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

John F. Kincaid,1 Spero R. Catland,2 Johan R. Walle,1 Yahsou Delmas,1 Gianluigi Ardissino,3 Jimmy Wang4

1Alexion Pharmaceuticals, Inc., Cheshire, CT, USA; 2Ohio State University, Columbus, OH, USA; 3University Hospital Gasthuis, Ghent, Belgium; 4Centre Hospitalier Universitaire, Brest, France; 5Ospedale Maggiore Policlinico, Milan, Italy

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 hereditary intrinsic uremic syndrome (HUS), which are both rare but have different etiologies.1

No definitive test for complement-mediated atypical HUS (aHUS) exists, but TTP can be distinguished from aHUS by characteristic features in laboratory testing.2–4 Complement C3 and C5 levels may be increased in TTP whereas decreased in aHUS.3 Serological evidence of Complement factor H (CFH) autoantibody and/or dysregulation of the classic complement pathway is often seen in aHUS.3,4

OBJECTIVE

To evaluate the effects of initiating eculizumab treatment ≤7 days or >7 days after presentation of aHUS renal outcomes, using pooled data from the 4 previously described prospective clinical trials.2,3,5,6

METHODS

Data from 4 phase 2, open-label, single-arm, prospective clinical trials including both pediatric and adult patients with aHUS (NCT00444444, NCT00838513, NCT00844545, NCT00844844, NCT01133348, NCT01194703) 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) ≥30 mL/min/1.73 m2 were included.

- eGFR changes from baseline and normalization (≥90 mL/min) were evaluated.

- Multivariate analyses using repeated measures analysis were performed to identify predictors of change in eGFR from baseline to 1 year.

RESULTS

Data were pooled from 971 patients out of a total of 1002 patients enrolled across the 4 studies. Three patients were excluded from the analysis because date of onset of aHUS manifestation was missing or baseline eGFR was ≥90 mL/min/1.73 m2. The time from the current aHUS manifestation to starting treatment with eculizumab was:

- ≤7 days in 21 patients

- >7 days in 76 patients

- 7 days in 29 patients

- 4 days in 5 patients

Predictors of eGFR improvement (Table 3)

- For all measured time points after baseline, the percentage of patients with sustained treatment for ≥1 year (≥421 days) had a higher percentage with earlier administration of eculizumab (P<0.012) at all time points (Figure 2)

- Time to treatment ≤7 days had a higher percentage of patients with sustained treatment for ≥1 year (≥421 days) compared to treatment >7 days (P<0.001; Table 4, Figure 3).

- For patients with aHUS manifestation prior to first dose, median eGFR changes from baseline and normalization (≥90 mL/min/1.73 m2) were not significant (P=0.327) (Table 5). P<0.05 between subgroups at all time points beginning at 1 month.

- For patients who received eculizumab within 7 days and >7 days after initiation of disease, the mean changes from baseline in eGFR were significantly different (P<0.001) for both eGFR changes from baseline and normalization (≥90 mL/min/1.73 m2) (Table 5).

- Median baseline eGFR was significantly higher with earlier administration of eculizumab (P<0.012) at all time points (Figure 2).

- Median baseline eGFR was significantly higher with earlier administration of eculizumab at all time points but only for median changes from baseline and normalization (≥90 mL/min/1.73 m2) (Table 5).

- Median changes from baseline in eGFR were significantly different (P<0.001) for both eGFR changes from baseline and normalization (≥90 mL/min/1.73 m2) (Table 5).

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.

- A higher percentage of patients who received eculizumab within 7 days had normal eGFR after 1 month of treatment which was sustained through 12 months in patients who received eculizumab within 7 days.

- In addition, there was a trend toward a lower lactate dehydrogenase level, and lower hemoglobin level at baseline were associated with eGFR improvement.

- These results further support the importance of rapid diagnosis and treatment of aHUS for recovery of renal function.

