A systematic review on the efficacy and safety of eculizumab for atypical hemolytic uremic syndrome

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A systematic review on the efficacy and safety of eculizumab for atypical hemolytic uremic syndrome

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Implication for health policy/practice/education: Eculizumab may be effective in the treatment of aHUS.

In this paper, we performed a systematic review of randomized trials and observational studies to evaluate the efficacy and safety of eculizumab in the treatment of aHUS.

Context: Atypical hemolytic uremic syndrome (aHUS) is a rare disease characterized by acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia. The etiology of aHUS is related to complement dysregulation, which can result in glomerular endothelial cell damage. Eculizumab is a monoclonal antibody that blocks the formation of the terminal complement complex (C5b-9).

Evidence Acquisition: An electronic literature search was conducted to identify relevant studies. We included randomized trials and observational studies using eculizumab in the treatment of aHUS. The literature search and reference mining yielded 571 potential relevant articles. After removing duplicates and articles that were not relevant, five studies were included in the systematic review.

Results: The systematic review showed that eculizumab was effective in the treatment of aHUS. However, further large randomized trials are suggested.

Conclusions: Eculizumab may be effective in the treatment of aHUS. Further studies are needed to confirm its efficacy and safety.

Keywords:
- Atypical hemolytic uremic syndrome
- Eculizumab
- Thrombotic microangiopathy
- Acute kidney injury
- Chronic kidney disease

Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare disease characterized by acute kidney injury, microangiopathic hemolytic anemia, and thrombocytopenia. The etiology of aHUS is related to complement dysregulation, which can result in glomerular endothelial cell damage. Eculizumab is a monoclonal antibody that blocks the formation of the terminal complement complex (C5b-9). Several studies done
on patients with aHUS have mentioned the efficacy of eculizumab in the treatment of aHUS (6,8-10). Age (being younger), higher baseline LDH and lower baseline hemoglobin are related to the improvement of greater estimated glomerular filtration rate (eGFR) (6). Early eculizumab initiation resulted in improved renal recovery, showing the necessity of fast diagnosis and treatment of aHUS (6). Our study aims to have a systematic review about the efficacy and safety of eculizumab for aHUS.

Evidence Acquisitions
We searched PubMed, the Cochrane Library, Science Direct, Scopus, and Web of Science (updated up to October 2017). The search term was "Hemolytic Uremic Syndrome" and (eculizumab or Soliris). We scanned bibliographies in relevant articles and conference proceedings. Studies by the same author were verified for possible overlapping participant groups. If the study was reported as duplicate, only the most recent or complete study was included. The following selection criteria were applied: We included all study designs except case histories.

Data extraction and quality assessment
Two independent reviewers extracted data from the articles, according to the selection criteria. Disagreements were resolved by discussion between two reviewers considering the opinion of a third reviewer. The following information was abstracted from each included study: first author and year of publication, design of study, sample size, mean age of patients, intervention regime, follow-up duration, and outcome measures for each group. All the analysis were based on previously published studies; thus, no ethical approval or patient consent was required.

3. Results
Search results and characteristics
The literature search and reference mining yielded 571 potential relevant articles. We removed 173 articles because of duplication. We also excluded 245 articles after reviewing the titles and abstracts because they were books, book sections or review papers, and therefore not relevant. Then, we reviewed the full-text of selected articles and removed 61 studies because the topics were not relevant to the subject. At last, 5 studies (2,6,11-13) were included in the systematic review. The flow diagram of the study selection is given in Figure 1. Characteristics and the details of the studies are summarized in Table 1.

Outcomes and adverse effects
The summary of outcomes of our study is provided in Table 2. Efficacy of eculizumab for treatment of aHUS in most of the studies was assessed with platelet count normalization, TMA event-free status, and complete TMA response and also eGFR improvement greater than 15 mL/min/1.73 m². Note that in Table 2, two different trials of the Lichen study each with 2-year, 1-year and 26-week follow-up have been considered. However, the conclusion of both trials was the same.

Discussion
In this systematic review, five studies were included, but none of them was a randomized control trial. Therefore, we couldn’t do a quantitative synthesis (meta-analysis). In Table 2, we reported two separate entries from the Walle study (6) and six entries (sub-studies) from the Licht study (13). From Walle studies (6), the two sub-studies were different and were therefore provided as two entries because of their time-to-treatment from last aHUS manifestation (<7 days and >7 days). The Licht study (13) was combined of two trials, each of them was divided into three separate entries because of different follow-up time (Table 2). Most of the reported studies were done on adult patients except for the studies by Greenbaum (14) and Sheerin et al (2), where 15 out of 43 patients were children.

