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ORIGINAL ARTICLE

Outcome of atypical haemolytic uraemic syndrome relapse after eculizumab withdrawal

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ABSTRACT

Background. The introduction of eculizumab has significantly improved the outcome of patients with atypical haemolytic uraemic syndrome (aHUS). Because of the risk of relapse after discontinuation, eculizumab was proposed as life-long therapy. However, data on the outcome of relapse are limited. In the Netherlands, patients with aHUS are treated with a restrictive eculizumab regime and are included in a national observational study (CUREiHUS, Dutch Trial Register NTR5988/NL5833).

Methods. For this interim safety analysis, we evaluated the outcome of all adult patients with a suspected relapse, defined as the need to intensify eculizumab after tapering or withdrawal of therapy.

Results. We describe 11 patients who received renewed eculizumab therapy because of suspected relapse. In three patients with aHUS in native kidneys, estimated glomerular filtration rate (eGFR) returned to baseline value and remained stable without overt proteinuria after follow-up. Six out of eight transplanted patients responded to eculizumab therapy with improvement in eGFR. After a median follow-up of 24.6 months, a reduction of eGFR $\geq$25% was observed in three of these transplanted patients, which was attributed to the aHUS relapse in only one patient.

Conclusions. This interim analysis suggests that re-treatment with eculizumab after relapse is safe and feasible. We will continue to use our restrictive treatment strategy.

Keywords: atypical haemolytic uraemic syndrome, eculizumab, kidney transplantation, relapse, restrictive therapy

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INTRODUCTION

The introduction of eculizumab, a complement C5 blocker, changed the prospects of patients with atypical haemolytic uraemic syndrome (aHUS). Treatment resulted in resolution of thrombotic microangiopathy activity (TMA) and a significant improvement in renal function in the majority of patients [1]. Because of the expected risk of relapse after discontinuation, eculizumab was proposed as life-long therapy. Based on limited, and likely biased, data, the relapse rate is estimated at 20–67% [2]. Although rapid re-introduction of eculizumab after relapse often results in recovery of renal function, there is concern that a relapse will lead to chronic kidney injury. Therefore, many physicians and patients prefer to continue eculizumab therapy indefinitely, despite the costs of eculizumab and the risk of meningococcal infections. Since 2016, treatment of patients with aHUS in the Netherlands follows national consensus guidelines [2]. This guideline advocates eculizumab tapering and/or withdrawal after 3 months of therapy. We here report an interim safety analysis focusing on the course of kidney injury markers in patients who developed a suspected relapse after eculizumab withdrawal.

MATERIALS AND METHODS

In 2016, eculizumab was approved for treatment of aHUS, according to a restrictive treatment protocol developed by University Medical Centers in the Netherlands. The rationale and the details of the protocol have been described [2]. In brief, adult patients who present with TMA are initially treated with plasma exchange for a maximum period of 5 days, while the underlying cause is analysed. In patients with a suspected diagnosis of aHUS who do not respond to plasma exchange, induction therapy with eculizumab is started and continued for 3 months according to the standard dosing regimen [3]. After 3 months, when the patient's renal function has normalized/stabilized, eculizumab is tapered or withdrawn. Treatment is individualized based on patient characteristics, kidney function and patient and physician preferences. Possible treatment strategies have been presented [2]. Furthermore, recipients of a kidney transplantation are not routinely treated with prophylactic eculizumab. The safety and cost-efficacy of this restrictive treatment protocol are monitored in a national, prospective, observational study (CUREiHUS study, NTR5988/NL5833) [2, 4]. The CUREiHUS study started in January 2016, with planned reporting of the final outcome in 2021. An interim analysis was performed in 2019. Relapse rate was considered acceptable at 41% [5].

All patients who were diagnosed with aHUS after 1 January 2016 and who started eculizumab were asked informed consent to be included in the CUREiHUS study. Furthermore, aHUS patients who were already using eculizumab on 1 January 2016 were also asked to participate in the study. The CUREiHUS study was approved by the Medical Ethical Committee (NL52817.091.15) and all patients have given written informed consent.

