Received: 3 July 2020 | Revised: 15 October 2020 | Accepted: 16 October 2020

DOI: 10.1111/petr.13914

ORIGINAL ARTICLE

WILEY

Transplantation in pediatric aHUS within the era of eculizumab therapy

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Abstract

aHUS is caused by the over-activation and dysregulation of the alternative complement pathway. Data regarding outcomes of pediatric aHUS patients after kidney transplantation are still very scarce. Accordingly, the aim of this study was to describe the clinical findings and outcomes of pediatric aHUS patients after renal transplantation. This is a retrospective, multicenter study including 12 patients from the national registry system. Among the 12 patients, eight had received prophylactic eculizumab and none of those patients (except one) had experienced aHUS recurrence during a median follow-up period of 58.5 (min-max, 4-94) months. Although eculizumab had been started on the day before transplantation in one of them, aHUS recurrence occurred during the transplantation procedure. Eculizumab had been stopped in only one patient who had no complement gene mutation after 35 months of therapy, and recurrence had not been observed during the 19 months of follow-up. In three patients, maintenance doses had been spaced out without any recurrence. One additional patient with anti-CFH antibody received only two doses of eculizumab for transplantation and had been followed for 46 months without aHUS recurrence.

Abbreviations: aHUS, atypical hemolytic uremic syndrome; AMR, antibody-mediated rejection; BKV, BK virus; CFH, complement factor H; CMV, cytomegalovirus; ESRD, end-stage renal disease; FFP, fresh frozen plasma; GFR, glomerular filtration rate; hom, homozygous; IVIG, intravenous immunoglobulin; KDIGO, kidney disease: improving global outcomes; LDH, lactate dehydrogenase; MLPA, multiplex ligation-dependent probe amplification; MMF, mycophenolate mofetil; MRC, manufacturer's recommendation; TMA, thrombotic microangiopathy.

The remaining three patients had not received anti-C5 therapy and none of those patients experienced aHUS recurrence during a median follow-up period of 21 (min-max, 9-42) months. Prophylactic eculizumab is a safe and effective treatment for the prevention of aHUS recurrence. Eculizumab interval prolongation, discontinuation, and transplantation without eculizumab prophylaxis can be tried in selected patients with close follow-up.

KEYWORDS
aHUS, children, eculizumab, transplantation

1 | INTRODUCTION

aHUS is a rare and severe disorder characterized by TMA which causes anemia, thrombocytopenia, and acute renal injury. The disease is caused by over-activation and dysregulation of the alternative complement pathway, and an underlying genetic defect has been detected in 50%-60% of the patients.[1,2] Renal transplantation has long been considered as a contraindication in patients with aHUS—due to the increased risk of recurrence-related graft loss.[3] Over the last decade, different options for renal transplantation in aHUS patients have emerged—including combined liver and kidney transplantation or isolated kidney transplantation with prophylactic plasma exchange or eculizumab therapy.[4,5]

Eculizumab is a fully humanized monoclonal antibody that binds to the terminal complement protein C5—preventing membrane attack complex formation. It is the only approved treatment for patients with aHUS and has been demonstrated to inhibit the complement-mediated TMA in patients with both native and transplanted kidneys.[6,7] Although the efficacy of eculizumab in transplanted patients has been increasingly reported, detailed data regarding long-term outcomes (especially in the pediatric age group) are still very scarce. Accordingly, the aim of this study was to describe the clinical findings and outcomes of 12 pediatric aHUS patients after renal transplantation.

2 | PATIENTS AND METHODS

This is a retrospective, multicenter study describing the outcomes of pediatric aHUS patients after renal transplantation. The study included all transplanted pediatric aHUS patients (n = 12) from the national registry system which was established in 2013 (Turkish aHUS Registry, ahusnet.org).[8] Patients with an onset of aHUS at age <18 years and who had been transplanted between January 2001 and December 2018 were recruited. Diagnosis of aHUS was based on the presence of Coombs-negative hemolytic anemia, thrombocytopenia, and acute renal injury. STEC HUS was excluded with specific cultures of stool specimens and PCR method. Patients who had reduced ADAMTS13 activity (ie, ≤ 5%), metabolic, autoimmune, concomitant diseases, or drug-related HUS were excluded. Demographic, clinical, and laboratory data were obtained from the registry. Additional information regarding their follow-up was obtained from the medical records. The study covered detailed data concerning the followings: transplantation type, genetic analysis, rejection episodes, immunosuppression regimen, infections and causes for graft dysfunction.

