Eculizumab Inhibits Thrombotic Microangiopathy and Improves Renal Function in Pediatric Patients With Atypical Hemolytic Uremic Syndrome

Larry A. Greenbaum, 1 Marc Fäb, 1 Michel Tsimaratos, 1 Gianluigi Ardissono, 1 Samhar I. Al-Ashkar, 1 Jonathan Evans, 1 Paul Henning, 1 Kenneth V. Lieberman, 1 Silvio Maringhini, 1 Lars Page, 2 Lesley Rees, 1 Nicole Regev, 1 Johan Vanelderen, 1 Massimo Vale, 1 Camille L. Bedoschin, 1 Christoph Licht

1 University of Melbourne, Melbourne, Australia; 2 National Institute for Health Research Southampton Biomedical Research Centre, Southampton, UK

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INTRODUCTION

Atypical Hemolytic Uremic Syndrome (aHUS) is a rare systemic microangiopathy of unknown etiology that results in thrombotic microangiopathy, usually characterized by hemolytic anemia, thrombocytopenia, and acute kidney injury. Eculizumab (Soliris®; Alexion Pharmaceuticals, Inc., Cheshire, CT) is a humanized monoclonal antibody that binds to C5 and prevents its cleavage to C5b-9, thus inhibiting terminal complement activation.

METHODS

Study Design

A total of 22 pediatric patients (ages 1 month to 17 years) with aHUS and known complement pathway abnormalities were recruited to the study. All patients received eculizumab, and those on dialysis at baseline were randomized to continue or discontinue dialysis. The study was approved by all institutional review boards and conducted in accordance with the Declaration of Helsinki. All patients or parents provided written informed consent.

RESULTS

Patient Disposition

Twelve patients had evidence of hemolytic anemia and thrombocytopenia, 10 patients had acute kidney injury, 1 patient had mesangiocapillary glomerulonephritis, and 1 patient had an atypical protein-losing nephropathy. The demographic characteristics of the patients are shown in Table 1.

Table 1. Demographics of Pediatric Patients With aHUS Enrolled in the Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male/Female</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median (Range)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Median (Range)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Median (Range)</td>
</tr>
<tr>
<td>Prior renal transplant, n (%)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Asian 5, African American 8, Caucasian 9, Other 1</td>
</tr>
<tr>
<td>C5b-9 immunoassay, n (%)</td>
<td>Positive 14, Negative 8</td>
</tr>
<tr>
<td>Factor H, n (%)</td>
<td>&lt;0.01 Immunodiffusion 11, Factor H autoantibody positive 1</td>
</tr>
<tr>
<td>Patients with CFHR1/3 polymorphism, n (%)</td>
<td>1</td>
</tr>
</tbody>
</table>

Efficacy Outcomes

Significant and continuous improvement over time in eGFR was observed (Figure 1). A total of 19 patients (86%) had eGFR improvement from baseline ≥15 mL/min/1.73 m2, and 18 patients (82%) had ≥25% decrease in SCr from baseline (sustained for ≥2 consecutive measurements obtained ≥4 weeks apart).

Dosing

Enrolled 27

Positive test for Shiga toxin 6

Family request to withdraw patient 1

Treated 22

Median duration (range) from aHUS diagnosis until screening (months) 0.6 (0.03–191)

Table 4. Summary of Renal Outcomes

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR improvement from baseline ≥15 mL/min/1.73 m2</td>
<td>19 (86)</td>
</tr>
<tr>
<td>≥25% decrease in SCr from baseline (sustained for ≥2 consecutive measurements obtained ≥4 weeks apart)</td>
<td>18 (82)</td>
</tr>
<tr>
<td>Normalized eGFR (≥90 mL/min/1.73 m2)</td>
<td>10 (45)</td>
</tr>
<tr>
<td>Normalized eGFR (≥45–59 mL/min/1.73 m2)</td>
<td>7 (31)</td>
</tr>
<tr>
<td>Normalized eGFR (&lt;15 mL/min/1.73 m2)</td>
<td>5 (23)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Eculizumab is a well-tolerated and efficacious treatment for pediatric patients with aHUS. The median time from current manifestation to first dose of eculizumab was 6 days. Further studies are needed to determine the optimal dosing strategy for pediatric patients with aHUS.

REFERENCES