Analysis of relapses

For this interim safety analysis, we identified all adult patients who participated in the CUREiHUS study, and who had a suspected relapse after tapering (≥2-week interval between eculizumab administration) or withdrawal of eculizumab. A suspected relapse was defined as the need for intensivation of eculizumab therapy (either re-start of therapy or shortening of the dosing interval). The decision to intensify therapy was made by the treating physician. We retrieved relevant clinical and laboratory information from the patient charts. We defined TMA by the presence of at least two of the following three criteria: thrombocytopenia (platelet count $<150 \times 10^9$/L), lactate dehydrogenase greater than the upper limit of normal (>250 U/L) and low haptoglobin (<0.3 mg/L). Kidney biopsies were reviewed for signs of acute and/or chronic TMA and other aetiologies of kidney injury. Histological evidence of 'active' TMA was defined as the presence of glomerular capillary, arterial and/or arteriolar thrombosis [6]. Patients were classified as having a definite clinical relapse in case of any kidney graft dysfunction with laboratory evidence of TMA and/or histological evidence of 'active' TMA. Baseline kidney function was defined as the last stable estimated glomerular filtration rate (eGFR) before the suspected relapse. We calculated the time between the first increase in serum creatinine (≥20%) from baseline and the re-introduction or intensivation of eculizumab therapy.

RESULTS

We identified 11 patients who received renewed therapy with eculizumab. Clinical characteristics are shown in Table 1. Eight patients were recipient of a kidney transplant. Seven of them had been transplanted without eculizumab prophylaxis and had received eculizumab therapy because of a posttransplant aHUS recurrence. One patient (Case 5) was transplanted while on eculizumab therapy. At the time of the suspected relapse, all 11 patients had evidence of deteriorating kidney function (median increase in serum creatine of 50%, range 24–98%) (Table 2). The rate of eGFR loss varied among the patients. A diagnosis of definite recurrent aHUS was made in five patients (Table 2) based on laboratory evidence of TMA and/or histological evidence of 'active' TMA. In two patients without laboratory evidence of TMA, the kidney biopsy showed findings compatible with chronic TMA. We retrospectively analysed the eGFR course in all patients. The median time between the first observation of a 20% increase in serum creatinine (compared with baseline) and the start of eculizumab was 12 days (range 0–199) and was 0 day in patients with aHUS in native kidneys versus 43 days (range 0–199) in transplanted patients.

We evaluated eGFR and proteinuria as markers of kidney injury (Table 2). Kidney function returned to baseline values in all three patients with aHUS in native kidneys and has remained stable without overt proteinuria during follow-up. Outcome was less favourable in kidney transplant patients (Table 2). Detailed case descriptions are given in the Supplementary Appendix. In two patients, there was no response to renewed eculizumab therapy. Both patients had no laboratory evidence of TMA and a kidney biopsy was not performed. In six patients, eGFR improved with eculizumab therapy and initially returned to baseline in all but one (Table 2). After prolonged follow-up (median 24.6 months; range 4.1–39.5 months), we observed a reduction of eGFR ≥25% compared with baseline in three patients. Based on the clinical and histopathological data, we attributed the persistent kidney injury to the aHUS relapse in one patient, possibly caused by delayed re-introduction of eculizumab. In the other two patients, chronic kidney injury was, respectively, attributed to chronic antibody-mediated rejection and CNI toxicity. Of note, these two patients had persistent overt proteinuria after treatment with eculizumab for the first aHUS episode.

Table 1. Clinical characteristics of the patients with a suspected relapse of aHUS

Case	Age at relapse (years)/ gender	Previous history of KTx	Recent KTx / prophylactic ECU	Kidney donor	Genetic variant	KDIGO risk stratification for recurrence after Tx	IS regime	Anti-rejection therapy	sCr at BL[a] (μmol/L)	UPCR at BL (g/10 mmol creatinine)
1	34/M	NA	No	NA	C3: c.481C>T (p.Arg161Trp)	NA	NA	NA	92	0.05
2	27/F	NA	No	NA	CFH: c.2572T>A (p.Trp858Arg)	NA	NA	NA	150	0.19
3	26/M	NA	No	NA	Duplication/deletion CFRH operon[b]	NA	NA	NA	142	1.60
4	42/M	Yes, graft loss (1 year), aHUS	Yes/no	DCD	C3: C.193A>C (p.Lys65Gln)	High	TAC, MMF, pred	No	162	0.14
5	38/F	No	Yes/Yes	LU	C3: c.1774 C>T (p.Arg592Trp)	High	TAC, MMF, pred	No	134	0.50
6	41/F	No	Yes/No	DCD	Negative[c]	Moderate	TAC, MMF, pred	Yes[d]	156	1.91
7	50/F	Yes, graft loss (19 years) aHUS	Yes/No	DCD	C3: c.26T>C (p.Leu9Pro) CFH: 388 G>A (p.Asp130Asn)	Moderate	TAC, MMF, pred	No	228	0.05
8	47/F	Yes, graft loss (6 weeks), aHUS	Yes/No	DBD	CFH: c.1520-1G>A	High	TAC, MMF, pred	Yes[e]	150	0
9	32/F	Yes, graft loss (1 year), aHUS	Yes/No	DCD	CFH-CRHR1 hybrid gene	High	TAC, MMF, pred	No	138	0.10
10	29/F	No	Yes/No	LR	CFH: c.1548T>A (p.Asn516Lys)	Moderate	TAC, MMF, pred	Yes[f]	197	1.20
11	42/F	Yes, graft loss (3 years), aHUS	Yes/No	LU	CFH: c.2034G>T (p.Trp678Cys)	High	TAC, belatacept pred	Yes[f]	128	0.10

