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RESEARCH LETTER

Eculizumab for pregnancy-related atypical hemolytic uremic syndrome

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To the Editor,

Atypical hemolytic uremic syndrome (aHUS) is a rare disease caused by uncontrolled activation of the alternative pathway of complement leading to systemic thrombotic microangiopathy (TMA) [1–4]. In the Global aHUS Registry, pregnancy was the cause of aHUS in 9% of 302 female patients [5]. Pregnancy is associated with moderate elevation in the activity of the complement system that is essential for host defense against infection and plays an integral role in normal pregnancy [6]. Uncontrolled activation of the complement system can result from interaction between complement-activating complications of pregnancy, such as preeclampsia, surgery, or bleeding [7], and pathogenic complement gene variants, which could be detected in 40%–60% of females with pregnancy-associated aHUS (p-aHUS) [8]. Loss of complement regulatory proteins expressed in placenta may also facilitate the development of p-aHUS after delivery. p-aHUS is associated with high perinatal and maternal morbidity and mortality and frequent transition of acute kidney injury (AKI) to chronic kidney disease requiring renal replacement therapy [9].

Eculizumab is a humanized monoclonal antibody that inhibits the cleavage of complement protein C5 and prevents progressive TMA-mediated endothelial damage and vascular microthrombosis. Data on p-aHUS treated with eculizumab are limited, although its efficacy and safety has been supported by case reports and series and Global aHUS Registry data [10–13]. The objective of this retrospective study was to evaluate the efficacy of the early and delayed therapy with eculizumab in females with p-aHUS.

We enrolled 85 females with the first-episode p-aHUS who were referred to our tertiary care hospital over the 10-year period from the regional perinatal medical centers (Supplementary Table S1). We used the algorithm proposed by Fakhouri *et al.* to diagnose p-aHUS and to rule out the other potential causes of TMA in pregnancy (Supplementary Data) [14]. All patients presented with profound thrombocytopenia, microangiopathic hemolytic anemia, and severe AKI that usually required therapy with hemodialysis within the first days after disease onset. Moreover, 95% of patients had various extrarenal manifestations, including acute respiratory distress syndrome (54%), coma (20%), acute heart failure (12%), stroke (6%), and myocardial infarction (1%) (Supplementary Table S2). As in the previous studies [10, 11], most patients developed p-aHUS within the first few days of the postpartum period. In all females, TMA was preceded by obstetric complications or infection that amplify the activity of the complement system.

Therapy with eculizumab (at a weekly dose of 900 mg for the first 4 weeks, followed by 1200 mg 1 week later, then 1200 mg every 2 weeks) was administered to 56 (65.8%) of 85 females with p-aHUS (Table 1). Treatment with eculizumab was early (initiated within 7 days after disease onset) in 28 patients, delayed (on day 8 to 20) in 15 patients, and late (on day 21 or more) in 13 patients. Fifty-one patients completed the induction therapy with eculizumab (four infusions), whereas five patients received only one infusion of the complement inhibitor. From 2013 to 2019, we used the original eculizumab (Soliris, Alexion Pharmaceuticals Inc.), whereas from April 2019 all patients were treated with a biosimilar of eculizumab (Elizaria, Generuim) [15, 16].

The data were compared using a Mann–Whitney test for continuous data and Chi-square test or Fisher's exact test for categorical data as appropriate. The event-free survival was studied by the Kaplan–Meier method. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for the study endpoints were calculated by a logistic regression model.

At 4 months, the primary composite endpoint (death or chronic renal failure requiring regular dialysis treatment) was achieved in 11 (19.6%) of 56 patients treated with eculizumab and in 14 (48.2%) of 29 patients treated without eculizumab (OR 0.26; 95% CI 0.10–0.70; $P = 0011$) (Fig. 1). In patients who received early, delayed, or late complement inhibition therapy, the occurrences of the primary endpoint were 0% (0/28), 26.7% (4/15), and 53.8% (7/13), respectively. ORs of death or end-stage renal disease versus control were 0.39 (95% CI 0.10–1.51, $P = 0.208$) with delayed eculizumab and 1.25 (95% CI 0.34–4.64, $P = 0.669$) with late eculizumab.

