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Original Investigation

Insights From the Use in Clinical Practice of Eculizumab in Adult Patients With Atypical Hemolytic Uremic Syndrome Affecting the Native Kidneys: An Analysis of 19 Cases

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Background: Atypical hemolytic uremic syndrome (aHUS) is a devastating form of renal thrombotic microangiopathy. Despite plasma exchange, the standard treatment of aHUS for decades, the renal prognosis for patients with aHUS has remained poor. We assessed the off-trial use of eculizumab in adult patients with aHUS affecting the native kidneys.

Study Design: A retrospective study was conducted. aHUS was defined as the presence of 3 or more of the following: acute kidney injury (serum creatinine >1.4 mg/dL [120 μmol/L]), mechanical hemolytic anemia, thrombocytopenia, and the presence of thrombotic microangiopathy features in a kidney biopsy specimen. Patients who had received 4 or more weekly 900-mg infusions of eculizumab were included.

Setting & Participants: 19 patients were identified through a query sent to all French nephrology centers.

Outcomes & Measurements: Evolution of kidney function, hemolysis, and thrombocytopenia after the initiation of eculizumab therapy.

Results: All patients had acute kidney injury (serum creatinine range, 2.2-17.0 mg/dL) and 12 required hemodialysis. Thirteen patients carried a mutation in 1 complement gene and 1 had anti–factor H antibodies. For first-line therapy, 16 patients underwent plasma exchange and 3 patients received eculizumab. Median time between aHUS onset and eculizumab therapy initiation was 6 (range, 1-60) days and median time to platelet count normalization after eculizumab therapy initiation was 6 (range, 2-42) days. At the 3-month follow-up, 4 patients still required dialysis, 8 had non–dialysis-dependent chronic kidney disease, and 7 had normalized kidney function. At last follow-up (range, 4-22 months), 3 patients remained dialysis dependent, 7 had non–dialysis-dependent chronic kidney disease (estimated glomerular filtration rate, 17-55 mL/min/1.73 m^2), and 9 had normal kidney function. Risks of reaching end-stage renal disease within 3 months and 1 year of aHUS onset were reduced by half in eculizumab-treated patients compared with recent historical controls.

Limitations: Retrospective study and use of historical controls.

Conclusions: Our data indicate that eculizumab improves kidney disease outcome in patients with aHUS.
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INDEX WORDS: Atypical hemolytic uremic syndrome; eculizumab; complement; thrombotic microangiopathy.

Atypical hemolytic uremic syndrome (aHUS) is a devastating form of renal thrombotic microangiopathy (TMA).[1] Plasmatherapy has been the standard treatment of aHUS for decades. However, this treatment was largely empirical because the pathogenesis of aHUS has long remained elusive and plasmatherapy did not significantly improve the outcome of aHUS. Despite plasmatherapy, half the

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aHUS patients reached end-stage renal disease (ESRD) at the first flare of the disease, and two-thirds, by 5 years of follow-up.[2,3] Moreover, the access of patients with aHUS to kidney transplantation has been limited due to the high risk of disease recurrence leading to transplant loss.[4-6]

The dissection of the pathogenic mechanisms underlying aHUS during the past 15 years has paved the way for a disease-specific targeted treatment for patients with aHUS. As constitutional (mutations in complement factor H [CFH], complement factor I [CFI], membrane cofactor protein [MCP], complement factor B [CFB], and C3 genes) or acquired (anti-CFH antibodies) dysregulation of the alternative C3 convertase emerged as a major risk factor for aHUS, targeted inhibition of the complement alternative pathway became a promising treatment option for these patients.[7-9] The availability of the first complement inhibitor, the anti-C5 monoclonal antibody eculizumab,[10] has profoundly modified the management of aHUS. Following encouraging data derived from several case reports (reviewed by Zuber et al[8]) and results from prospective open-label studies,[11] eculizumab is used increasingly in the setting of aHUS. However, indications, timing of use, and treatment regimens vary widely in clinical practice. We assessed the off-trial use of eculizumab in France in adult patients with aHUS affecting the native kidneys.