[a]Baseline kidney function was defined as the last stable eGFR/serum creatinine before the suspected relapse.
[b]Heterozygous duplication for CFH exon 22 to CFHR3 exon 3 and heterozygous deletion for CFHR1.
[c]Genetic analysis of the following genes was performed: CFH, CFI, MCP, CFB, C3, CFHR 1–5 (including MLPA CFHR operon), DGKE, THBD. No auto-antibodies against factor H were found.
[d]Anti-rejection therapy included methylprednisolone, bortezomib, intravenous immunoglobulins, plasmapheresis and anti-thymocyte globulin.
[e]Anti-rejection therapy included methylprednisolone and anti-thymocyte globulin.
[f]Anti-rejection therapy included methylprednisolone.
C3, complement factor 3; CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; DBD, donation after brain death; DCD, donation after cardiac death; DGKE, diacylglycerol kinase ε; IS, immunosuppressive therapy; F, female; KTx, kidney transplantation; LU, living unrelated; LR, living related; M, male; MCP, membrane cofactor protein; MLPA, multiplex ligation-dependent probe amplification; MMF, mycophenolate mofetil; NA: not applicable; pred, prednisolone; sCr, serum creatinine; TAC, tacrolimus; THBD, thrombomodulin; UPCR, urine protein–creatinine ratio.

Table 2. Laboratory values at baseline, relapse and after re-treatment with eculizumab

Case	Clinical relapse[a]	Systemic TMA at relapse	KBx at relapse	sCR at BL[b] (μmol/L)	Max sCr at relapse (μmol/L)	Max UPCR at relapse (gr/10 mmol creatinine)	Nadir sCr after relapse (μmol/L)	FU duration after relapse (months)	sCr at last FU (μmol/L)	CKD-EPI at last FU (mL/min/1.73[c])	UPCR at last FU (gr/10 mmol creatinine)	Chronic kidney injury (remarks)
1	Y	Y	NA	92	166	0.40	82	17	83	105	0	N
2	–	N	NA	150	292	2.76	155	12	158	38	0.14	N
3	Y	Y	NA	142	281	Not done	139	11	139	59	0.26	N
4	–	N	NA	162	201	0.11	No response	38	207	32	0.59	Y (diagnosis of aHUS relapse unlikely)
5	Y	N	Active TMA	134	196	0.77	128	15	142	40	0.78	N
6	Y	Y	Antibody-mediated rejection[c]	156	216	2.54	162	20	257	19	5.65	Y (chronic humoral rejection)
7	–	N	NA	228	386	3.10	No response	4	542	7	4.22	Y (diagnosis of aHUS relapse unlikely)
8	–	N	Chronic TMA[c]	150	225	0.09	132	40	158	32	0	N
9	–	N	No TMA[c]	138	269	0.11	134	21	134	44	0.08	N
10	–	N	Chronic TMA	197	246	0.83	203	35	338	15	1.79	Y (CNI toxicity)
11	Y	Y	Active TMA	128	184	0.15	152	25	168	31	0.10	Y (aHUS relapse with treatment delay)

[a]Clinical relapse was defined as any kidney graft dysfunction with laboratory evidence of TMA and/or histological evidence of active TMA.
[b]Baseline kidney function was defined as the last stable eGFR/serum creatinine before the suspected relapse.
[c]In these patients, no electron microscopy was performed.
BL, baseline; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CNI, calcineurin inhibitor; ECU, eculizumab; FU, follow-up; KBx, kidney biopsy; NA, not applicable; N, no; sCr, serum creatinine; UPCR, urine protein–creatinine ratio; Y, yes.