REFERENCES


ACKNOWLEDGMENTS

The authors would like to acknowledge Pinston Advantage, LLC, which provided editorial support with funding from Alexion Pharmaceuticals, Inc.
Effect of Early Initiation of Eculizumab in Patients With aHUS on Renal Outcomes: A Pooled Analysis

John F. Kincaid,* Spero R. Cataland,† Johan Vande Walle,* Yahoua Delmas,* Gianluigi Ardissino,* Jimmy Wang

*Alexion Pharmaceuticals, Inc., Cheshire, CT, USA; †Ohio State University, Columbus, OH, USA; ‡University Hospital Ghent, Ghent, Belgium; §Centre Hospitalier Universitaire, Bordeaux, France; ‡‡Ospedale Maggiore Policlinico, Milan, Italy

For all measured time points after baseline, the percentage of patients with sustained

INTRODUCTION

Time to Treatment

>7 days

The most common disorders with the above clinical features are thrombotic

P

n=21

n=76

P value

≤7 days

rare but have different etiologies

1,2

≥18 10 (48) 15 (20) 25 (26)

<18 11 (52) 61 (80) 72 (74)

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

No complement mutation or

autoantibody, n (%) 12 (57) 28 (37) 40 (41)

A higher percentage of patients who received eculizumab within 7 days had normal

–
eGFR after 1 month of treatment which was sustained through 12 months

‡

These results further support the importance of rapid diagnosis and treatment of aHUS for recovery of renal function

ACKNOWLEDGMENTS

The authors would like to acknowledge Peloton Advantage, LLC, which provided editorial

support with funding from Alexion Pharmaceuticals, Inc.

REFERENCES


4. European Medicines Agency. Soliris (eculizumab) [summary of product characteristics], Paris, France:


7. European Medicines Agency. Soliris (eculizumab) [summary of product characteristics], Paris, France:


Patients Achieving Sustained

Figure 2. Proportions of Patients With Sustained Response* in eGFR

Figure 1

0.25 1 2 3 4 5 6 9 12

Patients (n)

0 1 2 3 4 5 6 9 12

Time From Start of Eculizumab Treatment (months)

Predictors of eGFR Improvement

Table 2

Comparison between ≤7-day and >7-day groups; †

• Predictors of change in eGFR from baseline to 1 year

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

• These results further support the importance of rapid diagnosis and treatment of aHUS for recovery of renal function
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.
Multivariate regressions using repeated measures analysis were performed to identify effective management for each disorder is distinct and should be initiated rapidly to avoid the most common disorders with the above clinical features are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), which are both only approved treatment for aHUS with 4 prospective clinical trials demonstrating its safety and efficacy.

METHODS

OBJECTIVE

INTRODUCTION

Data from 4 phase 2, open-label, single-arm, prospective clinical trials including both –>7 days in 76 patients. Three patients were excluded from the analysis because date of onset of aHUS manifestation was missing or baseline eGFR was >90 mL/min/1.73 m². Only data from patients who had a documented date of onset of the current aHUS manifestation prior to first dose, ≤7 days or >7 days after the current manifestation and a baseline estimated glomerular filtration rate (eGFR) of ≤7 days or >7 days after the current aHUS manifestation prior to first dose, ≤7 days or >7 days after the current aHUS manifestation.

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 m², respectively, after 1 year.

