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Discontinuation of Eculizumab treatment after hematological remission in patients with atypical and drug-induced hemolytic uremic syndrome

HASAN H. YETER, ULVER DERICI, TURGAY ARINSOY, KADRIYE ALTOK, YASEMIN ERTEN, GALIP GUZ

Department of Nephrology Dialysis and Transplantation, Gazi University Faculty of Medicine, Ankara, Turkey

Introduction. The aim was to evaluate the effect of therapeutic plasma exchange (TPE) and eculizumab on hematological and renal survival in atypical hemolytic uremic syndrome (aHUS), and additionally, to examine the reliability of discontinuation of eculizumab treatment.

Methods. This was an observational and retrospective study of 18 patients diagnosed with aHUS.

Results. The median age of the study population was 30 (22–66) years. Four of 18 patients achieved hematological remission with the TPE alone. However, one patient died after three sessions of TPE. Eculizumab was used in 13 patients and no death was observed. One year after treatment, improved kidney function was observed in 2 of 3 (66%) patients for TPE and 5 of 9 (56%) patients for Eculizumab. We discontinued eculizumab treatment in 9 patients. One of the patients who had a C3 gene mutation experienced disease relapse after Eculizumab discontinuation. None of the patients who had drug associated aHUS developed disease relapse after Eculizumab discontinuation.

Conclusion. Eculizumab treatment is a life-saving therapy in aHUS. Treatment discontinuation may be considered at least six months after hematologic remission in patients who had stable renal function or no expectancy for renal survival. Moreover, drug-associated cases seem to tend not to develop disease relapse in the long term.

Key words: atypical hemolytic uremic syndrome, eculizumab, therapeutic plasma exchange, discontinuation, prognosis.

What is new? What is important?

Eculicuzmab is a life saving therapy that provides favorable hematological and renal outcomes. Eculizumab discontinuation may be considered at least six months after hematologic remission in patients who had stable renal function or no expectancy for renal survival, in condition with monitoring regularly.

INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a rare disease that occurs in less than one person per million [1]. aHUS, which may affect the brain, lung, heart, pancreas, and intestine, is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and kidney failure [1–3]. Complement gene mutations or polymorphisms that cause complement pathway dysregulation are found in approximately 40–60% of patients, but the phenotype penetrance of the mutations or polymorphisms is approximately 50% [4]. Dysregulation in the complement pathway leads to the uncontrolled generation of C5 convertase, which results in the overactivation of the membrane attack complex in vascular endothelial cells [4]. This process triggers endothelial cell damage, platelet activation, and thrombus formation [1–4].

Historically, outcomes of aHUS were poor when aHUS was treated with plasma therapy. The disease may cause death, and the development of end-stage kidney disease (ESRD) was observed in 50% of patients who survived the disease [5]. Eculizumab (Soliris, Alexion Pharmaceuticals, Cheshire, CR, USA), a humanized monoclonal antibody that has an inhibitory action on complement factor C5, was approved to treat aHUS in 2011 [5, 6]. Clinical trials and observational studies showed reduced mortality, and renal recovery and survival increased with eculizumab treatment compared to therapeutic plasma exchange (TPE) [7]. On the other hand, the optimal treatment duration with Eculizumab is not known. Eculizumab could facilitate the development of

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infections, especially with capsulated micro-organisms, and limited access to drugs and high cost of treatment are the main challenges of therapy.

The aim of the study was to examine the clinical course after eculizumab treatment was discontinued. Also, we evaluated the effectiveness of Eculizumab and TPE on hematological and renal improvements in patients with aHUS.

MATERIAL AND METHODS

This was a single-center observational and retrospective study. The study protocol conformed to ethical guidelines of the 1975 declaration of Helsinki, and all participants who could be reached gave written informed consent and willingness to participate. Data were collected from consecutive adult patients diagnosed with aHUS from 2010 to 2020 in the Gazi University nephrology department. The main inclusion criterion was being older than 18 years of age. aHUS was defined as the presence of at least 3 of the following four criteria: acute kidney injury (AKI), non-autoimmune hemolytic anemia (hemoglobin <11 g/dl, lactate dehydrogenase [LDH] ≥400 UI/L, haptoglobin <36 mg/dl, negative results for direct and indirect coombs tests and schistocytes in peripheral blood), thrombocytopenia (platelet count $<150x10^3$ μL) and/or thrombotic microangiopathy features in kidney biopsy specimens. AKI was defined according to Kidney Disease Improving Global Outcomes guidelines [8]. The exclusion criteria were as follows: HUS due to an enteric infection by Shiga toxin-producing *Escherichia coli* (STEC HUS -typical HUS-), metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) activity < 10%, thrombotic microangiopathy due to malignancy, glomerulo-pathies, autoimmune disease, presence of sepsis or septic shock and diagnosis of disseminated intravascular coagulopathy.