Genetic analyses were performed at the Hacettepe University Nephrogenetics Laboratory. DNA was extracted from the peripheral blood using a commercial kit according to the MRC (Invitrogen PureLink Genomic DNA Mini Kit). All patients were run with a gene panel containing the relevant complement system genes (ie, complement *C3*, *CFH*, *CFB*, *CFI*, *CD46 (MCP)*, *CFHR1,2,3,4,5*) as well as other relevant genes (ie, *THBD*, *PLG*, and *DGKE*) via next-generation sequencing method using Ion S5 System® (Thermo Fisher Scientific) according to the MRC. Data were analyzed using Ingenuity® Variant Analysis™ software (Qiagen). All mutations were confirmed by direct sequencing using BigDye v3.1 chemistry and ABI3130 Genetic Analyzer (Applied Biosystems). Variations that were identified through panel sequencing were confirmed by Sanger sequencing. *CFHR1-3* deletion was also evaluated via MLPA analysis using a commercial kit according to the MRC(MRC Holland™).

The study was approved by the ethics committee of Hacettepe University (FON10/03-22), and it conforms to recognized standards of Declaration of Helsinki. Written informed consent was obtained from the parents of all patients.

3 | RESULTS

Among the 12 patients, eight had received prophylactic eculizumab to prevent post-transplant aHUS recurrence. One additional patient with CFH antibody received only two doses of eculizumab for transplantation. The remaining three patients had not used anti C5 therapy.

3.1 | Findings of patients who had been given prophylactic eculizumab

Eight patients (3 M, 5 F; mean age 13.5 ± 6.0 years) had been treated with eculizumab for recurrence prophylaxis in the long term (Table 1,

Patients 1-8). Median age at aHUS onset and ESRD onset was 39 (min-max, 6-101) and 59 (min-max, 7-101) months, respectively. During aHUS onset, one patient had received FFP infusions, two had plasmapheresis, two had both plasmapheresis and eculizumab and three of them received no specific therapy. One of the patients (Patient 2, with *CFHR5* mutation) previously received a renal transplant at the age of 9.5 years which had been lost from aHUS recurrence in the first year of follow-up.

The median age at the time of transplantation was 87.5 (min-max, 52-216) months. All patients except two received kidney from a deceased donor (one had en-bloc kidney transplantation). In five patients, eculizumab had been started immediately before the transplantation; with the second dose given after 24 hours, the third dose in the first week and, thereafter, the maintanence every 2 weeks. One of the patients had received eculizumab at day 0, in the first week and then every 2 weeks. The other one (Patient 2) had received four doses of eculizumab starting 2 months prior to transplantation. Although eculizumab had been started on the day before transplantation in Patient 8, aHUS recurrence occurred during the transplantation (with anemia, thrombocytopenia, increased LDH and decreased haptoglobulin levels). As such, she had received the second dose after the transplantation and had been followed with weekly eculizumab for 3 weeks and then every 2 weeks. Plasma exchange (six times) had additionally been performed in two patients (Patients 2 and 8) before the transplantation. All patients received meningococcal vaccination prior to eculizumab therapy. Continuous antibiotic prophylaxis had been given in Patient 1. The rest of the patients had received only 2-4 weeks of antibiotic prophylaxis after meningococcal vaccination.

Seven patients received induction therapy either with antithymocyte globulin (n = 5) or basiliximab (n = 2). Six patients received standard triple-drug immunosuppression with prednisone, tacrolimus, and MMF.

None of the patients (except Patient 8, during the transplantation procedure) had experienced aHUS recurrence during a median follow-up period of 58.5 (min-max, 4-94) months. Eculizumab had been continued in all patients except one. Eculizumab was stopped in Patient 6, who had not have complement gene mutation, after 35 months of therapy. Recurrence had not been observed in that patient during the 19 months of follow-up. In three patients, maintenance doses had been spaced out to every 3 weeks without any recurrence.