Figure 1. Flow chart of study selection process.
<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Year</th>
<th>Design</th>
<th>Sample size</th>
<th>MEAN age (y)</th>
<th>Sex (female) No. (%)</th>
<th>Follow-up</th>
<th>Intervention regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Walle (group 1)</td>
<td>2017</td>
<td>Prospective study</td>
<td>21</td>
<td>30</td>
<td>11 (52)</td>
<td>1 year</td>
<td>Not Reported</td>
</tr>
<tr>
<td>2</td>
<td>Walle (group 2)</td>
<td>2017</td>
<td>Prospective study</td>
<td>76</td>
<td>29</td>
<td>49 (64)</td>
<td>1 year</td>
<td>Not Reported</td>
</tr>
<tr>
<td>3</td>
<td>Fakhouri</td>
<td>2016</td>
<td>Trial</td>
<td>41</td>
<td>40.6</td>
<td>28 (68)</td>
<td>1 year</td>
<td>Intravenously at 900 mg once a week for 4 weeks, 1200 mg at week 5, and then 1200 mg every 2 weeks.</td>
</tr>
<tr>
<td>4</td>
<td>Sheerin</td>
<td>2016</td>
<td>Descriptive</td>
<td>43</td>
<td></td>
<td>15 were children and 28 were adult.</td>
<td>1 year</td>
<td>All adult patients received an initial dose of 900 mg via 35-min IV infusion and then 900 mg every 7 days for the first 4 doses, followed by 1200 mg for the fifth dose 7 days later. The maintenance dose was 1200 mg every 14 days. The pediatric dosing schedule was adjusted according to weight</td>
</tr>
<tr>
<td>5</td>
<td>Greenbaum</td>
<td>2016</td>
<td>Prospective study</td>
<td>22</td>
<td>6.5</td>
<td>10 (45)</td>
<td>26 weeks</td>
<td>Eculizumab was administered at doses prespecified by body weight</td>
</tr>
<tr>
<td>6</td>
<td>Licht 1</td>
<td>2015</td>
<td>Trial</td>
<td>17</td>
<td>28</td>
<td>12 (71)</td>
<td>2 year</td>
<td>Not reported</td>
</tr>
<tr>
<td>7</td>
<td>Licht 1</td>
<td>2015</td>
<td>Trial</td>
<td>17</td>
<td>28</td>
<td>12 (71)</td>
<td>1 year</td>
<td>Not reported</td>
</tr>
<tr>
<td>8</td>
<td>Licht 1</td>
<td>2015</td>
<td>Trial</td>
<td>17</td>
<td>28</td>
<td>12 (71)</td>
<td>26 weeks</td>
<td>Not reported</td>
</tr>
<tr>
<td>9</td>
<td>Licht 2</td>
<td>2015</td>
<td>Trial</td>
<td>20</td>
<td>28</td>
<td>12 (60)</td>
<td>2 year</td>
<td>Not Reported</td>
</tr>
<tr>
<td>10</td>
<td>Licht 2</td>
<td>2015</td>
<td>Trial</td>
<td>20</td>
<td>28</td>
<td>12 (60)</td>
<td>1 year</td>
<td>Not reported</td>
</tr>
<tr>
<td>11</td>
<td>Licht 2</td>
<td>2015</td>
<td>Trial</td>
<td>20</td>
<td>28</td>
<td>12 (60)</td>
<td>26 weeks</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Table 2. Outcome of studies