TPE was performed for all patients as soon as possible after the insertion of the central venous catheter. The response to TPE treatment was assessed by normalization of the platelet count and haptoglobin. TPE treatment stopped if the platelet count was still > 150×10^3 μL two days after reaching the normal value. Eculizumab treatment was considered under these conditions: platelet count was under $150x10^3$ μL after five TPE sessions, platelet counts fell under $150x10^3$ μL after TPE discontinuation, continued hemodialysis need or no improvement in kidney function (<25% decrease in plasma creatinine). Eculizumab was administered as an intravenous infusion of 900 mg weekly for four weeks, followed by 1,200 mg at the fifth week and then 1,200 mg every two weeks thereafter.

When clinical remission was reached, eculizumab treatment was evaluated. With the mandatory condition that hematological remission lasts at least six months, if kidney function has not improved or if the patient's need for maintenance hemodialysis continues or complete kidney recovery has been achieved, discontinuation of eculizumab treatment was considered. In case of therapy discontinuation, patients were closely monitored for signs of disease recurrence. Blood and urine (for not on hemodialysis) workups were performed weekly in the first month, then once every two weeks for three months and then every month until the end of the year, and every two months thereafter. All patients who received Eculizumab were vaccinated for protection from the capsulated bacterial agent, and prophylactic antibiotics were given until the vaccine's effectiveness was revealed.

The primary outcome of our study was to evaluate the effects of TPE and Eculizumab on hematologic remission, kidney function recovery, end-stage kidney disease, relapse, and death one year from diagnosis. Hematologic remission was defined as hemoglobin >11 gr/dl, LDH within normal limits, haptoglobin within normal limits, and platelet count >150 $x10^3$ μL. Complete kidney function recovery was accepted if the serum creatinine was below 1.1 mg/dl and proteinuria was below 500 mg/d. Patients were considered to have disease relapse if their initial symptoms returned after Eculizumab treatment. In this case, Eculizumab was restarted with the initial treatment protocol.

Data obtained in the study were analyzed statistically using Statistical Package for the Social Science software. 20 (IBM Corpn., SPSS for Windows. Armonk, NY, USA). According to data distribution, numerical variables in the text and tables are shown as the mean ± standard deviation or median (minimum-maximum). Categorical variables were stated as numbers (n) and percentages (%). The Mann-Whitney U test was used to compare continuous variables. Fisher's exact test was used to compare categorical variables, and yate correction was applied when the group's size was less than 5. A value of $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics and one-year outcome

Among the 26 patients diagnosed with HUS between 2010 and 2020, three of them had malignancy-associated HUS, and five of them had insufficient data to evaluate. As a result, 18 patients with complete demographic and laboratory data were evaluated (Figure 1). The median age of the study population was 30 (22–66) years with the same distribution of gender [F/M:9(50%)/9(50%)]. The median follow-up time for the total study population was 15.5 (1–108) months. No significant differences were observed in baseline characteristics between the patients who had hematologic and renal remission with TPE and those who needed eculizumab treatment for hematologic or renal remission (Table 1). While the most common facilitator factor of the development of aHUS and drug-associated HUS was infections (n=5, 27%), the condition that could trigger the development of aHUS was not detected in 39% of the total study population. The drug, which was thought to be the cause, was discontinued at TMA suspicion in all three drug-associated HUS cases, and TPE was started in all patients. Eculizumab was started in two patients without TPE response. The mean serum creatinine was 6.17±4.55 mg/dl at the time of diagnosis, and 15 of the total patients (83%) needed hemodialysis. While the mean hemoglobin was 9.1±2.36 g/dl for all patients, the median platelet count was $84x10^3$ xμl (20–370). Seven of the total patients (39%) had hypertension requiring intravenous medication. One patient had vision loss (6%), four patients had central nervous system involvement (CNS) (22%), and one patient had dilated cardiomyopathy (6%).