Eculizumab intervals had been prolonged in Patient 1 twice. Between the post-transplant 3.5-7 months, eculizumab had been given every 3 weeks. In that time period, proteinuria (max. 24 mg/m^2/hr) and mild elevations in LDH levels had developed and she needed triple antihypertensive therapy. Kidney biopsy was not compatible with disease recurrence or rejection. After eculizumab had been switched to biweekly intervals; LDH normalized, proteinuria disappeared and hypertension improved. On the post-transplant 18th month, eculizumab interval had been prolonged again to every 3 weeks, and on the 24th month to every 4 weeks. On the 32th month, creatinine increased (0.8 mg/dL), GFR decreased (60 mL/min/1.73 m^2) and mild proteinuria had developed. Since the biopsy had shown acute cellular rejection, steroid therapy had been given and her creatinine returned to 0.6 mg/dL. One month after the biopsy, proteinuria (max 42 mg/m^2/hr) and LDH levels increased and the patient again returned to tripple antihypertensive therapy. Eculizumab was switched to biweekly intervals on the post-transplant 35th month after which proteinuria had disappeared, LDH levels normalized and hypertension improved. Since then she had received biweekly eculizumab therapy; and on her last visit, her creatinine was 0.6 mg/dL, proteinuria was 6.8 mg/m^2/hr, had normal LDH level and she was on single antihypertensive therapy.

Patient 5 had developed severe mixed type rejection after 5 years of transplantation due to non-compliance to the treatment. Despite corticosteroid treatment, plasmapheresis, and intravenous immunoglobulin (IVIG); partial response was observed (final creatinine, 5.1 mg/dL). Patient 7 had developed acute humoral rejection on the 10th month, had been treated with corticosteroids, plasmapheresis, IVIG, and rituximab had partially responded and had recurrent rejection episodes (final creatinine, 2.3 mg/dL).

Four patients had suffered from ≥5 infections requiring hospitalization, that is, acute gastroenteritis, urinary tract infection, upper and lower respiratory infections. Two patients had viral infections including CMV and BKV. In the last visit, median creatinine and GFR levels of the patients were 0.87 (min-max, 0.6-5.1) mg/dL and 70 (min-max, 12.5-114) mL/min/1.73 m^2, respectively.

Other than the aforementioned eight patients, Patient 12—who had anti-CFH antibody with hom *CFHR1-3* deletion—received only two doses of eculizumab (before the transplantation and on the 1st week) (Table 1). His anti-CFH antibody level was unknown at the time of transplantation. He had also been given corticosteroid and MMF 20 days prior to transplantation; seven courses of plasma exchange + IVIG and rituximab. He received basiliximab and standard triple-drug immunosuppression with prednisone, tacrolimus, and MMF. He had been followed for 46 months after the transplantation without aHUS recurrence (last creatinine, 0.4 mg/dL).

3.2 | Findings of patients who had been transplanted without prophylactic eculizumab

Three patients (mean age 13.8 ± 4.5 years) in our cohort had not received prophylactic eculizumab therapy (Table 1, Patients 9-11). Median age at aHUS and ESRD onset were 56 (min-max, 10-69) and 84 (min-max, 56-206) months, respectively. During aHUS onset, plasma exchange had been done in two patients and one had received both FFP infusions and eculizumab without response. Two patients had hom *CFHR1-3* deletion and one had no mutations in the studied genes.

The median age at the time of transplantation was 98 (min-max, 88-207) months. All patients had received kidneys from deceased donors (one had en-bloc kidney transplantation). Induction therapy either with antithymocyte globulin (in one patient) or basiliximab and

TABLE 1 Demographic and clinical findings of the patients

Patients	1	2	3	4	5	6
Gender	F	F	F	M	F	M
Current age (years)	14.5	20	7	21	13.5	9
Age (months) at						
aHUS onset	6	101	36	64	63	36
ESRD	7	101	42	68	64	36
Transplantation	82	216	68	184	93	52
Complement genetics (NCBI Accession #)	CFB (NM_001710.6) c.1050G > T (p.Lys350Asn) (het) CFHR1-3 deletion (het)	CFHR5 (NM_030787.4) c.1504A > T, (p. Arg502*) (het)	No mutation	No mutation	No mutation	No mutation
Anti-CFH antibody	Negative	Not available	Not available	Negative	Not available	Not available
N of rejections	1	0	0	0	1	0
N of infections requiring hospitalization	13	0	5	1	5	2
Viral infection	CMV	0	0	CMV, BKV	0	0
Graft loss	None	None	None	None	None	None
Last creatinine (mg/dL)	0.62	0.6	0.64	1.5	5.1	1.03
Last GFR (mL/min/1.73 m^2)	114	99	77.4	43	12.5	68
Follow-up period after transplantation (months)	94	18	27	72	72	54
Eculizumab	Continuing Biweekly	Continuing Biweekly	Continuing Every 3 wk (For 15 mo)	Continuing Biweekly	Continuing Every 3 wk (For 6 mo)	Stopped after 35 mo

Abbreviations: M:male, F: female, NCBI: national center for biotechnology information, CFB: complement factor B, CFHR: CFH related, h et: heterozygous; N: number

standard triple-drug immunosuppression with prednisone, tacrolimus, and MMF had been given to all the three patients.