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Platelet count normalization</th>
<th>TMA event-free status</th>
<th>Complete TMA response</th>
<th>eGFR improvement ≥15 mL/min/1.73 m²</th>
<th>Adverse effects</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Walle, group 1</td>
<td>18 (86)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>17 (81)</td>
<td>Not reported</td>
<td>Early eculizumab initiation resulted in renal recovery improvement. Showing the importance of quick diagnosis and treatment of patients with aHUS.</td>
</tr>
<tr>
<td>2</td>
<td>Walle group 2</td>
<td>42 (55)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>36 (47)</td>
<td>Not reported</td>
<td>Results show the advantages of eculizumab in adult aHUS patients where hematologic, renal, and quality-of-life parameters improved, and dialysis discontinuation and transplant protection were reported.</td>
</tr>
<tr>
<td>3</td>
<td>Fakhouri</td>
<td>40 (98)</td>
<td>77%-97%</td>
<td>30 (73)</td>
<td>22 (54)</td>
<td>Meningococcal infections=2</td>
<td>They discussed the experience of a providing a locally delivery national specialized service in England for the assessment and treatment of aHUS patients. The patients could therefore receive eculizumab when they needed it for the whole period of treatment.</td>
</tr>
<tr>
<td>4</td>
<td>Sheerin</td>
<td>Not reported</td>
<td>41</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Patients with treatment-emergent adverse events related to eculizumab=9 (Including abdominal discomfort, agitation, alopecia, diaper dermatitis, diarrhea, dyspepsia, ear infection, eye discharge, eczema, fungal infection, headache, injection site rash, muscle spasms, nasopharyngitis, pain, rash, respiratory syncytial virus infection, viral respiratory tract infection, viral upper respiratory tract infection) The stated the efficacy and safety of eculizumab for aHUS pediatric patients, and proposed an immediate eculizumab initiation after diagnosis in children.</td>
</tr>
<tr>
<td>5</td>
<td>Greenbaum</td>
<td>21 (95)</td>
<td>21 (95)</td>
<td>14 (64)</td>
<td>19 (86)</td>
<td></td>
<td>Eculizumab had no new safety concerns or meningococcal infections. Clinical benefits were observed sooner by eculizumab treatment of aHUS which maintained during a 2-year follow-up.</td>
</tr>
<tr>
<td>6</td>
<td>Licht 1 2 year</td>
<td>15 (88)</td>
<td>15 (88)</td>
<td>13 (76)</td>
<td>10 (59)</td>
<td>Serious adverse events: Accelerated hypertension=2, Asymptomatic, bacteriuria=1, Hypertension=1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Licht 1 1 year</td>
<td>15 (88)</td>
<td>15 (88)</td>
<td>13 (76)</td>
<td>9 (53)</td>
<td>Serious adverse events: Accelerated hypertension=2, Asymptomatic bacteriuria=1, Hypertension=1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Licht 1 26 weeks</td>
<td>14 (82)</td>
<td>15 (88)</td>
<td>11 (65)</td>
<td>8 (47)</td>
<td>Serious adverse events, Accelerated hypertension=1, Hypertension=1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Licht 2 2 year</td>
<td>18 (90)</td>
<td>19 (95)</td>
<td>11 (55)</td>
<td>8 (40)</td>
<td>Serious Adverse events, Influenza=1 (5) Peritonitis= 1 (5), Venous sclerosis at infusion site= 2 (10)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Licht 2 1 year</td>
<td>18 (90)</td>
<td>17 (85)</td>
<td>7 (35)</td>
<td>3 (15)</td>
<td>Serious adverse events Influenza=1 (5), Peritonitis= 1 (5), Venous sclerosis at infusion site= 2 (5)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Licht 2 26 weeks</td>
<td>18 (90)</td>
<td>16 (80)</td>
<td>5 (25)</td>
<td>1 (5)</td>
<td>Serious Adverse events, Peritonitis= 1 (5) Venous sclerosis at, infusion site= 1 (5)</td>
<td></td>
</tr>
</tbody>
</table>
Only in the study by Licht et al, the follow-up was 2 years, other studies had 26 weeks up to 1 year. Some disparities were seen in outcomes of the chosen studies; for example, in the study by Sheerin (2), only TMA event-free status was reported for outcome measures. Some studies such as Greenbaum (14) and Licht et al (13) reported adverse events by details. The studies by Walle et al (6) and Greenbaum et al (12) emphasized early eculizumab initiation for aHUS treatment. Fakhouri et al (11) suggested the benefits of eculizumab in the treatment of adult patients with aHUS, such as quality-of-life parameters, which are noticeable outcomes in treatment of any disease.

Sheerin et al (2) discussed the necessity of having locally available national specialized services for the investigation and treatment of patients with aHUS. They reported that such a system enabled aHUS patients to receive eculizumab when they need it (2). In the study of Macia et al (15), the authors researched eculizumab discontinuation. They showed that the reasons for treatment discontinuation include both medical and economic concerns as well as patients' request (15). That study suggested that TMA manifestations following discontinuation are unpredictable in both severity and timing (15). They indicated an evidence-based decision making, better risk stratification and valid monitoring strategies for eculizumab (15).

Nowadays, eculizumab is not administered for the treatment of aHUS in Iran. One of the main reasons is the high cost. Sheerin et al (2) discussed the necessity of having a subsidized system for aHUS patients. The findings of a systematic review conducted in 2013 (16) on the application of eculizumab in aHUS match our findings. They performed two small, uncontrolled prospective multinational, multicenter studies, and one small uncontrolled multinational, multicenter retrospective study (16). That systematic review concluded that eculizumab is clinically effective for the treatment of aHUS. They however suggested further research to evaluate eculizumab for the treatment of aHUS. In another review study conducted in 2013 (8) on the application of eculizumab, eculizumab was shown to be effective in both pediatric and adult patients (8). They presented an association between eculizumab and increased susceptibility to meningococcal infection such that the patients were recommended to receive meningococcal vaccine (8). In the study of Fakhouri et al (11), two cases with meningococcal infections were reported, but in two trials of the Licht study, no meningococcal infection case was reported. We suggest confirmation of their findings by further controlled and prospective studies.

Conclusion

Acknowledging the limitations of our research work due to the size and nature of the studies included, our systematic review shows that eculizumab is effective in the treatment of aHUS. However, further large randomized trials are recommended.

Authors' contribution

MGS, YR, ME and AO searched the data and prepared the primary draft. AA edited and finalized the paper. All authors read and signed the final manuscript. MM and HN contributed equally to prepare the paper.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely taken into account by the authors.

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Eculizumab for hemolytic uremic syndrome


