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Outcomes of Patients With Atypical Hemolytic Uremic Syndrome With Native and Transplanted Kidneys Treated With Eculizumab: A Pooled Post Hoc Analysis

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Abbreviations

aHUS, atypical hemolytic uremic syndrome

CFB, complement factor B

CFH, complement factor H

CFHR3/1, CFH-related protein 3/1 polymorphism

CFI, complement factor I

CI, confidence interval

CKD, chronic kidney disease

eGFR, estimated glomerular filtration rate

ESRD, end-stage renal disease

LDH, lactate dehydrogenase

MCP, membrane cofactor protein

NA, not assessed

ND, none detected

PE/PI, plasma exchange/plasma infusion

SD, standard deviation

TEAE, treatment-emergent adverse event

TMA, thrombotic microangiopathy

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) often leads to end-stage renal disease (ESRD) and kidney transplantation; graft loss rates are high due to disease recurrence. A post hoc analysis of four prospective clinical trials in aHUS was performed to evaluate eculizumab, a terminal complement inhibitor, in patients with native or transplanted kidneys. The trials included 26-week treatment and extension periods. Dialysis, transplant, and graft loss were evaluated. Study endpoints included complete thrombotic microangiopathy (TMA) response, TMA event-free status, hematologic and renal parameters, and adverse events. Of 100 patients, 74 had native kidneys and 26 in the transplant subgroup had a collective history of 38 grafts. No patients lost grafts and only one with preexisting ESRD received a transplant on treatment. Efficacy endpoints were achieved similarly in both subgroups. After 26 weeks, mean absolute estimated glomerular filtration rate increased from baseline to 61 and 37 mL/min/1.73 m^2 in native (n=71; P<0.0001) and transplanted kidney (n=25; P=0.0092) subgroups. Two patients (one/subgroup) developed meningococcal infections; both recovered, one continued therapy. Eculizumab was well tolerated. Eculizumab improved hematologic and renal outcomes in both subgroups. In patients with histories of multiple graft losses, eculizumab protected kidney function.

(ClinicalTrials.gov numbers: NCT00844545, NCT00844844, NCT00838513, NCT00844428, NCT01193348, and NCT01194973)

INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a rare, progressive, and potentially life-threatening disease caused by chronic, uncontrolled activation of the complement alternative pathway [1,2]. Complement gene abnormalities occur in approximately 50% to 70% of patients [2,3]. The resulting complement dysregulation leads to thrombotic microangiopathy (TMA), which is generally characterized by hemolytic anemia, thrombocytopenia, and acute kidney injury [1] and frequently other organ impairment [2,3]. Patients who remain untreated are at lifelong risk for end-stage renal disease (ESRD), other organ dysfunction, and premature death [2-4]. Patients may require kidney transplantation [2], and posttransplant TMA occurs in approximately 68% of patients with transplanted kidneys and is associated with a high rate of graft failure within 5 years (64%) [5]. Graft loss due primarily to clinical manifestations of aHUS has invalidated plasma exchange/plasma infusion (PE/PI) as a viable management option for patients with aHUS and renal transplants [5].

Eculizumab (Soliris®, Alexion Pharmaceuticals, Inc., New Haven, CT, USA) is a fully humanized monoclonal antibody that binds to terminal complement protein C5, inhibiting its cleavage into C5a, a potent anaphylatoxin, and C5b, which goes on to form the membrane attack complex (C5b-9) [6,7]. It is the only approved treatment for patients with aHUS [6,7]. Eculizumab has been demonstrated to inhibit complement-mediated TMA and to be well tolerated in four prospective clinical trials in pediatric and adult patients with aHUS [8-11].

Extent of previous renal injury is known to influence changes in renal function in patients with aHUS [12], and particularly in those with transplanted kidneys [13]. The objective of the current analysis was to characterize the efficacy and safety of eculizumab in patients with native and transplanted kidneys in a pooled population from the eculizumab clinical trial program in aHUS, in order to understand potential differences in these patient subgroups.

MATERIALS AND METHODS

A post hoc analysis was conducted on the pooled results of four prospective, open-label, nonrandomized, single-arm, multicenter, phase 2 clinical trials, which were reported previously (NCT00844545/NCT00844844 and NCT00838513/NCT00844428 [8,9], NCT01193348 [10], and NCT01194973 [11]). These trials assessed the efficacy and safety of eculizumab in patients with aHUS over 26-week treatment periods followed by extension periods. All patients received meningococcal vaccination and/or antibiotic prophylaxis before initiation of eculizumab. Eculizumab was administered either: (a) intravenously 900 mg every week for 4 weeks, 1200 mg at the fifth week, then 1200 mg every 2 weeks; or (b) for pediatric patients, at doses prespecified by body weight.