One of the patients developed acute cellular rejection. Patient 10 developed acute humoral rejection on the 3rd month and had been treated with corticosteroids, plasmapheresis, IVIG, and rituximab (with a partial response). None of the patients had >2 infections requiring hospitalization. One patient had CMV and the other had BKV infection.

None of the patients had experienced aHUS recurrence during a follow-up period of 21 (min-max, 9-42) months. In the last visit, median creatinine and GFR levels were 1 (min-max, 0.28-1.2) mg/dL and 96 (min-max, 57-124) mL/min/1.73 m^2, respectively.

4 | DISCUSSION

In this report, we present a reasonably large group of renal transplanted pediatric aHUS patients (n = 12) with a relatively long-term follow-up. Although we do not have a national guideline for the management of aHUS patients in our country, majority of our patients had been treated with prophylactic and long-term eculizumab therapy. Eculizumab was stopped in one patient and interval prolongation had been done in three patients during the follow-up. Three patients had not received prophylactic therapy. Apart from recurrence during the transplantation procedure (n = 1), none of our patients had suffered apparent aHUS recurrence and/or graft loss as a consequence.

Post-transplant aHUS recurrence occurs in 60% of the patients and is associated with a high rate of graft failure within 5 years. Majority of the recurrences occur within the 1st year of transplantation. Presence of complement mutations is a significant, independent risk factor for recurrence. The risk is higher in patients with *CFH*, *C3*, or *CFB* mutations and moderate in the presence of *CFI* mutation. On the contrary, the risk is low in patients with isolated *CD46 (MCP)* mutation and in the absence of complement mutation or if the antibody titer is low at the time of transplantation in cases with

7	8	9	10	11	12
M	F	M	M	M	M
18	5	19	12	10.5	14.5
42	24	56	10	69	50
96	54	56	84	206	51
153	59	88	98	207	135
CFH (NM_000186.4) c.1839delC (p. Phe614fs*51) (het) CD46 (NM_002389.4) c.668G > A (p.Cys223Tyr) (het)	CFHR1-3 deletion (hom)	No mutation	CFHR1-3 deletion (hom)	CFHR1-3 deletion (hom)	CFHR1-3 deletion (hom)
Not available	Negative	Not available	Not available	Not available	Positive
3	0	1	1	0	0
5	1	1	1	0	1
0	0	BKV	CMV	0	BKV
None	None	None	None	None	None
2.3	0.72	0.28	1.2	1	0.4
35	72	124	57	96	125
63	4	21	42	9	46
Continuing Every 3 wk (For 4 mo)	Continuing Biweekly	None	None	None	Received only 2 doses

anti-CFH antibody-associated aHUS.[3,9,10] In 2009, the safety and effectiveness of eculizumab treatment for post-transplant aHUS recurrence were reported for the first time.[11] To evaluate eculizumab in aHUS patients with native (n = 74) and transplanted (n = 26) kidneys, Legendre et al[12] performed a post hoc analysis of four prospective clinical trials. Compared with patients with native kidneys, those with transplanted kidneys required longer time to reach complete TMA response and hematologic normalization. After 26 weeks, mean eGFR increased from baseline to 61 and 37 mL/min/1.73 m^2 in native and transplanted kidney patients, respectively. The first case series of aHUS patients who had been treated with prophylactic eculizumab was presented by Zuber et al[13] in 2012. Recently, the KDIGO conference group recommended eculizumab prophylaxis in patients with high recurrence risk including patients with pathogenic variants and previous early recurrence. In patients with moderate recurrence risk, the decision to use eculizumab prophylaxis is left to the treating clinician.[14] In 2019, Siedlecki et al[15] compared aHUS patients who received eculizumab before and during transplantation with a group treated post-transplantationally. Graft function was found to be significantly better in the first group. Moreover, Zuber et al[16] showed that the use of prophylactic eculizumab was independently associated with a reduced risk of recurrence and a significantly longer graft survival in a large French registry and suggested its use in patients with high and moderate risk of post-transplant recurrence. Likewise, majority of our patients (n = 8) had received prophylactic eculizumab therapy. One of our patients had disease recurrence during the transplantation procedure, although she had received a dose of eculizumab on the day before the surgery. The disease had been controlled with successive doses of eculizumab therapy. None of the remaining seven patients (five had ≥54 months of follow-up) had apparent aHUS recurrence and severe side effects. Interestingly, two of our patients had experienced AMR under eculizumab therapy, with partial response to antirejection therapies and decreased GFR levels in the last controls. In 2017, Levi et al[17] presented 12 adult renal transplanted aHUS patients—who were treated with eculizumab and followed for 24 months among whom

they encountered three AMRs. Similar to our findings, they suggested that eculizumab might not fully block the AMR pathogenesis.

