Effect of Early Initiation of Eculizumab in Patients With aHUS on Renal Outcomes: A Pooled Analysis

John F. Kincaid,[1] Spero R. Cataland,[2] Johan Vande Walle,[3] Yahsou Delmas,[4] Gianluigi Ardissino,[5] Jimmy Wang[1]

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INTRODUCTION

- Patients presenting with hemolytic anemia, thrombocytopenia, and organ dysfunction in the intensive care unit are clinical emergencies and can be difficult to diagnose
- The most common disorders with the above clinical features are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), which are both rare but have different etiologies[1,2]
- No definitive test for complement-mediated atypical HUS (aHUS) exists, but TTP can be excluded with ADAMTS13 activity level >5—10%[3]
- Effective management for each disorder is distinct and should be initiated rapidly to avoid irreversible organ damage or death.[2,3] Eculizumab, a terminal complement inhibitor, is the only approved treatment for aHUS[4,5] with 4 prospective clinical trials demonstrating its safety and efficacy[6-9]

OBJECTIVE

- To evaluate the effects of initiating eculizumab treatment ≤7 days or >7 days after presentation of aHUS on renal outcomes, using pooled data from the 4 previously described prospective clinical trials[6-9]

METHODS

- Data from 4 phase 2, open-label, single-arm, prospective clinical trials including both pediatric and adult patients with aHUS (NCT00844545, NCT00844844, NCT00838513, NCT00844428, NCT01193348, NCT01194973) were pooled
  - Only data from patients who had a documented date of onset of the current aHUS manifestation and a baseline estimated glomerular filtration rate (eGFR) of <90 mL/min/1.73 m^2 were included
- eGFR changes from baseline and normalization (≥90 mL/min/1.73 m^2) over time were evaluated
  - Results were stratified according to whether patients received eculizumab treatment ≤7 days or >7 days after the current aHUS manifestation
  - Two-group *t*-tests were used to evaluate differences between the subgroups for changes from baseline in eGFR
- Baseline characteristics were compared between the 2 groups using the Wilcoxon rank-sum test for continuous variables and the Fischer exact test for categorical variables
- Multivariate regressions using repeated measures analysis were performed to identify predictors of change in eGFR from baseline to 1 year

RESULTS

Patients

- Data were pooled from 97 patients out of a total of 100 patients enrolled across the 4 studies
  - Three patients were excluded from the analysis because date of onset of aHUS manifestations was missing or baseline eGFR was >90 mL/min/1.73 m^2
- The time from the current aHUS manifestation to starting treatment with eculizumab was:
  - ≤7 days in 21 patients
  - >7 days in 76 patients
- Demographic and baseline clinical characteristics of the included patients are shown in **Table 1**

Table 1. Demographics and Baseline Clinical Characteristics

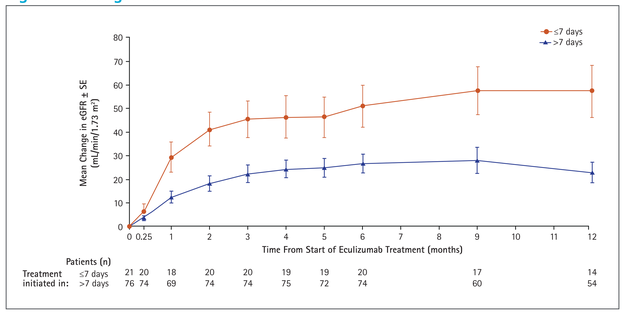
Characteristic	Time to Treatment ≤7 days n=21	Time to Treatment >7 days n=76	All N=97	*P* Value*
Median age, years (range)	30 (0–69)	29 (0–80)	29 (0–80)	–
Age group in years, n (%)				0.029†
<18	10 (48)	15 (20)	25 (26)	
≥18	11 (52)	61 (80)	72 (74)	
Female gender, n (%)	11 (52)	49 (64)	60 (62)	0.323†
Complement mutation or autoantibody, n (%)				0.133†
Any mutation or autoantibody	9 (43)	48 (63)	57 (59)	
CFH mutation	5 (24)	19 (25)	24 (25)	
No complement mutation or autoantibody, n (%)	12 (57)	28 (37)	40 (41)	
Median time from last aHUS manifestation to eculizumab treatment, months (range)	0.13 (0.03–0.20)	1.02 (0.23–47.40)	0.75 (0.03–47.40)	–
Median number of TMA events, n (range)	1 (1–6)	1 (1–9)	1 (1–9)	0.421†
Receiving PE/PI at baseline, n (%)	11 (52)	60 (79)	71 (73)	0.001†
Median PE/PI duration during last aHUS manifestation prior to first dose, months (range)	0.10 (0.03–0.20)	0.67 (0.03–46.46)	0.49 (0.03–46.46)	<0.001†
Dialysis at baseline, n (%)	12 (57)	31 (41)	43 (44)	0.219†
Median dialysis duration during last aHUS manifestation prior to first dose, months (range)	0.05 (0.03–0.20)	0.39 (0.03–34.85)	0.30 (0.03–34.85)	0.007†
History of kidney transplantation, n (%)	7 (33)	19 (25)	26 (27)	0.578†
Median baseline platelet count x 10^9/L (range)	81.5 (18.0–193.0)	133.5 (16.0–420.5)	127.5 (16.0–420.5)	0.002†
Platelet count <150 x 10^9/L, n (%)	19 (90)	45 (59)	64 (66)	0.008†
Median hemoglobin, mg/dL (range)	n=18 84.0 (41.0–117.0)	n=71 92.0 (54.0–131.0)	n=89 89.0 (41.0–131.0)	0.122†
Median LDH, U/L (range)	669.1 (131.0–7164.0)	297.5 (134.0–3682.0)	343.0 (131.0–7164.0)	<0.001†
Median creatinine, µmol/L (range)	n=20 214.0 (112.0–1007.8)	n=74 243.1 (28.0–1169.6)	n=94 238.7 (28.0–1169.6)	0.708†
Median baseline eGFR, mL/min/1.73 m^2 (range)[§]	11.0 (5.6–53.2)	16.0 (7.3–76.1)	15.9 (5.6–76.1)	0.299†