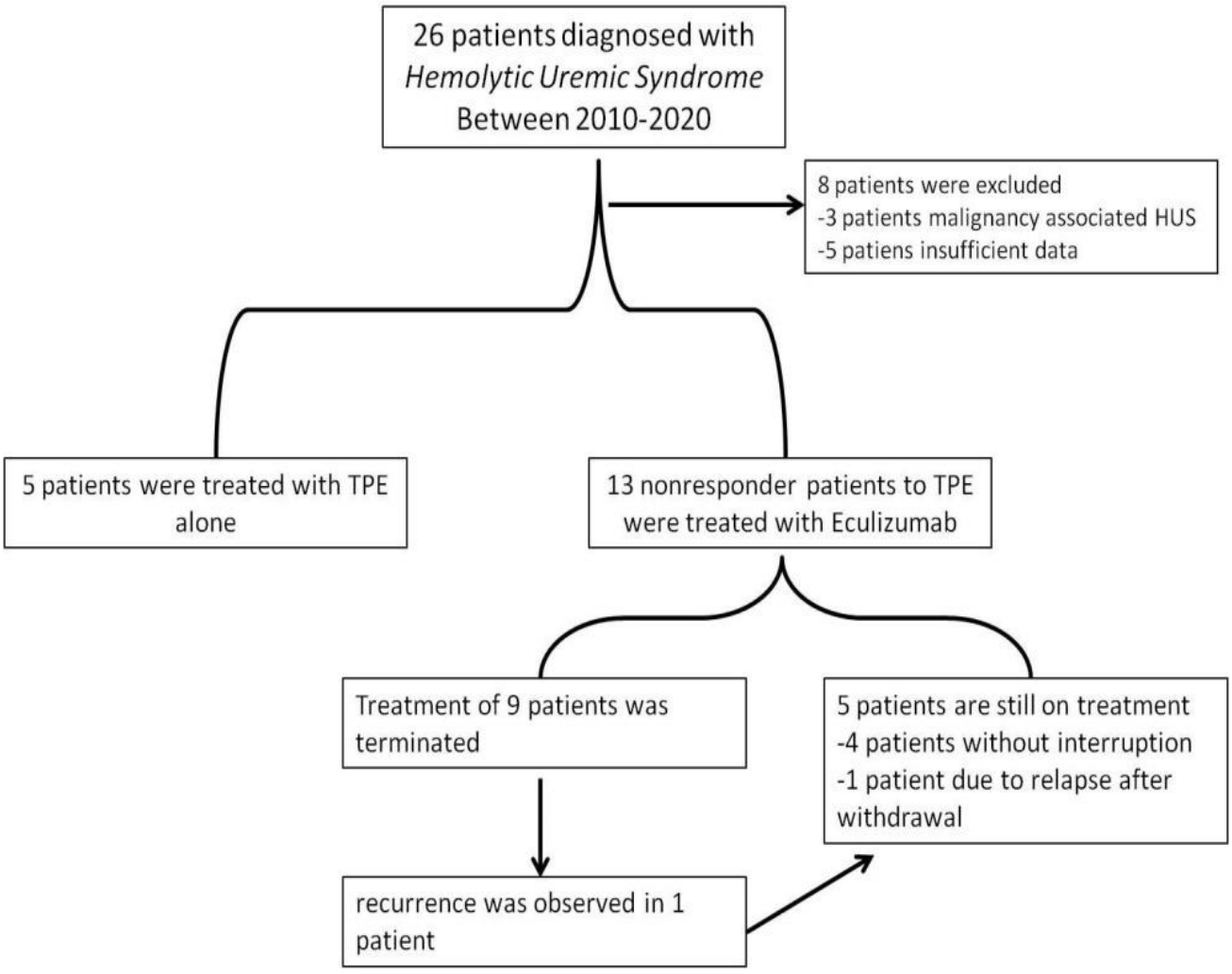

Figure 1. Flow chart of patients

Table 1

Baseline characteristics of study population according to treatment group

	All patients n=18	**TPE n=5 (28%)**	**Eculizumab † n=13 (72%)**	**P value**
Age (years) *median(min-max)*	30(22–66)	31 (25–66)	30 (22–52)	0.8
Gender (n,%)				0.1
Male	9 (50%)	4 (80%)	5 (39%)	
Female	9 (50%)	1 (20%)	8 (61%)	
Associated Conditions (n,%)				
No	7 (39%)	1 (20%)	6 (47%)	
Pregnancy	3 (17%)	0	3 (23%)	0.3
Infection	5 (27%)	3 (60%)	2 (15%)	0.06
Drug	3 (17%)	1 (20%)	2 (15%)	0.5
Kidney involvement				
Serum Creatinine (mg/dl)*(mean±SD)*	6.17±4.55	6.75±4.81	5.95±4.6	0.7
HD at diagnosis (n,%)	15 (83%)	4 (80%)	11 (85%)	0.9
Hematological findings				
Hemoglobin (g/dl) *median(min-max)*	9.1±2.36	9.7±1.96	8.9±2.54	0.5
PLT (10^3 xµl) *median(min-max)*	84 (20–370)	82 (22-168)	86 (20–370)	0.7
>1% schistocytes (n,%)	15 (94%)	5 (100%)	12 (93%)	0.4
LDH (UI/L) *median(min-max)*	872 (340–4724)	705 (468–4724)	903 (340–3852)	0.8
Haptoglobin (mg/dl) *median(min-max)*	2 (1–30)	5 (2–30)	2 (1–9)	0.3
Other involvements(n,%)				
Vision loss	1 (6%)	0	1 (8%)	
CNS	4 (22%)	1 (20%)	3 (23%)	
HT requiring IV medication	7 (39%)	2 (40%)	5 (39%)	
CVS	1 (6%)	0	1 (8%)	
Kidney biopsy (n,%)	5/18	1/5	4/13	
Glomerular thrombi	2	0	2	
Glomerular/extraglomerular thrombi	3	1	2	
Genetic mutation (n,%)	11/18	2/5	9/13	
CFH	3 (27%)	2	1	
MCP(CD46)	1 (9%)	0	1	
C3 ‡	2 (18%)	0	2	
CFHR3	1 (9%)	0	1	
No	4 (46%)	0	4	
Follow-up (months) *median(min-max)*	15.5 (1–108)	9 (1–108)	16 (3–57)	0.4

†Eculizumab was started after at least five sessions of TPE
‡One patient with C3 mutation also had CFB gene mutation
TPE: Therapeutic plasma exchange, **HD:** Hemodialysis, **PLT**: Platelet **LDH:** Lactate dehydrogenase, **CNS:** Central nervous system, **HT:** Hypertension, **IV:** Intravenous, **CVS:** Cardiovascular system; **CHF:** Complement factor H, **MCP:** Membrane cofactor protein, **C3:** Complement factor 3, **CFHR3:** Complement factor H related protein 3, **CFB:** Complement factor B