Thirteen (12.9%) of 85 patients with p-aHUS died from progressive multiple organ system failure within 2 to 40 days after disease onset, including 3 (5.7%) of 53 patients from eculizumab group and 10 (34.5%) of 29 patients from the control group (OR 0.11, 95% CI 0.03–0.43, P =0.0008). All-cause mortality values were 0% (0/28), 6.7% (1/15), and 15.4% (2/13) with early, delayed, and late eculizumab administration, respectively. ORs of death versus control were 0.14 (95% CI 0.02–1.19, $P = 0.670$) and 0.35 (95% CI

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Table 1: Demographic and clinical characteristics of patients treated and not treated with eculizumab

	Eculizumab* (*n* = 56)	Without eculizumab (*n* = 29)	*P*
Age, years	28.5 (24.5; 33.0)	29.0 (25.0; 36.0)	0549
Acute kidney injury, *n* (%)	56 (100)	29 (100)	0996
Anuria, *n* (%)	52 (92.9)	22 (75.9)	0028
Hemoglobin, g/l	53 (94.6)	22 (75.9)	0028
Serum creatinine, mmol/l	499.0 (366.5; 640.5)	393.0 (260.0; 490.0)	0011
Hemoglobin, g/l	62.0 (53.0; 72.0)	67.0 (55.0; 78.0)	0501
Lactate dehydrogenase (U/l)	2750.0 (1355.0; 4299.0)	2038.0 (843.0; 3062.0)	0105
Platelet count, $\times 10^9$/l	47.0 (27.0; 65.0)	56.0 (36.0; 89.0)	0177
Multiple organ failure, *n* (%)	50 (89.3)	26 (89.7)	0965
Extrarenal manifestations, *n* (%)	52 (92.9)	29 (100)	0146
Acute respiratory distress syndrome	27 (48.2)	17 (58.6)	0368
Mechanical ventilation	27 (48.2)	17 (58.6)	0368
Coma	8 (14.3)	8 (27.6)	0117
Stroke	3 (5.4)	2 (6.9)	0558
Seizures	8 (14.3)	6 (20.7)	0457
Acute heart failure	7 (12.5)	3 (10.3)	0935
Liver damage	44 (78.6)	25 (86.2)	0399

[a]All patients receiving eculizumab were treated with antimicrobial agents penetrating the blood–brain barrier (e.g. carbapenems, third or fourth generation cephalosporins, fluoroquinolones) to prevent serious meningococcal infection and were immunized by Menactra vaccine after recovery. Antibacterials were continued for at least 2 weeks after vaccination. Eculizumab was discontinued in 34 (64.2%) of 53 surviving patients immediately after induction period (*n* = 12) or after maintenance therapy (*n* = 22) for a median of 6.0 months (IQR 1.5; 12.0). Median follow-up after discontinuation of the complement inhibition therapy was 6.0 years (IQR 4.0; 7.0). Nineteen patients continued maintenance treatment with eculizumab for a median of 4.0 years (IQR 3.0; 5.0). There were no recurrencies of aHUS both in patients who stopped eculizumab or continued to receive maintenance treatment.

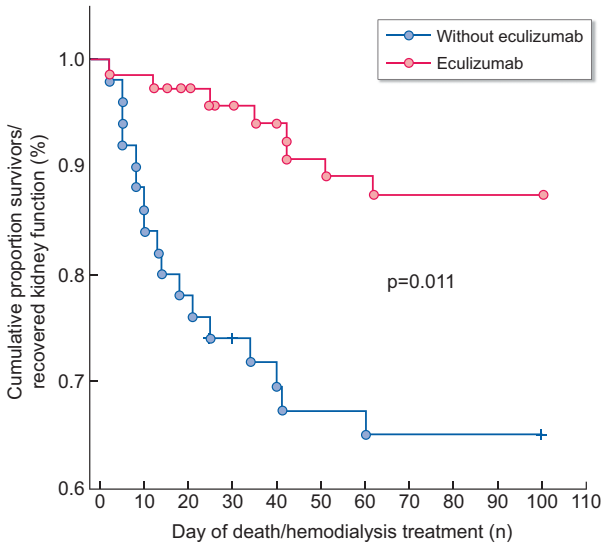

Figure 1: Survival without reaching end stage renal disease in patients with p-aHUS treated and not treated with eculizumab (Kaplan-Meier method).

