016;51:1241–1244.
58 Ikeda T, Okumi M, Unagami K, et al: Two cases of kidney transplantation-associated thrombotic microangiopathy successfully treated with eculizumab. Nephrology (Carlton). 2016;21(suppl 1):35–40.
59 Abusin GA, Abu-Arja R, Bajwa RPS, Horwitz EM, Auletta JJ, Rangarajan HG: Severe transplant-associated thrombotic microangiopathy in patients with hemoglobinopathies. Pediatr Blood Cancer 2017;64.
60 Nozawa A, Ozeki M, Hori T, et al: A heterozygous CFHR3-CFHR1 gene deletion in a pediatric patient with transplant-associated thrombotic microangiopathy who was treated with eculizumab. J Pediatr Hematol Oncol 2017, Epub ahead of print.

Downloaded from http://karger.com/ajn/article-pdf/48/2/96/2212586/000492033.pdf by guest on 28 September 2023