Outcomes at year one after aHUS and drug-associated HUS diagnosis of patients with or without eculizumab treatment are displayed in Table 2. The median time until eculizumab treatment initiation was 7 (6–14) days. The median application time of eculizumab treatment was 21 (6–61) months. Complete kidney function recovery was observed in 33% of patients within three months in both groups (1/3 for TPE and 3/9 for Eculizumab). Improvement of kidney function (complete recovery and increase in estimated glomerular filtration rate) was observed in 2 of 3 (66%) patients for TPE and 5 of 9 (56%)

patients for Eculizumab. Four of 9 patients (33%) in the eculizumab group developed ESRD. One patient in the TPE group died after three sessions of TPE. We observed hematologic normalization in all patients with eculizumab treatment, and the median time for remission was 10 (3–27) days.

Table 2

Outcomes at 1 year after diagnosis (n=12)

	TPE n=3	**Eculizumab † n=9**
Kidney function(n,%)		
Complete recovery (sCr<1.1 mg/dl)	1 (33%)	3 (33%)
Time to complete recovery	Within 1 months	1 month for 2 patients and 3 months for 1 patients
Increase in eGFR >50% over	1 (33%)	1 (11%)
Increase in eGFR 25-50% over baseline	0	1 (11%)
ESRD	0	4 (44%)
Proteinuria ‡ (g/d) *median(min-max)*	1 (0.48–1.05)	0.78 (0.1–2.5)
Hematologic remission §(n,%)	2 (67%)	9 (100%)
-remission time, (days) *median(min-max)*		10(3–27)
Relapse(n,%)	0	1 (11%)
Death(n,%)	1 (33%)	0
Number of PE session *median(min-max)*	9 (3–12)	6 (5–18)
Time until Eculizumab initiation (days) *median(min-max)*	–	7(6–14)
Total time of eculizumab treatment (months) *median(min-max)*	–	21 (13–61)