0.06–1.87, *P* = 0.281) with delayed and late complement inhibition therapy, respectively.

At day 28 after initiation of eculizumab, hematologic response (platelet recovery and normalization of lactate dehydrogenase activity) was achieved in all surviving patients. Platelet count and serum lactate dehydrogenase were normal on the third day after initiation of complement inhibition therapy in 87.3% (48/55) and 14.5% (8/55) patients, on the seventh day in 90.9% (50/55) and 56.4% (31/55) patients, and on the 28th day in 100% (53/53) and 100% (53/53) patients, respectively.

Among 72 surviving patients, kidney function completely recovered in 71.7% (38/53) females treated with eculizumab and 52.6% (10/19) females treated without eculizumab (*P* = 0.392), whereas 15.1% (8/53) and 21.1% (4/19) patients, respectively, developed end-stage renal disease (*P* = 0.035). Recovery of kidney function rates in patients who received early, delayed, or late eculizumab therapy were 100% (28/28), 78.6% (11/14), and 54.5% (6/11), respectively, whereas dialysis dependency following AKI was observed in 0% (0/28), 21.4% (3/14), and 45.5% (5/11) cases, respectively. Adverse events requiring discontinuation of eculizumab were not recorded.

Our findings confirmed the low efficacy of plasma exchange therapy alone in p-aHUS [17]. Approximately half of our patients treated without eculizumab died from progressive multiple organ system failure or developed end-stage renal disease following AKI. However, plasma exchange remains a standard treatment for thrombotic thrombocytopenia purpura. Rapid differential diagnosis between p-aHUS and thrombotic thrombocytopenia purpura may be challenging in clinical practice, whereas plasma exchange therapy may be beneficial in a proportion of aHUS patients. Therefore, we recommend immediate initiation of plasma exchange in all females who present with persisting TMA after delivery.

Induction therapy with eculizumab in 56 patients with p-aHUS resulted in a 74% reduction in the risk of composite primary endpoint that included death and end-stage renal disease and an 89% reduction in the risk of death from all causes as compared to plasma therapy alone. Complement inhibition therapy was most effective in 28 patients, who started eculizumab within the first week after p-aHUS presentation. All females from this group survived and completely recovered kidney function. Later initiation of eculizumab treatment was not associated with a significant reduction in the risk of composite primary endpoint. However, delayed and late complement inhibition therapy was associated with a trend to a lower all-cause mortality compared to plasma therapy alone.

The limitations of our study were retrospective design and lack of randomization. The sample size was relatively small limiting the power of statistical analysis. Nevertheless, we conducted one of the largest studies evaluating the outcomes and the efficacy of eculizumab treatment in patients with p-aHUS.

In summary, induction treatment with eculizumab in women with p-aHUS resulted in rapid hematologic response and a 74% reduction in the risk of death or end-stage renal disease requiring regular treatment with dialysis following AKI. Early initiation of eculizumab within the first week after p-aHUS presentation was most effective at reducing mortality and preventing progressive loss of kidney function, even in patients who have already started therapy with hemodialysis.

SUPPLEMENTARY DATA

Supplementary data is available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

Y.K., N.K., and E.S. designed the study. Y.K. and S.M. did the statistical analyses and drafted the tables and figures. Y.K. and S.M. wrote the first draft of the manuscript. All authors revised the article and approved the final version for publication.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

ETHICS APPROVAL

The protocol of the study was approved by the local ethics committee of the Sechenov University.

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