Demographic and baseline characteristics were summarized by transplant subgroup (native and transplanted kidneys) and for all patients. Differences between native kidney and transplant subgroups at baseline were tested using Wilcoxon rank sum tests for continuous variables and Fisher exact tests for categorical variables. Dialysis, transplant, and graft loss statuses were evaluated at baseline and prospectively. Efficacy endpoints for this post hoc analysis were defined by the study protocols and included complete TMA response (platelet count ≥150 x 10^9/L, lactate dehydrogenase [LDH] levels less than the upper limit of normal, and ≥25% decrease from baseline in serum creatinine level), TMA event-free status (no decrease in platelet count >25% from baseline, no PE/PI, and no new dialysis), hematologic normalization (platelet count ≥150 x 10^9/L and LDH levels less than the upper limit of normal), mean change from baseline in platelet count, mean estimated glomerular filtration rate (eGFR), mean proteinuria level, and chronic kidney disease (CKD) improvement by ≥1 stage. Categorical endpoints were required to be sustained for two or more consecutive measurements obtained ≥4 weeks apart and *P* values between subgroups were calculated using Fisher exact tests. Time to achievement of endpoints also was assessed. Platelet counts and eGFR values were summarized descriptively at each visit by transplant subgroup. Comparisons between post-dose visits and baseline were made within each subgroup using paired *t*-tests. *P* values were reported for descriptive purposes only, rather than to imply statistical significance. Safety was assessed by reported treatment-emergent adverse events (TEAEs).

RESULTS

A total of 100 patients were included in this post hoc, intention-to-treat analysis, comprising 74 patients with native kidneys and 26 patients with transplanted kidneys at baseline (**Fig. 1**). There were significant differences at baseline between the native and transplanted kidney subgroups (**Table 1**). Patients with transplanted kidneys were older (median age: 41.5 versus 24.0 years; *P*=0.0002) and had a longer time from aHUS diagnosis to screening (median: 34.8 versus 0.85 months; *P*<0.0001), lower proportion of patients with their first TMA manifestation (27% versus 69%; *P*=0.0002), and lower proportion of patients on dialysis at baseline (23% versus 50%; *P*=0.0214).

Median (range) duration of eculizumab treatment was 71 (0–186) weeks overall; 64 (0–186) weeks in patients with native kidneys and 100 (3–170) weeks in patients with transplanted kidneys. The 26 kidney transplant recipients received a total of 38 grafts before initiating eculizumab (**Fig. 2**). No patient experienced graft loss after initiating eculizumab. One patient with ESRD for more than 4 months before inclusion into the study received a kidney transplant 217 days after initiation of eculizumab, as described previously [8].

The majority of patients with both native and transplanted kidneys achieved endpoints by end of study (**Table 2**), including complete TMA response (74% and 65%, respectively), TMA event-free status (93% and 88%, respectively), and hematologic normalization (96% and 85%, respectively). Compared with patients with native kidneys, those with transplanted kidneys required longer time

to reach complete TMA response (median time: 66 and 98 days for n=55 patients with native kidneys and n=17 patients with transplanted kidneys who attained response, respectively) and hematologic normalization (median time: 33 and 56 days for n=71 patients with native kidneys and n=22 patients with transplanted kidneys who attained the endpoint, respectively).

In addition, Kaplan-Meier methods were used to compute median time to achievement of the endpoints, treating nonresponders as censored observations. For complete TMA response, the medians were 85 and 287 days for patients with native and transplanted kidneys, respectively (**Fig. 3**). Median time to hematologic normalization with Kaplan-Meier methods (33 and 55 days, respectively, for patients with native and transplanted kidneys; **Fig. 4**) was similar to that reported above.

Patients with platelet count <150 x 10^9/L at baseline in both subgroups (native kidneys, n=51; transplanted kidneys, n=14) had significant improvements after initiation of eculizumab. After 1 week of treatment, the mean (standard deviation [SD]) change from baseline in platelet count was 115 (99) x 10^9/L in patients with native kidneys (n=50; *P*<0.0001) and 104 (141) x 10^9/L in patients with transplanted kidneys (n=14; *P*=0.0161). The mean (SD) change from baseline after 26 weeks was 165 (98) x 10^9/L (n=48; *P*<0.0001) and 116 (126) x 10^9/L (n=13; *P*=0.006), respectively. After 18 months, the mean (SD) change from baseline was 136 (69) x 10^9/L (n=20; *P*<0.0001) and 83 (94) x 10^9/L (n=10; *P*=0.0211), respectively.