†Eculizumab was started after at least five sessions of TPE
‡Patients who did not need maintenance hemodialysis
§Hemoglobin >11 gr/dl, LDH within normal limits, Haptoglobin within normal limits and platelet count >150 x10^3 µL
sCr: Serum Creatinine, e**GFR:** Estimated Glomerular filtration rate, **CKD:** Chronic kidney disease, **ESRD:** End-stage kidney disease

Eculizumab treatment withdrawal

When the drug has been used in our country, a total of 13 patients have been treated with Eculizumab. Eculizumab treatment was discontinued in nine patients. Currently, five patients have been receiving eculizumab therapy two weeks apart for at least three months (Figure 2).

Table 3 was designed for the laboratory evaluation of nine patients after discontinuation of eculizumab treatment. Case #1, a 23-year-old male, was followed up with a diagnosis of C3 glomerulopathy for six years. He has been using calcineurin inhibitor (cyclosporine) and mycophenolate mofetil for his treatment of primary glomerulonephritis. He was referred to our center with vision loss, high blood pressure, acute kidney injury on chronic kidney disease (Grade 3), and hematologic involvement. We established a CHFR3 gene mutation. Although his vision started to be normalized, his hematologic and renal conditions were resistant to TPE. We started eculizumab treatment, and hematologic parameters were normalized within one month. However, his kidney function tests continued to deteriorate, and we started to maintain hemodialysis one year after initiating eculizumab treatment. We considered discontinuation of eculizumab therapy, and he had stable hematologic parameters twelve months after the withdrawal of Eculizumab. Similar to case 1#, Cases 7# and 8# applied to our center with hematological involvement and acute kidney injury on chronic kidney disease while using calcineurin inhibitor (cyclosporine) due to the diagnosis of focal segmental glomerulosclerosis. Both patients needed hemodialysis at the time of drug-associated HUS diagnosis. After achieving hematologic remission, eculizumab treatment was discontinued at month six for case 7# and month 21 for case 8#. Both patients had stable hematologic parameters for more than one year.

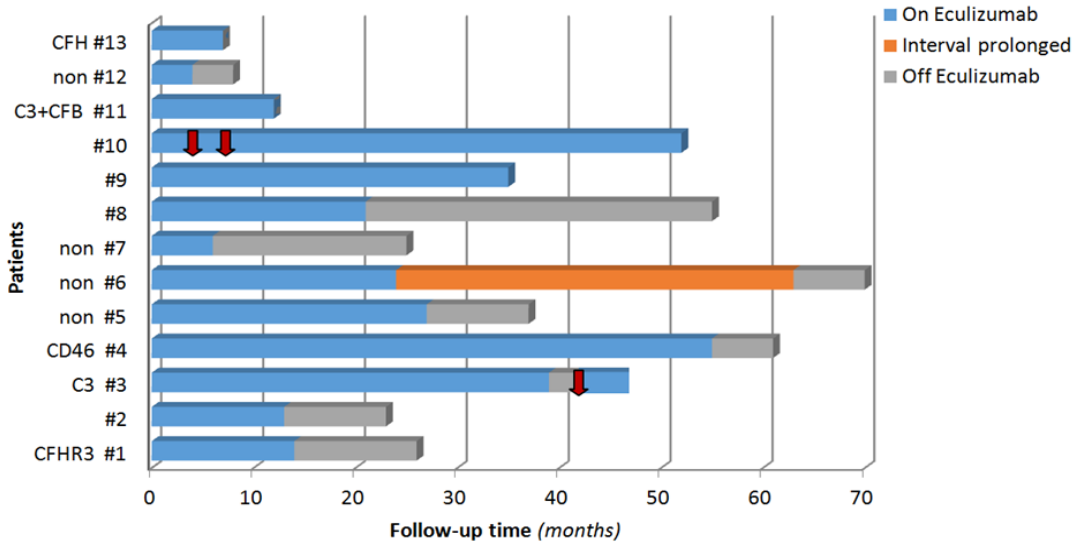

Figure 2. Follow-up and clinical course of 13 patients with aHUS during the follow-up. Red arrows indicate that disease relapse.

