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

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ABSTRACT

Context: To date, several studies have been done regarding the treatment of atypical hemolytic uremic syndrome (aHUS) which discussed eculizumab as a potential treatment for this syndrome. However, the safety and efficacy of eculizumab were not fully assessed. This study aims to do a systematic review about the efficacy and safety of eculizumab in treatment of aHUS.

Evidence Acquisitions: An electronic literature search was conducted to identify appropriate studies. We included all randomized trials and observational studies about using eculizumab in aHUS. Two independent reviewers extracted data from the articles according to the selection criteria.

Results: Eligible studies were included in this systematic review. 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, and removed 61 studies because the topics were not relevant to the subject. Finally, five studies were included in the systematic review.

Conclusions: Acknowledging the limitations of the study due to the size and nature of the included studies, our systematic review shows that eculizumab was effective in the treatment of aHUS. However, further large randomized trials are suggested.

Implication for health policy/practice/research/medical education:

Eculizumab may be effective in the treatment of aHUS.

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Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare disease, which is usually characterized by acute kidney injury (AKI), thrombocytopenia and microangiopathic hemolytic anemia (MAHA) (2). Using suitable bacteriological, molecular and serological investigations, aHUS can be differentiated from typical HUS (Shiga toxin-producing *Escherichia coli*), which is related to a preceding enterohemorrhagic *E. coli* infection (EHEC) (1,2). The atypical form of aHUS has a poor prognosis where up to 50% of cases may result in end-stage renal disease, and up to 25% of lethal outcomes progress to an acute phase (3-5). Complement dysregulation which

results in glomerular endothelial cell damage is known to be a significant element in aHUS etiology (3-5). Along with possible irreversible damages to other organs due to aHUS, fast progress of thrombotic microangiopathy (TMA) is an indication of a need for urgent treatment (6,7). TMA may result in acute renal dysfunction in early phases of the disease (6,7). It has also been discussed that AKI and chronic kidney disease (CKD) are correlated where each one can be seen as a risk factor for the other (6,7). Eculizumab (Soliris) is a monoclonal antibody which binds to C5 and prevents its division into C5a and C5b. Therefore, it fully blocks the formation of terminal complement complex (C5b-9) (5). Several studies done

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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.

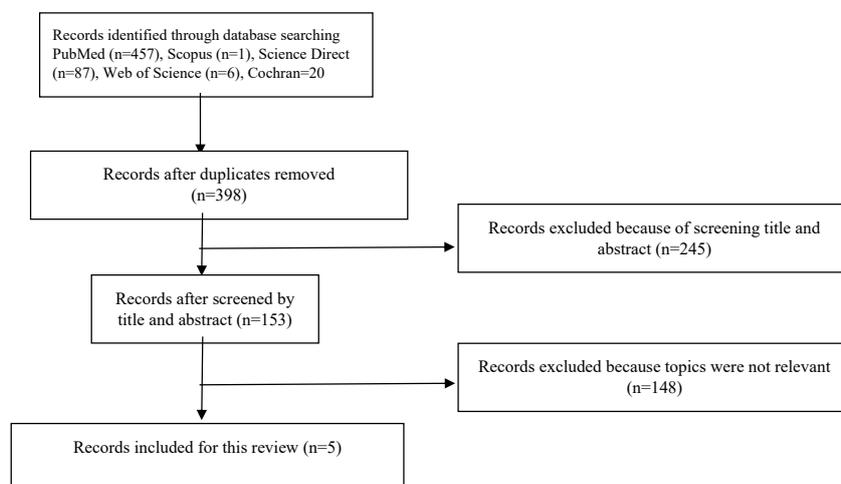


Figure 1. Flow chart of study selection process.

Table 1. General characteristics of trials included in this systematic review

No.	Name	Year	Design	Sample size	MEAN age (y)	Sex (female) No. (%)	Follow-up	Intervention regime
1	Walle (group 1)	2017	Prospective study Time to treatment from last aHUS manifestation <7 days	21	30	11 (52)	1 year	Not Reported
2	Walle (group 2)	2017	Prospective study Time to treatment from last aHUS manifestation >7 days	76	29	49 (64)	1 year	Not Reported
3	Fakhouri	2016	Trial	41	40.6	28 (68)	1 year	Intravenously at 900 mg once a week for 4 weeks, 1200 mg at week 5, and then 1200 mg every 2 weeks.
4	Sheerin	2016	Descriptive	43	15 were children and 28 were adult.	23	1 year	All adult patients received an initial dose of 900mg via 35-min IV infusion and then 900mg every 7 days for the first 4 doses, followed by 1200mg for the fifth dose 7 days later. The maintenance dose was 1200mg every 14 days. The pediatric dosing schedule was adjusted according to weight
5	Greenbaum	2016	Prospective study	22	6.5	10 (45)	26 weeks	Eculizumab was administered at doses prespecified by body weight
6	Licht 1 2 year	2015	Trial	17	28	12 (71)	2 year	Not reported
7	Licht 1 1 year	2015	Trial	17	28	12 (71)	1 year	Not reported
8	Licht 1 26 weeks	2015	Trial	17	28	12 (71)	26 weeks	Not reported
9	Licht 2 2 year	2015	Trial	20	28	12 (60)	2 year	Not Reported
10	Licht 2 1 year	2015	Trial	20	28	12 (60)	1 year	Not reported
11	Licht 2 26 weeks	2015	Trial	20	28	12 (60)	26 weeks	Not reported

Table 2. Outcome of studies

No.	Name	Platelet count normalization	TMA event-free status	Complete TMA response	eGFR improvement ≥ 15 mL/min/1.73 m ²	Adverse effects	Conclusion
1	Walle, group 1	18 (86)	Not reported	Not reported	17 (81)	Not reported	Early eculizumab initiation resulted in renal recovery improvement. Showing the importance of quick diagnosis and treatment of patients with aHUS.
2	Walle group 2	42 (55)	Not reported	Not reported	36 (47)	Not reported	
3	Fakhouri	40 (98)	77%-97%	30 (73)	22 (54)	Meningococcal infections=2	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.
4	Sheerin	Not reported	41	Not reported	Not reported	Not reported	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.
5	Greenbaum	21 (95)	21 (95)	14 (64)	19 (86)	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.
6	Licht 1 2 year	15 (88)	15 (88)	13 (76)	10 (59)	Serious adverse events: Accelerated hypertension=2, Asymptomatic, bacteriuria=1, Hypertension=1	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.
7	Licht 1 1 year	15 (88)	15 (88)	13 (76)	9 (53)	Serious adverse events: Accelerated hypertension=2, Asymptomatic bacteriuria=1, Hypertension=1	
8	Licht 1 26 weeks	14 (82)	15 (88)	11 (65)	8 (47)	Serious adverse events, Accelerated hypertension=1, Hypertension=1	
9	Licht 2 2 year	18 (90)	19 (95)	11 (55)	8 (40)	Serious Adverse events, Influenza=1 (5) Peritonitis= 1 (5), Venous sclerosis at infusion site= 2 (10)	
10	Licht 2 1 year	18 (90)	17 (85)	7 (35)	3 (15)	Serious adverse events Influenza=1 (5), Peritonitis= 1 (5), Venous sclerosis at infusion site= 2 (5)	
11	Licht 2 26 weeks	18 (90)	16 (80)	5 (25)	1 (5)	Serious Adverse events, Peritonitis= 1 (5) Venous sclerosis at, infusion site= 1 (5)	

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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