DISCUSSION

In the Netherlands, patients with aHUS are treated with eculizumab according to a restrictive treatment protocol. Obviously, this strategy carries a risk of relapse. It is unknown if a relapse can be effectively treated without causing persistent kidney injury. Therefore, we performed an interim safety analysis of patients included in the CUREiHUS study who had a suspected relapse after tapering or withdrawal of eculizumab therapy. The data show that kidney function fully recovered without long-term sequelae in patients with a clinical relapse in their native kidneys. By contrast, the clinical course was less favourable in kidney transplant patients, with five patients (out of eight) experiencing a decline of kidney function despite re-treatment with eculizumab. This could be interpreted as evidence that recurrent aHUS in kidney transplant patients carries a high risk of graft failure and that life-long therapy with eculizumab should be maintained. However, assessment of kidney injury in kidney transplant patients is difficult since many transplant patients will develop graft failure due to various causes, such as antibody-mediated rejection, chronic CNI toxicity, BK virus nephropathy, recurrent urinary tract infections and vascular disease. A detailed evaluation of the patients with persistent/chronic kidney injury revealed an underlying cause of slowly and progressively deteriorating graft function in two patients (respectively, antibody-mediated rejection and CNI toxicity). Two other patients showed no response to renewed treatment with eculizumab. These patients had no clinical signs of TMA. Unfortunately, a kidney biopsy was not performed. This is remarkable, but is likely explained by the fact that in patients with a known diagnosis of aHUS, deterioration of kidney function is often attributed to recurrent disease, without obtaining histological evidence repeatedly. The absence of clinical signs of TMA and the absence of response to the timely start of eculizumab therapy also suggest that kidney failure was not caused by a relapse of aHUS. All but one of the patients from the pivotal trials who were treated with eculizumab because of a posttransplant recurrence responded to therapy [7]. To our knowledge, no patients have been described in literature with a biopsy-proven aHUS recurrence who were treated with timely re-start (≤7 days after recurrence) of eculizumab and did not respond to therapy.

One patient developed persistent, chronic kidney injury as a consequence of the relapse. In retrospect, this case (see Supplementary Appendix, Case 11) illustrates the difficulties in diagnosing recurrent aHUS when there is only limited TMA activity. We would like to emphasize that in such patients the absence of active TMA in the kidney biopsy should not be considered sufficient evidence to rule out recurrent, low-grade disease activity, after the exclusion of other well-known causes of deteriorating transplant function [6]. In the absence of a well-defined cause, re-introduction of eculizumab is advised.

The interim safety analysis was performed to evaluate our strategy of restrictive treatment with eculizumab in patients with aHUS. The data have provided insufficient arguments to stop our treatment strategy. Still, it is evident that more stringent measures are needed in kidney transplant recipients. We need a more detailed evaluation of the cause of kidney function deterioration in kidney transplant recipients in whom eculizumab has been tapered or stopped. In patients with an increase in serum creatinine (≥20%) without laboratory evidence of TMA, a kidney biopsy should be performed to evaluate histopathological signs of TMA and to exclude other aetiologies of kidney injury. In the absence of a defined cause, re-introduction of eculizumab is advised. The difficulty in evaluating kidney transplant patients was also illustrated by the delay in re-initiating eculizumab therapy.

Literature data on the outcome of relapse after eculizumab withdrawal in aHUS patients with native kidneys are limited. We recently summarized the data of 44 patients with aHUS in the native kidney, with a relapse after eculizumab withdrawal. After a follow-up time of 12 months, no chronic sequelae were reported in the majority of the patients [8].

The literature on recurrent aHUS in kidney transplant recipients is more complex to interpret. A relevant question is whether aHUS patients can be transplanted without eculizumab prophylaxis. There are no randomized studies. It is evident that eculizumab prophylaxis is safe, with few patients developing a relapse [9]. However, this strategy adds costs and side effects, and may not benefit all patients. We have shown that the risk of recurrence is low (approximately 10%) in recipients of a living donor kidney transplant [10]. The international aHUS registry showed that eGFR at 2 years after transplantation was significantly better in patients treated with prophylactic eculizumab compared with patients who were treated because of a post-transplant aHUS recurrence. The data did not allow evaluation of kidney function recovery in patients with a posttransplant recurrence who were treated with timely initiation of eculizumab [11].