### Table 1. Demographics and Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Time to Treatment</th>
<th>&lt;7 days</th>
<th>&gt;7 days</th>
<th>All</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=21</td>
<td>n=76</td>
<td>N=97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>30 (0–69)</td>
<td>29 (0–80)</td>
<td>29 (0–80)</td>
<td>-</td>
<td>0.029†</td>
</tr>
<tr>
<td>Age group in years, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.133†</td>
</tr>
<tr>
<td>&lt;18</td>
<td>10 (48)</td>
<td>15 (20)</td>
<td>25 (26)</td>
<td>11 (52)</td>
<td>49 (64)</td>
</tr>
<tr>
<td>≥18</td>
<td>11 (52)</td>
<td>61 (80)</td>
<td>72 (74)</td>
<td>12 (57)</td>
<td>28 (37)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement mutation or autoantibody, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.133†</td>
</tr>
<tr>
<td>Any mutation or autoantibody</td>
<td>9 (43)</td>
<td>48 (63)</td>
<td>57 (59)</td>
<td>5 (24)</td>
<td>19 (25)</td>
</tr>
<tr>
<td>CFH mutation</td>
<td>5 (24)</td>
<td>19 (25)</td>
<td>24 (25)</td>
<td>12 (57)</td>
<td>28 (37)</td>
</tr>
<tr>
<td>No complement mutation or autoantibody, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.133†</td>
</tr>
<tr>
<td>Median time from last aHUS manifestation to eculizumab treatment, months (range)</td>
<td>1 (0.03–0.20)</td>
<td>1 (0.23–47.40)</td>
<td>0.75 (0.03–47.40)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Median number of TMA events, n (range)</td>
<td>1 (1–6)</td>
<td>1 (1–9)</td>
<td>1 (1–9)</td>
<td>0.421†</td>
<td></td>
</tr>
<tr>
<td>Receiving PE/PI at baseline, n (%)</td>
<td>11 (52)</td>
<td>60 (79)</td>
<td>71 (73)</td>
<td>0.001†</td>
<td></td>
</tr>
<tr>
<td>Median PE/PI duration during last aHUS manifestation prior to first dose, months (range)</td>
<td>0.10 (0.03–0.20)</td>
<td>0.67 (0.03–46.46)</td>
<td>0.49 (0.03–46.46)</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>Dialysis at baseline, n (%)</td>
<td>12 (57)</td>
<td>31 (41)</td>
<td>43 (44)</td>
<td>0.219†</td>
<td></td>
</tr>
<tr>
<td>Median dialysis duration during last aHUS manifestation prior to first dose, months (range)</td>
<td>0.05 (0.03–0.20)</td>
<td>0.39 (0.03–34.85)</td>
<td>0.30 (0.03–34.85)</td>
<td>0.007†</td>
<td></td>
</tr>
<tr>
<td>History of kidney transplantation, n (%)</td>
<td>7 (33)</td>
<td>19 (25)</td>
<td>26 (27)</td>
<td>0.578†</td>
<td></td>
</tr>
<tr>
<td>Median baseline platelet count x 10⁹/L (range)</td>
<td>81.5 (18.0–193.0)</td>
<td>133.5 (16.0–420.5)</td>
<td>127.5 (16.0–420.5)</td>
<td>0.002†</td>
<td></td>
</tr>
<tr>
<td>Platelet count &lt;150 x 10⁹/L, n (%)</td>
<td>19 (90)</td>
<td>45 (59)</td>
<td>64 (66)</td>
<td>0.008†</td>
<td></td>
</tr>
<tr>
<td>Median hemoglobin, mg/dL (range)</td>
<td>84.0 (41.0–117.0)</td>
<td>92.0 (54.0–131.0)</td>
<td>89.0 (41.0–131.0)</td>
<td>0.122†</td>
<td></td>
</tr>
<tr>
<td>Median LDH, U/L (range)</td>
<td>669.1 (131.0–7164.0)</td>
<td>297.5 (134.0–3682.0)</td>
<td>343.0 (131.0–7164.0)</td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>Median creatinine, µmol/L (range)</td>
<td>214.0 (112.0–1007.8)</td>
<td>243.1 (28.0–1169.6)</td>
<td>238.7 (28.0–1169.6)</td>
<td>0.708†</td>
<td></td>
</tr>
<tr>
<td>Median baseline eGFR, mL/min/1.73 m² (range)</td>
<td>11.0 (5.6–53.2)</td>
<td>16.0 (7.3–76.1)</td>
<td>15.9 (5.6–76.1)</td>
<td>0.299†</td>
<td></td>
</tr>
</tbody>
</table>

*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 m²; 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.
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

![Graph showing change from baseline in eGFR over time](image)