*Comparison between ≤7-day and >7-day groups; †*P* values calculated using the Fisher exact test; ‡*P* values calculated using the Wilcoxon rank-sum test; §eGFR for patients on dialysis was imputed to 10 mL/min/1.73 m^2.
aHUS, atypical hemolytic uremic syndrome; CFH, complement factor H; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; PE/PI, plasma exchange/plasma infusion; TMA, thrombotic microangiopathy.

Changes in eGFR

- Patients in whom eculizumab treatment was initiated ≤7 days after the current aHUS manifestation had a greater improvement in eGFR than those initiating treatment after >7 days from 1 month onward (*P*<0.05) **(Figure 1)**
  - The mean changes from baseline in eGFR for patients starting eculizumab ≤7 days and >7 days after the current manifestation were 57 and 23 mL/min/1.73 m^2, respectively, after 1 year
- For all measured time points after baseline, the percentage of patients with sustained response in eGFR was significantly higher with earlier administration of eculizumab (*P*<0.05) at all time points **(Figure 2)**

Figure 1. Change From Baseline in eGFR Over Time



P<0.05 between subgroups at all time points beginning at 1 month.
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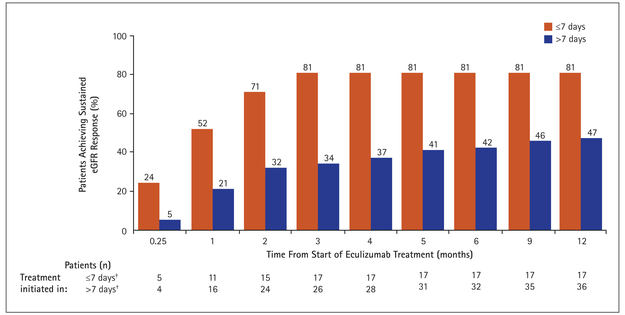
Figure 2. Proportions of Patients With Sustained Response* in eGFR



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Predictors of eGFR Improvement

- Repeated measures analysis of baseline characteristics identified several demographic and clinical features that independently contributed to eGFR improvements **(Table 2)**

Table 2. Repeated Measures Analysis of eGFR Change From Baseline to Post-Treatment Through 12 Months

Effect*	Time to Treatment (Continuous Variable) Coefficient	*P* value
aHUS duration (day)	-0.03	0.0181
Age group (child vs adult)	-	0.0061
Baseline LDH (U/L)	0.01	0.0078
Baseline hemoglobin (g/L)	-0.97	0.0002
Trial visit	-	<0.0001
Baseline eGFR	0.21	0.1964

*Interaction terms that remain significant in the final model are visit (scheduled post-dose visits in months) by time to treatment, visit by age group, visit by baseline LDH, visit by baseline hemoglobin, and age group by baseline hemoglobin.
aHUS, atypical hemolytic uremic syndrome; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase.