Mean absolute eGFR values also increased significantly with eculizumab treatment in both subgroups. Compared with baseline, the mean (SD) absolute eGFR value after 26 weeks of treatment was 61 (41) mL/min/1.73 m^2 (mean [SD] change from baseline, 38 [36] mL/min/1.73 m^2) in patients with native kidneys (n=71; *P*<0.0001) and 37 (25) mL/min/1.73 m^2 (mean [SD] change from baseline, 11 [20] mL/min/1.73 m^2) in patients with transplanted kidneys (n=25; *P*=0.0092). The mean (SD) eGFR value after 18 months was 66 (31) mL/min/1.73 m^2 (mean [SD] change from baseline, 44 [34] mL/min/1.73 m^2) in patients with native kidneys (n=35; *P*<0.0001) and 42 (27) mL/min/1.73 m^2 (mean [SD] change from baseline, 13 [23] mL/min/1.73 m^2) in patients with transplanted kidneys (n=20; *P*=0.0188).

Overall, proteinuria decreased with eculizumab treatment in both subgroups. At baseline, mean (SD) proteinuria levels were 200 (294) mg/dL in patients with native kidneys (n=54) and 209 (379) mg/dL in patients with transplanted kidneys (n=21). After 26 weeks, mean (SD) levels were 53 (52) mg/dL (n=49) and 74 (68) mg/dL (n=20), respectively. After 18 months of eculizumab, patients with native kidneys (n=30) had a mean (SD) proteinuria level of 46 (66) mg/dL and for patients with transplanted kidneys (n=17), the proteinuria level was 52 (72) mg/dL.

CKD improvement by ≥1 stage occurred in 47 patients (64%) with native kidneys and 13 patients (50%) with transplanted kidneys at 26 weeks. At study end, 55 patients (74%) with native kidneys and 15 patients (58%) with transplanted kidneys had CKD improvement by ≥1 stage.

Eculizumab was well tolerated in both patient subgroups, with most TEAEs being of mild or moderate severity. TEAEs judged at the discretion of the investigator to be related to eculizumab treatment were reported in 35 patients (47%) with native kidneys and 14 (53%) with transplanted kidneys. Related TEAEs occurring in >5% of the subgroup population included alopecia, headache, leukopenia, and vomiting in the native kidney subgroup, and BK virus infection, headache, leukopenia, lymphopenia, pyelonephritis, and urinary tract infection in the transplanted kidney subgroup. Severe TEAEs considered by the investigator to be possibly/probably related to eculizumab treatment included dyspnea (n=1), gonococcal genitourinary tract infection (n=1), hypertension (n=1), influenza (n=1), peritonitis (n=1), and venous thrombosis (n=1) in the native kidney subgroup, and meningococcal meningitis (n=1), pyelonephritis (n=2), renal impairment (n=1), and vein disorder (n=1) in the kidney transplant subgroup. Overall, two cases of meningococcal infection occurred in the pooled population and were reported previously [11]. One patient was a transplant recipient and the other had native kidneys. Both patients had received meningococcal vaccinations against serogroups A, C, W, and Y, but neither had received long-term prophylactic antibiotics. Both patients recovered with antibiotic therapy, and the patient with native kidneys continued to receive eculizumab. One death occurred in a patient in the kidney transplant subgroup, as reported previously [9], and was attributed to complications from intestinal hemorrhage that were deemed unrelated to eculizumab.

DISCUSSION

This pooled post hoc analysis demonstrates the efficacy and safety of eculizumab in improving renal function and hematologic parameters in the aHUS clinical trial program in patients with native kidneys and those with transplanted kidneys. The majority of patients in both subgroups achieved efficacy endpoints as well as significant increases in platelet counts and improvements in eGFR that were maintained over 18 months of follow-up. Gains in eGFR were also associated with improvements in CKD stage and proteinuria for patients in both subgroups.

Overall, patients with transplanted kidneys had lower magnitudes of improvement in renal function and platelet count, perhaps due, in some measure, to factors related to transplantation (e.g., ischemia and reperfusion injury, delayed graft function, potential nephrotoxicity of immunosuppressive agents). Time to complete TMA response was longer in this subgroup compared with patients with native kidneys due to the renal requirement (i.e., ≥25% decrease from baseline in serum creatinine level) of this composite endpoint. Median time to complete TMA response, especially in patients with transplanted kidneys, was longer with Kaplan-Meier methods compared with descriptive summary. This is likely due to the small number of patients in the transplanted kidney group and the censoring pattern. A recent publication from a Kidney Disease: Improving

Global Outcomes (KDIGO) Controversies Conference [14] states that for patients with high risk of disease recurrence, recovery of renal function in grafts may be limited compared with native kidneys. Additionally, 9 (35%) of the kidney transplant recipients in this cohort originated from the study in which the patients with aHUS had been deemed responsive to PE/PI (NCT00838513/NCT00844428) [8]. Eleven (42%) of the transplant patients had normal platelet counts at baseline, which may account, at least in part, for a lower magnitude of platelet count improvement compared with patients with native kidneys.