**Patients (n)**

<table>
<thead>
<tr>
<th>Treatment initiated in:</th>
<th>≤7 days</th>
<th>&gt;7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤7 days</td>
<td>21</td>
<td>76</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>20</td>
<td>49</td>
</tr>
</tbody>
</table>

**Coefficients and P values**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.583</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>0.577</td>
</tr>
<tr>
<td>History of aHUS</td>
<td>0.493</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>0.619</td>
</tr>
<tr>
<td>Time from aHUS manifestation</td>
<td>0.0001</td>
</tr>
<tr>
<td>Eculizumab treatment</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Predictors of eGFR Improvement**

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

Figure 2. Proportions of Patients With Sustained Response* in eGFR

![Graph showing proportions of patients with sustained eGFR response](image)

**Patients (n)**

<table>
<thead>
<tr>
<th>Time From Start of Eculizumab Treatment (months)</th>
<th>≤7 days</th>
<th>&gt;7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>46</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>47</td>
<td>46</td>
</tr>
</tbody>
</table>

*P<0.05 between subgroups at all time points.
*Defined as an increase in eGFR by ≥15 mL/min/1.73 m².
*Number of patients achieving sustained eGFR response at each visit.

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

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0061</td>
<td></td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>0.0181</td>
<td></td>
</tr>
<tr>
<td>History of aHUS</td>
<td>0.1964</td>
<td></td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>0.03</td>
<td>0.0181</td>
</tr>
<tr>
<td>Time from aHUS manifestation</td>
<td>-0.03</td>
<td>0.0181</td>
</tr>
<tr>
<td>Eculizumab treatment</td>
<td>0.21</td>
<td>0.1964</td>
</tr>
</tbody>
</table>

Figure 7. Change From Baseline in eGFR Over Time

![Graph showing change from baseline in eGFR over time](image)
Effective management for each disorder is distinct and should be initiated rapidly to avoid progression to multiorgan failure. Patients presenting with hemolytic anemia, thrombocytopenia, and organ dysfunction in the intensive care unit are clinical emergencies and can be difficult to diagnose and manage. To evaluate the effects of initiating eculizumab treatment ≤7 days or >7 days after the current manifestation of aHUS, the present study pooled data from four phase 2, open-label, single-arm, prospective clinical trials (NCT00844428, NCT01193348, NCT01194973) that included both pediatric and adult patients with aHUS (NCT00844545, NCT00844844, NCT00838513). Results were stratified according to whether patients received eculizumab treatment ≤7 days in 21 patients or >7 days in 71 patients from baseline in eGFR. A total of 97 patients were included in the analysis; three patients were excluded because date of onset of aHUS was >7 days from 1 month onward.

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

<table>
<thead>
<tr>
<th>Effect*</th>
<th>Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>aHUS duration (day)</td>
<td>-0.03</td>
<td>0.0181</td>
</tr>
<tr>
<td>Age group (child vs adult)</td>
<td>-</td>
<td>0.0061</td>
</tr>
<tr>
<td>Baseline LDH (U/L)</td>
<td>0.01</td>
<td>0.0078</td>
</tr>
<tr>
<td>Baseline hemoglobin (g/L)</td>
<td>-0.97</td>
<td>0.0002</td>
</tr>
<tr>
<td>Trial visit</td>
<td>-</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>0.21</td>
<td>0.1964</td>
</tr>
</tbody>
</table>

*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.

### 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.
  - A higher percentage of patients who received eculizumab within 7 days had normal eGFR after 1 month of treatment which was sustained through 12 months.
- In addition to early treatment initiation with eculizumab, younger patient age, higher lactate dehydrogenase level, and lower hemoglobin level at baseline were associated with eGFR improvement.
- These results further support the importance of rapid diagnosis and treatment of aHUS for recovery of renal function.

### REFERENCES

5. US Food and Drug Administration. Soliris (eculizumab) [prescribing information], Cheshire, CT: Alexion Pharmaceuticals, Inc.; 2014.

### ACKNOWLEDGMENTS

The authors would like to acknowledge Peloton Advantage, LLC, which provided editorial support with funding from Alexion Pharmaceuticals, Inc.