Table 3

Laboratory and clinical evaluation of patients after Eculizumab withdrawal

	Case 1#	Case 2#	Case 3#	Case 4#	Case 5#	Case 6#	Case 7#	Case 8#	Case12#
Gender	M	F	F	F	F	F	F	M	M
Age at diagnosis (year)	23	34	29	27	30	52	22	31	33
Possible Disease Cause	CNI? C3GP?	Pregnancy	Pregnancy	unknown	unknown	unknown	CNI	CNI	unknown
Mutation	CFHR3	-	C3	CD46	non	non	non	-	non
Hg first visit (g/dl)	11.3	9.4	14	14.3	12.9	12.3	12.4	9.9	9.8
Hg 6th month (gr/dl)	11.8	11	-	-	12.8	-	13.1	11.8	10.2
Hg last visit (gr/dl)	-	11.2	12.3	14.2	-	12.7	14	10.7	10.5
Plt first visit (10^3 xµl)	299	266	275	207	276	273	215	164	208
Plt 6th month (10^3 xµl)	255	263	-	-	266	-	255	142	125
Plt last visit (10^3 xµl)	-	276	233	177	-	268	263	139	118
LDH first visit (UI/L)	222	155	186	175	174	229	224	182	156
LDH6th month (UI/L)	186	179	-	-	178	-	198	236	158
LDH last visit (UI/L)	-	177	239	172	-	237	220	198	232
Kidney Function	ESRD	ESRD	Stable kidney function With stage 3B CKD	Stable kidney function With stage 2 CKD	Total kidney recovery	Stable kidney function With stage 4 CKD	ESRD	ESRD	ESRD
Eculizumab free Follow-up time *(months)*	12	10	3	6	10	7	19	34	4
Relapse	No	No	Yes	No	No	No	No	No	No

M: Male, **F:** Female, **Hg:** Hemoglobin, **CNI:** Calcineurin inhibitor, **C3GP:** C3 glomerulopathy, **CFHR3:** Complement factor H related protein 3, **MCP: Plt:** Platelet, **LDH:** Lactate dehydrogenase, **ESRD:** End-stage renal disease, **CKD:** Chronic kidney disease,

Case 2# and case 3# were diagnosed with aHUS after pregnancy. Case 2# was admitted to our center with elevated liver function test, hematologic and kidney involvement, and seizure. In terms of other organ involvement, global myocardial hypokinesia was detected on echocardiography in patient evaluation. After eculizumab treatment, all of the organ involvement was resolved except for kidney damage. One year after hematologic normalization, the patient still needed twice-weekly hemodialysis. Eculizumab treatment was discontinued because we detected that her kidney was atrophic. After eculizumab withdrawal, her need for hemodialysis did not increase. Case 3# presented with hematological and kidney involvement. Despite five sessions of TPE, the need for maintenance HD continued, and Eculizumab was started. The need for HD disappeared in the 4th month of treatment. Eculizumab treatment was discontinued after 36 months of therapy. However, the patient experienced disease relapse at the third month of Eculizumab discontinuation. Serum creatinine gradually increased, and platelet counts decreased. She also had low haptoglobin and increased serum LDH. We restarted eculizumab treatment with the initial treatment protocol. While hematologic remission was observed after the first dose of treatment, the serum creatinine level gradually decreased and reached baseline at the six doses of treatment.

Case 4# was a 27 year-old female admitted to the hospital with hematological, kidney, and CNS involvement. After the initiation of eculizumab CNS and hematological symptoms resolved. However, she needed maintenance HD for two months. After the disappearance of HD need, the kidney function was stabilized as stage 2 CKD. She was followed up for 52 months under Eculizumab treatment. Although she had CD46 mutation, she had stable kidney function and hematologic remission at the 6th-month clinical visit after discontinuation of Eculizumab. Case 5#, a 30-year-old female, was referred to our center with seizures, acute kidney injury, and hematologic involvement. We found no genetic abnormality in the complement pathway. She had been followed up for 27 months under eculizumab treatment with complete kidney recovery. She had stable kidney function and hematologic remission at the 10th-month clinical visit after discontinuation of Eculizumab. Case 6#, a 52-year-old female, was referred to our center with acute kidney injury and hematologic involvement. The patient started Eculizumab treatment, whose hematologic involvement did not improve, and progressive impairment of kidney function continued with TPE. After hematologic normalization, the need for hemodialysis continued for 23 months. After the need for hemodialysis disappeared, the eculizumab treatment interval was increased once monthly. Treatment was continued for 39 months and discontinued for seven months. She has been followed up as stage 4 CKD for more than three years. Case #12, a 33-year-old male, was referred to our center with acute kidney injury and hematologic involvement. The patient started Eculizumab treatment, whose hematologic involvement did not improve, and progressive impairment of kidney function continued with TPE. Although hematological remission was achieved, the kidney function was deteriorating, and he needed maintenance HD. Six months after hematological remission, Eculizumab was discontinued, and he has been followed up for four months without relapse.