CONCLUSIONS

- This pooled analysis indicates that patients treated with eculizumab within 7 days of presentation of aHUS manifestation had greater improvement in eGFR over time than patients in whom treatment was delayed
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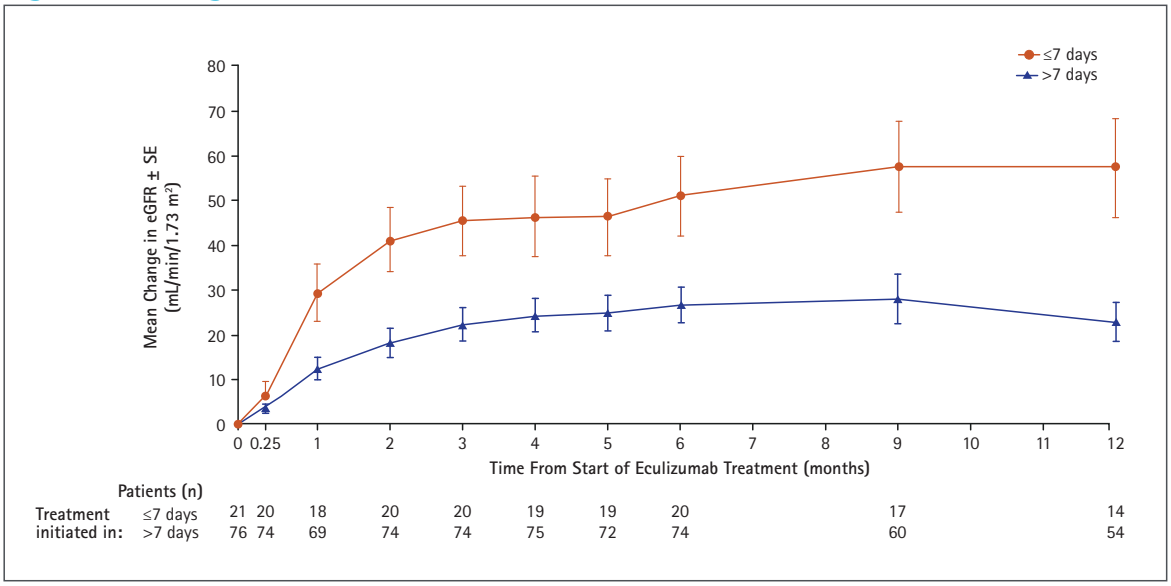

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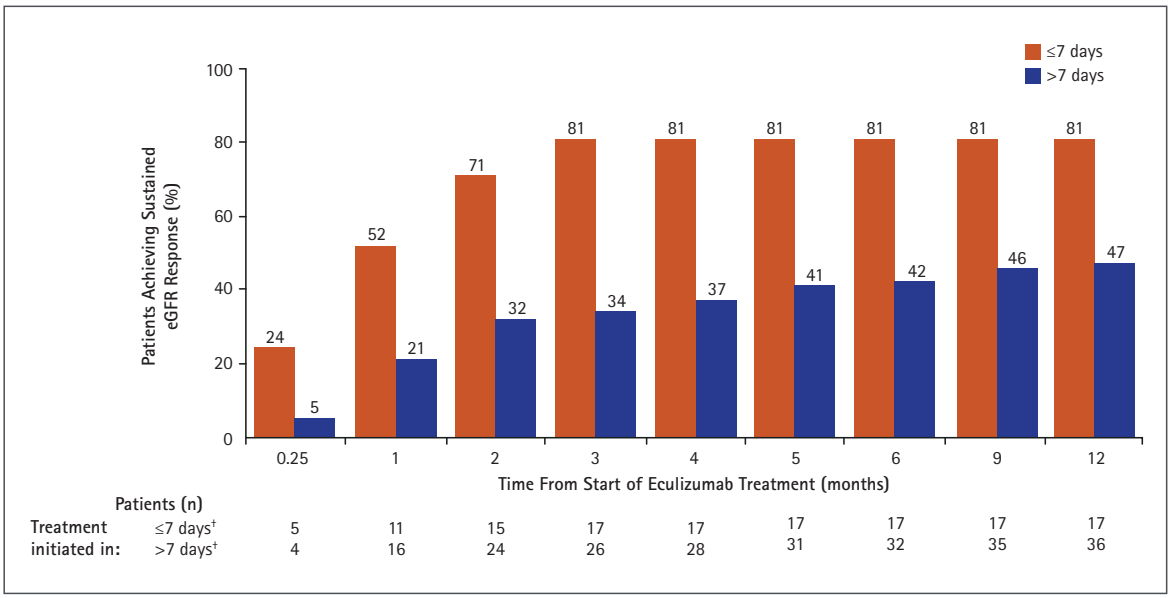

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