Graft loss is known to occur at a high rate in patients with aHUS and previously transplanted kidneys [5,15], due primarily to recurrence of TMA within the transplanted kidney. Eculizumab therapy has been shown to be effective in preventing and treating aHUS recurrence posttransplant in a retrospective study of 22 patients [13]. In the current analysis, eight of 26 patients (31%) with transplanted kidneys had a history of one or more kidney transplants before treatment initiation. Of importance, no patient who received a transplant before initiating eculizumab experienced graft loss while on therapy, with a median eculizumab exposure of 71 weeks. The patient who required a kidney transplant after starting eculizumab therapy had preexisting ESRD. Following the KDIGO Controversies Conference, Goodship *et al* [14] recommend that patients with aHUS and kidney transplants, especially those who have lost previous grafts, should not discontinue eculizumab therapy.

While outcomes for patients treated with eculizumab who received transplants were favorable in the current study and previously published observational studies [13,16,17] and case reports [18-30], care should be taken when applying these findings in clinical practice. In limited case studies, mainly with reduced dosages of eculizumab compared with the approved treatment regimen, patients lost grafts or otherwise had kidney injury progression [13,16,17]. In addition, a complex case of aHUS has been reported in a pediatric patient with complement factor H mutation who initiated eculizumab, and was transplanted after a severe disease course approximately 5 years after the initial aHUS diagnosis. However, the patient had disease recurrence while receiving sufficient eculizumab dose and eventually required a liver transplant [31]. Therefore, additional studies in larger patient populations and outside of the clinical trials are needed to more fully evaluate the efficacy of eculizumab. The global aHUS Registry was initiated in 2012 to evaluate long-term disease outcomes in eculizumab-treated and untreated patients [32]. Ongoing analyses include timing of eculizumab initiation and effects on rates of TMA and dialysis requirements in patients with aHUS undergoing kidney transplantation. Preliminary findings suggest that initiating eculizumab pretransplant compared with posttransplant may be associated with better outcomes [33].

A previous pooled post hoc analysis [34] of the clinical trial program for eculizumab in aHUS demonstrated that early (i.e., within 7 days of presentation) initiation of treatment was associated with optimal renal outcomes. Younger age and certain laboratory criteria (i.e., relatively higher LDH and lower hemoglobin levels) were also independently associated with better renal outcomes on eculizumab. In the current analysis, age and baseline characteristics pertaining to length of disease

history (i.e., time from diagnosis to study screening and history of previous TMA manifestations) differed significantly between native and transplanted kidney subgroups, although these differences may have been expected due to study eligibility criteria. More studies are needed to determine the potential role of such demographic and baseline clinical characteristics on renal outcomes in aHUS.

Eculizumab was well tolerated in patients with native and transplanted kidneys, with most TEAEs reported as mild or moderate. As discussed previously [9], there was one patient death following complications from intestinal hemorrhage that were deemed unrelated to eculizumab. The two meningococcal infections that occurred in the study in an exclusively adult population with aHUS [11] underscore the need for vigilant monitoring of meningococcal symptoms in patients receiving eculizumab therapy. Overall, mounting evidence from the clinical trial program in aHUS [8-11] and a 10-year study of patients with paroxysmal nocturnal hemoglobinuria [35] suggests that meningococcal infection is an uncommon event with eculizumab therapy.

For patients with aHUS, optimal disease management should minimize potential for organ injury, reduce need for transplantation, and protect against graft loss while improving clinical outcomes. This analysis demonstrated that eculizumab therapy was associated with improvements in renal and hematologic outcomes, regardless of transplant status. Eculizumab treatment in patients with a history of transplant reduces the risk of graft loss due to aHUS recurrence, and enables ongoing improvements in renal graft function.

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FIGURE LEGENDS

Figure 1. Patient disposition.

Figure 2. Timing of kidney transplant in relation to aHUS diagnosis and eculizumab treatment. Patients 6, 7, 17, and 19 were diagnosed with aHUS prior to eculizumab initiation. *Patient withdrew due to an adverse event. **Approximate duration from diagnosis to first dose of eculizumab. After kidney transplantation on day 217, the patient's renal data were censored [8]. ***Did not enter long-term follow-up; no further information is available. aHUS, atypical hemolytic uremic syndrome; *CFH*, complement factor H; *CFHR3/1*, CFH-related protein 3/1 polymorphism; *CFI*, complement factor I; ND, none detected.