Although eculizumab is safe and well-tolerated, its potential side effects need to be taken into consideration. Susceptibility to infections—especially meningococcal disease—is the most important risk factor; however, it is reported to be uncommon. None of our patients had experienced meningococcal infection during the follow-up. The high cost of eculizumab is also a major problem; therefore, some countries tried to develop suggestions for limited use of eculizumab therapy. In 2017, Duineveld et al[18] from Netherlands published a prospective study including transplanted adult aHUS patients without prophylactic eculizumab therapy. Their protocol included preferential use of living kidney donors, low dose calcineurin inhibitor therapy, strict blood pressure control and drugs that should limit endothelial injury. They included 17 patients with high or moderate risk of recurrence whereby only one patient developed recurrence during a mean follow-up of 25 months. They suggested that kidney transplantation without prophylaxis is feasible—especially if living donor kidneys were used. The same group also suggested eculizumab withdrawal in patients with aHUS in remission after the first episode in native kidneys, and reduction of eculizumab dose in patients who need long-term therapy especially in adult patients. However, they still recommend prophylactic eculizumab therapy particularly in children, with previous graft loss due to recurrence of aHUS and in some other high-risk patients.[19] In our study, three patients had not received prophylactic eculizumab, two of them had hom *CFHR1-3* deletion, and one had no mutation in the complement genes studied. All received kidney from a deceased donor. None of them had suffered disease recurrence during the follow-up (median, 21 months).

The possibility of discontinuing eculizumab in aHUS patients with native kidneys may depend on the genetic background. International consensus guidelines for children and KDIGO suggested that discontinuation is not currently recommended in transplant patients especially with a previous graft loss.[9,14] Wijnsma et al[19] suggested that continued eculizumab treatment is not needed in all adult patients after the kidney transplantation. Very few data exist regarding the discontinuation of prophylactic eculizumab therapy in the literature.[13,16,17,20,21] Some of these patients develop recurrence after discontinuation while some other do well without recurrence. Eculizumab therapy was stopped in one of our patients and he had been followed up without recurrence for about 1.5 years. This patient had no mutation in the complement genes. There is no suggestion about safety of tapering eculizumab therapy after transplantation. The high cost of treatment lead physicians try to space out maintenance doses. Although patients who were successfully treated with eculizumab at extended intervals have been described,[13] some developed aHUS recurrence after the interval prolongation.[13,22] In three of our patients (two had no and one had combined *CFH/CD46 (MCP)* mutations), we could prolong the intervals; whereas in one of our patients with *CFB* mutation, we had two unsuccessful attempts.

Limitations of this study would be its retrospective nature, unavailability of data for anti-CFH antibody screening in some patients and CH50 levels during the follow-up.

In conclusion, prophylactic eculizumab is a safe and effective treatment for the prevention of aHUS recurrence in the long-term follow-up of pediatric patients. Eculizumab interval prolongation and discontinuation can be tried in selected patients; however, they should be cautiously followed for subclinical findings of aHUS recurrence. Patients with low risk of recurrence could be transplanted without eculizumab prophylaxis only if close and careful monitorization is possible.

CONFLICTS OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

ZB Özçakar, F Ozaltin, B Gülhan, O Söylemezoğlu: Primary responsibility for protocol development, patient enrollment, outcome assessment and writing the manuscript; F Ozaltin: Responsibility for genetic analysis; E Çomak, G Parmaksız, E Baskın, R Topaloglu, B Kasap Demir, N Canpolat, Z Yuruk Yıldırım, B Demircioğlu Kılıç, S Yüksel: Participation in the patient screening and enrollment; All authors: Contribution in revising the manuscript, read and approved the final version.

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How to cite this article: Özçakar ZB, Ozaltin F, Gülhan B, et al. Transplantation in pediatric aHUS within the era of eculizumab therapy. *Pediatr Transplant*. 2021;25:e13914. https://doi.org/10.1111/petr.13914