DISCUSSION

The treatment of Eculizumab is a life-saving therapy, especially in TPE-dependent or TPE-resistant patients with aHUS. Although Eculizumab is recommended for lifelong use in patients with aHUS, withdrawal of the treatment may be decided case by case. Discontinuation of treatment could be evaluated after a certain period after hematologic remission has been achieved in conditions with stable kidney function or ESRD development. Eculizumab discontinuation may be rational, especially in patients with drug-associated HUS. Additionally, patients must be followed closely due to the risk of disease relapse.

aHUS is a life-threatening condition; therefore, TPE should be considered standard care until a firm diagnosis is made [7]. When thrombotic thrombocytopenic purpura (TTP), HUS, and secondary thrombotic microangiopathy syndromes have been ruled out, switching to eculizumab treatment is generally recommended [7, 9]. Observational studies of patients with aHUS showed that 56%–67% of adults progressed to ESRD within 1 and 3 years, respectively [10, 11]. Although one patient died in the third

session of TPE therapy, none of the patients, who achieved complete remission with TPE, developed ESRD. Infection was the leading condition of aHUS in patients with achieved remission with TPE alone, and it is known that autoantibody development against factor H caused by complement activation induced by pathogens could lead to the development of aHUS [12]. It can be speculated that removing these autoantibodies from circulation with TPE may be sufficient for achieving hematologic remission. On the other hand, patients with MCP, THBD, or C3 mutations (90%, 62%, and 43%) could be provided with complete remission with TPE alone, according to the literature [6, 7, 9]. In our study population, two patients had CHF mutations. One of these patients had diabetes-associated nephropathy and chronic osteomyelitis. He had two aHUS episodes that were triggered by infections. However, hematological remission and nephrological stabilization were achieved with TPE alone in both episodes. The patients are still being followed up for stage 3A CKD.

Eculizumab, a monoclonal antibody that blocks the cleavage of C5, is suggested as the first-line treatment for patients with aHUS [1, 3, 7]. Eculizumab inhibits the breakdown of complement factors C5 to C5a and C5b by C5 convertase, thus preventing the formation of the C5b-9 complex, which is known as the membrane attack complex [6]. Eculizumab treatment completely halts inappropriate systemic coagulation and inflammation by preventing excess C5a and C5b-9 formation [3, 6].

It has been shown, which is designed as a phase 2 clinical trial with 20 patients, that eculizumab treatment was associated with 80% suppression of TMA at 26 weeks of therapy [13]. One-year renal survival rates are variable with eculizumab treatment due to heterogeneous patient populations. Cao M. *et al*. showed that in which patients with pregnancy, infection, and drugs were excluded, eculizumab treatment achieved 80% complete kidney recovery in patients with aHUS [1]. In another study, which examined 29 patients with primary aHUS, a more than 25% improvement in serum creatinine was observed in 57% of the patients [4]. In our study, 56% of the total patients achieved more than 25% serum creatinine improvement during the one-year follow-up, and three of these patients had complete kidney recovery. Three of four patients who developed ESRD had the primary glomerular disease and used a calcineurin inhibitor. Most likely, secondary HUS was developed due to the use of a calcineurin inhibitor. It is important to note that one of these patients had C3 glomerulopathy, and we detected CFHR3 mutations. It is well known that in both C3 glomerulopathy and aHUS, the complement pathway plays a primary role [14, 15], and in this patient, aHUS likely developed due to complement gene mutation rather than the use of calcineurin inhibitor. In this patient, it is not possible to differentiate the diagnosis of aHUS from drug-associated HUS completely. Although eculizumab treatment can result in a rapid improvement of renal function in patients with drug-induced TMA in some studies, there were no definite guidelines for the treatment of drug-induced TMA [7, 16]. According to our results, the treatment of Eculizumab is necessary to ensure hematologic remission in patients who do not achieve hematologic remission with TPE and whose kidney function is impaired. After hematologic remission is achieved, continued treatment with Eculizumab may be decided according to the amelioration of kidney function, and eculizumab treatment discontinuation may be considered in case of ESRD development.