Recently, Zuber *et al.* [9] evaluated the outcome of aHUS kidney transplant recipients and who did not receive eculizumab prophylaxis. A recurrence of aHUS was diagnosed in 39 out of 74 patients (53%). Thirty patients (77%) presented with a 'clinical recurrence', which was defined as any kidney graft dysfunction, with laboratory evidence of TMA and/or histological signs of TMA. The remaining nine patients (23%) had a 'subclinical recurrence', with histopathological signs of TMA in protocol biopsies, and no kidney dysfunction or laboratory evidence of TMA. In total, 29 patients (74%), all diagnosed with a 'clinical recurrence', received eculizumab. Twenty-four of them (83%) had laboratory signs of TMA at recurrence. Notably, treatment was started relatively late, at a median of 32 days (range 0–690 days) after recurrence. Analysis showed that timely initiation of eculizumab was associated with better graft survival. Five-year death-censored graft survival was 84% in the 13 patients who started eculizumab within 7 days after recurrence. This outcome is comparable to the 5-year death-censored graft survival of 89% reported for 10 349 kidney transplantations performed between 2007 and 2017 in France [12].

Still, these studies do not allow evaluation of the outcome of a relapse after eculizumab withdrawal in patients with a post-transplant aHUS recurrence. Zuber *et al.* [9] discontinued eculizumab in four patients after a posttransplant recurrence, leading to a relapse in two of them (50%), and graft failure despite eculizumab re-introduction. In contrast withdrawal of prophylactic eculizumab therapy in 12 patients resulted in a relapse in only one patient, successfully treated with re-start of eculizumab. Data from case reports and case series were recently summarized by our group and indeed suggested that the risk of a relapse after eculizumab withdrawal was higher in patients after a posttransplant recurrence, compared with patients who were treated with eculizumab prophylaxis [8]. Of note, in the majority of the patients with relapse after a post-transplant aHUS, renal function did improve with renewed eculizumab therapy, however not to baseline values. In most of these patients, timely restart of eculizumab could not be confirmed [8].

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We now demonstrate that short-term outcome of a relapse after withdrawal of eculizumab in transplant patients is reasonably good, with eGFR returning to baseline values in five out of eight patients after eculizumab intensivation. After follow-up, delayed eculizumab treatment resulted in moderate chronic kidney injury (chronic kidney disease Stage G3b) in one patient. Our data are limited by the small number of patients included. We would like to emphasize that evaluation of relapse in patients with a kidney transplantation is very complex. Despite a careful and individual evaluation of our patients, this may have influenced data interpretation. Prolonged follow-up is necessary to evaluate the long-term outcome of relapse in kidney transplant patients.

Our study is not a randomized, controlled trial. Still, observational studies provide meaningful data, especially in rare diseases. Open-label, interventional trials that evaluate eculizumab withdrawal are currently ongoing, with final results expected in 2021–22 (STOPECU trial nr NCT02574403 and SETS-HUS trial nr ISRCTN17503205). There is debate over whether it is acceptable to use a treatment strategy that puts patients at risk. The discussion on health care costs, cost-efficacy and equal access to health care is complex, and beyond the scope of this report.

In conclusion, this interim analysis suggests that re-treatment with eculizumab after relapse is safe and feasible. Importantly, kidney transplant recipients with aHUS recurrence may present with a slow decline in kidney function, without laboratory signs of TMA and/or histopathological evidence of active TMA. To ensure a timely restart of eculizumab at relapse, we recommended an early and detailed evaluation in case of kidney function loss in these patients. Our data have encouraged us to continue our current treatment strategy, aiming at evaluating overall outcome and cost-effectiveness in 2021. The final results of the CUREiHUS study are expected in 2021.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

C.D., R.B., J.W.v.d.H., S.P.B., N.C.A.J.v.d.K. and J.F.M.W. contributed to the study design and review of the manuscript. C.D. and J.F.M.W. drafted the first version of the manuscript. C.D. conducted the data analysis. C.D. had full access to all data in the study and takes responsibility for its integrity and the data analysis. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data available on request.

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