Figure 3. Kaplan-Meier analysis of time to complete TMA response. TMA, thrombotic microangiopathy.

Figure 4. Kaplan-Meier analysis of time to hematologic normalization.

TABLES

Table 1. Demographic and baseline clinical characteristics

Characteristic	All Patients (N=100)	Native Kidney (n=74)	Transplanted Kidney (n=26)	*P* Value Between Subgroups[a]
Age, median (range), y	28.0 (0–80)	24.0 (0–80)	41.5 (17–69)	0.0002
Female, n (%)	62 (62)	46 (62)	16 (62)	1.0000
Identified complement mutation or autoantibody, n (%)	59 (59)	46 (62)	13 (50)	0.3549
CFH	19 (19)	17 (23)	2 (8)	
CFI	9 (9)	5 (7)	4 (15)	
MCP	7 (7)	7 (9)	0	
C3	5 (5)	3 (4)	2 (8)	
CFH autoantibodies, *CFHR3/1*	4 (4)	4 (5)	0	
CFH autoantibodies	3 (3)	3 (4)	0	
CFHR3/1	3 (3)	1 (1)	2 (8)	
CFH, CFHR3/1	2 (2)	1 (1)	1 (4)	
C3, CFHR3/1	1 (1)	1 (1)	0	
CFB	1 (1)	1 (1)	0	
CFH, C3	1 (1)	1 (1)	0	

CFH, CFI, CFHR3/1	1 (1)	0	1 (4)	
CFH, MCP	1 (1)	1 (1)	0	
CFI, C3	1 (1)	0	1 (4)	
CFI, MCP	1 (1)	1 (1)	0	
Time from aHUS diagnosis to screening, median (range), mo	2.7 (0.03–311.3)	0.85 (0.03–235.9)	34.8 (0.13–311.3)	<0.0001
TMA events, median (range), n	1 (1–9)	1 (1–9)	2 (1–8)	0.0005
Duration of current TMA manifestation to first eculizumab dose, median (range), mo	0.72 (0.03–47.4)	0.69 (0.03–47.4)	1.25 (0.03–36.7)	0.4081
First TMA manifestation, n (%)	58 (58)	51 (69)	7 (27)	0.0002
No PE/PI during current manifestation, n (%)	28 (28)	18 (24)	10 (39)	0.2061
Platelet count, median (range), $x10^9$/L	126 (16.9–420.5)	118.5 (18.0–420.5)	139.8 (16.0–337.5)	0.1080
Hemoglobin level, median (range), mg/dL	89.5 (41.0–131.0)	85.5 (41.0–131.0)	96.5 (54.0–131.0)	0.0075
Lactate dehydrogenase level, median (range), U/L	369 (131.0–7164.0)	380.5 (134.0–7164.0)	304.5 (131.0–2693.0)	0.1313

eGFR, median (range), mL/min/1.73 m^2	16.0 (5.6–105.5)	12.0 (5.6–105.5)	22.2 (10.0–72.3)	0.1386
Dialysis at baseline, n (%)	43 (43)	37 (50)	6 (23)	0.0214

[a]*P* values were calculated using Wilcoxon rank sum tests for continuous variables and Fisher exact tests for categorical variables between native kidney and transplant subgroups at baseline.

aHUS, atypical hemolytic uremic syndrome; *CFB,* complement factor B; *CFH*, complement factor H; *CFHR3/*1, CFH-related protein 3/1 polymorphism; *CFI*, complement factor I; *eGFR*, estimated glomerular filtration rate; *MCP*, membrane cofactor protein; NA, not assessed; PE/PI, plasma exchange/plasma infusion; TMA, thrombotic microangiopathy

Table 2. Efficacy outcomes at end of study

Endpoint	All Patients (N=100)	Native Kidney (n=74)	Transplanted Kidney (n=26)	*P* Value[a]
Complete TMA response				
n (%)	72 (72)	55 (74)	17 (65)	0.4486
95% CI	62–81	63–84	44–83	
TMA event-free status				
n (%)	92 (92)	69 (93)	23 (88)	0.6433
95% CI	87–98	87–99	74–99	
Hematologic normalization				
n (%)	93 (93)	71 (96)	22 (85)	0.0727
95% CI	86–97	89–99	65–96	

[a]*P* values between native kidney and transplant subgroups were calculated using Fisher exact tests.

CI, confidence interval; TMA, thrombotic microangiopathy.