Eculizumab treatment has dramatically improved the outcomes and prognosis of aHUS. However, the optimal duration of therapy is still unknown because it is difficult to predict the time between relapses. There is no consensus regarding the time of eculizumab cessation. However, current recommendations emphasize case-by-case analysis in patients who have received the treatment for a minimum of 6–12 months [5, 9]. On the other hand, underlying genetic mutations in complement genes seem to have a higher risk of relapse after eculizumab cessation, and the risk for relapse was 72% for CFH variants and 50% for MCP variants in the literature; the frequency of disease relapse was reported to be between 20% and 30% [17-19]. In general, six months after the patients achieved hematological remission, we stopped eculizumab treatment if renal functions remained stable or in case of no renal survival expectancy. We discontinued eculizumab treatment in nine patients, and one of them experienced disease relapse within three months. The patient, who had a C3 gene mutation, was experienced disease relapse in the early course of Eculizumab discontinuation. It is known that C3 gene mutation is associated with disease relapse after treatment discontinuation and

the development of ESRD [20]. On the other hand, disease relapse did not occur in six months in one of our patients with CD46 mutation. However, it is early to mention that eculizumab cessation is perfectly safe in patients with CD46 gene mutations. The relapse-free follow-up time was short. The relapse time in the literature is between 1–12 months after discontinuation of treatment [21]. Additionally, it is known that CD46 mutation is characterized by frequent relapse [21, 22]. Therefore, case 4# should be followed closely for relapse. On the other hand, in four of eight patients, we discontinued the treatment because of ESRD development. The potentially triggering cause of the development of HUS in three of them was the use of CNI. Neither of these patients developed disease relapse without eculizumab treatment for more than two years. This supports that Eculizumab may be discontinued after achieving hematological remission in drug-associated HUS cases. In addition, the contribution of eculizumab treatment to renal survival seems to be limited in these patients.

This study had some limitations due to the very rare nature of the disease and observational design. First, the number of patients was low. Second, the association between treatment and outcomes cannot be interpreted as a cause-and-effect relationship because it is not a randomized clinical study. However, it is impossible to test Eculizumab in large randomized clinical trials because aHUS is a rare disease that could be fatal when the treatment is not immediately started. Third, we did not measure antibodies against the complement pathway. If we had measured antibodies, we could evaluate the effect of antibodies on TPE response.

CONCLUSION

Eculizumab treatment is a life-saving therapy that modifies hematological and renal outcomes in patients with aHUS. Treatment discontinuation may be considered at least six months after hematologic remission in patients with stable renal function or no expectancy for renal survival. However, patients should be monitored regularly due to the risk of disease relapse. Moreover, drug-associated HUS cases seem to tend not to develop disease relapse in the long term.

Introducere. *Scopul studiului a fost de a evalua efectul terapeutic al plasmaferezei (TPE) și eculizumab asupra supraviețuirii pacienților cu sindrom hemolitic-uremic atipic (aHUS).*

Metode. *A fost realizat un studiu observațional retrospectiv pe 18 pacienți.*

Rezultate. *Vârsta medie a fost de 30 de ani (22–66 ani). 4 din 18 pacienți au avut remisie hematologică numai după terapia cu TPE. 1 pacient a decedat după 3 sesiuni de TPE. Eculizumab a fost folosit la 13 pacienți și nu s-a observat niciun deces. La un an după tratament, 2 din 3 pacienți tratați cu TPE au avut o îmbunătățire a funcției renale (grupul TPE) și 5 din 9 pacienți cu eculizumab au avut o îmbunătățire. Eculizumab a fost oprit la 9 pacienți. 1 pacient cu o mutație a genei C3 a avut o recădere. Niciun pacient care a dezvoltat aHUS datorită terapiei nu a dezvoltat recădere după oprirea tratamentului cu Eculizumab.*

Concluzii. *Terapia cu Eculizumab salvează viața în aHUS. Oprirea tratamentului poate fi luată în considerare la cel puțin 6 luni după remisia hematologică. Pacienții cu aHUS datorat terapiei nu au risc de recădere pe termen lung.*

Correspondence to: Hasan H. Yeter, M.D, Department of Nephrology Dialysis and Transplantation, Gazi University Faculty of Medicine, TR-06560, Ankara, TURKEY
E-mail: hasanyeter@hotmail.com, Phone: +905542397449

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