METHODS

Adult (aged >18 years) patients with aHUS treated with eculizumab in 2011 and 2012 were identified through a query sent to all nephrology centers in France. Patients who had received at least 4 weekly 900-mg infusions of eculizumab were included. Patients with ADAMTS-13 deficiency (<10% serum activity); TMA associated with Shiga toxin, cancer, drug, bone marrow transplantation, or systemic disease; kidney transplantation; or less than 3-month follow-up were excluded from the study. Medical records of identified patients were reviewed, and relevant clinical and biological data, including the timing of eculizumab use and regimen and duration of treatment, were collected.

aHUS was defined as the presence of at least 3 of the following criteria: acute kidney injury (AKI) defined as serum creatinine (SCr) level >1.4 mg/dL (>120 μmol/L), mechanical hemolytic anemia (hemoglobin level <11 g/dL, lactate dehydrogenase [LDH] level greater than the upper limit of normal, undetectable haptoglobin, and the presence of schizocytes on blood smear), thrombocytopenia (platelet count $<150 \times 10^3$/μL), and the presence of TMA features in a kidney biopsy specimen (platelet and/or fibrin thrombi in the microvasculature, detachment of glomerular endothelial cells, and "double contours"). The occurrence of aHUS in at least one family member defined familial aHUS. Plasma resistance was defined as the persistence of thrombocytopenia (platelet count $<150 \times 10^3$/μL) and/or hemolysis (LDH greater than the upper limit of normal) and/or the absence of a decrease (>25%) in SCr level despite at least 5 plasma exchanges (PEs) performed using fresh frozen plasma. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) according to the MDRD (Modification of Diet in Renal Disease) Study equation persistently <60 mL/min/1.73 m^2.

Complement assays (C3, C4, CH50, CFH, CFI, CFB, and MCP expression on leukocytes) and gene analysis (*CFH*, *CFI*, *CD46* [which encodes MCP], *C3*, and *CFB*) were performed as previously described.[12]

Kidney disease outcomes of patients with aHUS treated with eculizumab in 2011 and 2012 were compared with kidney disease outcomes of a historical cohort of all patients with aHUS included in the French aHUS registry[2] who presented with the disease between 2004 and 2008 and did not receive eculizumab.

RESULTS

Nineteen (13 women and 6 men) adult patients with aHUS treated with eculizumab were identified. Their clinical and biological characteristics are shown in details in Tables S1 and S2 (provided as online supplementary material) and summarized in Tables 1 and 2. All patients had a negative screening result for Shiga toxin−secreting *Escherichia coli* and

Table 1. Summary of Patient Characteristics

Characteristic	Value
Female sex	13 (68)
Age (y)	28 (19-73)
Complement gene mutation	13 (68)
HD	12 (63)
Platelet count $>150 \times 10^3$/μL	4 (21)
Plasma exchange	16 (84)
Plasma exchange resistant	8/11 (72)
First-line therapy with eculizumab	3 (17)
Time between aHUS onset and eculizumab initiation (d)	6 (1-61)
Normal(ized) platelet count at eculizumab initiation	7/18 (39)
HD at eculizumab initiation	9 (47)
SCr in nondialyzed patients at eculizumab initiation (mg/dL)[a]	2.84 (1.64-7.41)
Time to normal platelet count after eculizumab initiation (d)[b]	6 (2-42)
Follow-up (mo)	9.5 (4-22)
HD dependent at last follow-up	3 (16)
SCr in nondialyzed patients at last follow-up (μmol/L)[c]	89 (55-340)
eGFR in nondialyzed patients at last follow-up (mL/min/1.73 m^2)[c]	69 (17-135)
Patients with CKD at last follow-up	6 (31)
Patients with normal kidney function at last follow-up	10 (53)
Eculizumab discontinuation	5 (26)

Note: N = 19. Values are given as number (percentage), n/N (percentage), or median (range). Conversion factor for serum creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: aHUS, atypical hemolytic uremic syndrome; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HD, hemodialysis; SCr, serum creatinine.

[a]Based on 9 patients (data not available for 1 patient with non–dialysis-dependent CKD).

[b]Based on 10 patients.

[c]Based on 16 patients.