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LETTER TO THE EDITOR

Relapse of aHUS after discontinuation of therapy with eculizumab in a patient with aHUS and factor H mutation

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Dear Editor,

Atypical hemolytic uremic syndrome (aHUS) is a rare thrombotic microangiopathy (TMA) that is a result of uncontrolled complement activation [1]. We describe an adult patient with aHUS and a mutation of factor H who achieved remission with eculizumab therapy, but suffered a recurrence following discontinuation of treatment.

A 20-year-old female, 7 days status post Cesarean section, presented with complaints of bilateral lower extremity edema, malaise, and bruising. Laboratory evaluation revealed a hemoglobin of 6.0 g/dL (reference range, 11.7–15.5 g/dL), a platelet count of 28×10^9/L (reference range, 150–400×10^9/L), a serum creatinine of 5.27 mg/dL (reference range, 0.6–1.10 mg/dL), an LDH of 2,114 U/L (reference range, 100–190 U/L), and 2+ schistocytes on the peripheral smear. ADAMTS13 activity was 100 % (reference range, >67.9 %), and a kidney biopsy revealed findings consistent with a TMA and acute tubular necrosis. She was started on therapeutic plasma exchange (TPE) and prednisone at a dose of 1 mg/kg. After 7 days, a partial hematologic response was achieved, but her kidney function steadily worsened with a peak creatinine of 8.18 mg/dL, and she was started on hemodialysis. Given her lack of improvement with TPE, normal ADAMTS13 activity, and findings consistent with a TMA on renal biopsy, a diagnosis of aHUS was made, therapy with eculizumab was initiated, and TPE discontinued. She received eculizumab of 900 mg intravenously weekly for 4 weeks, and then 1,200 mg intravenously every other week beginning on week 5. The platelet count and LDH normalized 2 weeks after her first dose, and she became independent of hemodialysis after 6 weeks. The serum creatinine returned to normal 12 weeks after the initiation of eculizumab. Genetic testing revealed a mutant allele for complement factor H, consistent with a diagnosis of aHUS.

After 9 months of continuous therapy, however, she elected to discontinue therapy with eculizumab. She presented again to our institution 6 months later complaining of fatigue, facial edema, and easy bruising that started following an upper respiratory infection 3 days prior. Laboratory studies were similar to her initial presentation with a platelet count of 54×10^9/L, a serum creatinine of 5.06 mg/dL, and 1+ schistocytes on the peripheral blood smear. She required hemodialysis, and therapy with eculizumab was again started as it was previously. She achieved remission and became independent of hemodialysis 3 weeks after restarting therapy with eculizumab.

Uncontrolled activation of the complement system resulting from a deficiency in regulatory complement proteins is the pathologic mechanism of aHUS [1]. Historically, aHUS carries a poor prognosis with 60–80 % of patients progressing to end-stage renal disease or death. Pregnancy and infectious diseases have been shown to precede acute aHUS episodes, likely due to increased complement activation [1].

Eculizumab is a monoclonal antibody directed against C5 that blocks terminal complement activity [2]. Therefore, unopposed production of the terminal membrane attack complex is halted, preventing pathologic end-organ injury. Eculizumab has previously been used effectively to treat PNH, with a recent published study documenting the long-term efficacy and safety [3]. There is an increased risk of infection with *Neisseria meningitidis* in patients receiving eculizumab; therefore, patients must be vaccinated against this organism and receive antibiotic prophylaxis if vaccination occurred less than 2 weeks prior to initiating therapy with eculizumab.

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Multiple reports have demonstrated the efficacy of eculizumab in the treatment of aHUS [4–11]. There are reports that demonstrated brief lapses or longer dosing intervals (>2 weeks) led to a recurrence of the TMA [8, 11]. We believe this case is unique, as to our knowledge, there are no known reports describing the discontinuation of eculizumab maintenance therapy after achieving remission and the subsequent relapse of aHUS. This report supports the hypothesis that following the discontinuation of eculizumab, patients with aHUS and a documented complement control protein mutation are at risk for recurrence. In this patient, renal failure quickly followed the onset of symptoms and did not allow time to intervene with eculizumab to prevent acute renal failure.

In the context of a patient with a known mutation of a complement control protein, caution should be exercised when considering the discontinuation of eculizumab. More detailed studies involving a larger number of subjects, both with and without mutations, will be required before definitive recommendations can be made regarding the discontinuation of therapy with eculizumab after achieving remission.

Conflict of interest The authors declare that they have no conflict of interest.

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