

Eculizumab in Anti-Factor H Antibodies Associated With Atypical Hemolytic Uremic Syndrome

abstract

Atypical hemolytic uremic syndrome (aHUS) is a life-threatening multi-systemic condition often leading to end-stage renal failure. It results from an increased activation of the alternative pathway of the complement system due to mutations of genes coding for inhibitors of this pathway or from autoantibodies directed against them. Eculizumab is a monoclonal antibody directed against complement component C5 and inhibiting the activation of the effector limb of the complement system. Its efficacy has already been demonstrated in aHUS. The present article reports for the first time the use of eculizumab in a patient presenting with aHUS associated with circulating anti-complement Factor H autoantibodies and complicated by cardiac and neurologic symptoms. Our observation highlights the efficacy of eculizumab in this form of aHUS not only on renal symptoms but also on the extra-renal symptoms. It also suggests that eculizumab should be used very promptly after aHUS presentation to prevent life-threatening complications and to reduce the risk of chronic disabilities. To obtain a complete inhibition of the effector limb activation, the advised dosage must be respected. After this initial therapy in the autoimmune aHUS form, a long-term immunosuppressive treatment should be considered, to prevent relapses by reducing anti-complement Factor H autoantibody plasma levels. *Pediatrics* 2014;133:e1764–e1768

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KEY WORDS

atypical hemolytic uremic syndrome, eculizumab, anti-Factor H autoantibodies, cardiomyopathy, thrombotic microangiopathy, neurologic involvement, multisystemic aHUS

ABBREVIATIONS

aHUS—atypical hemolytic uremic syndrome

ECG—electrocardiogram

FH—Factor H

HUS—hemolytic uremic syndrome

MCP—membrane cofactor protein

PE—plasma exchange

STEC—Shiga toxin-producing *Escherichia coli*

TMA—thrombotic microangiopathy

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Most cases of hemolytic uremic syndrome (HUS) in children are secondary to an infection by Shiga toxin–producing *Escherichia coli* (STEC). Non-STEC–related atypical HUS (aHUS) is associated with uncontrolled activation of the alternative complement pathway. This activation depends on spontaneous and constant hydrolysis of complement component C3 in plasma leading to the formation of C3b, which in turn bind to Bb to form the C3 convertase of the alternative pathway and to the C5 convertase. The splitting of C5 by the C5 convertase leads to the formation of C5b, which initiates the constitution of C5b-9 (membrane attack complex) that is able to damage the membrane of endothelial cells and finally leads to the mechanism of thrombotic microangiopathy (TMA). In normal conditions, this mechanism is inactivated by regulatory circulating factors (as Factor I and Factor H [FH]) or anchored in cell membranes (as membrane cofactor protein [MCP]) proteins.¹ If the genes coding for those factors are mutated or the latter factors are inhibited by autoantibodies, the alternative pathway of the complement system is continuously activated,^{2–5} which might result in TMA (Fig 1). TMA predominantly affects the renal microvasculature, but several other organs can also be affected (eg, brain, lung, heart, pancreas, gastrointestinal tract).

Eculizumab is a monoclonal antibody directed against C5 that prevents the activation of the effector limb of the complement system and the formation of the membrane attack complex. Eculizumab is reportedly very effective for the treatment of acute renal insufficiency due to aHUS.⁶ Evidence of its effect on aHUS extrarenal damage is very limited. We herein report the effect of eculizumab in a child presenting with multisystemic aHUS associated with anti-FH antibodies.

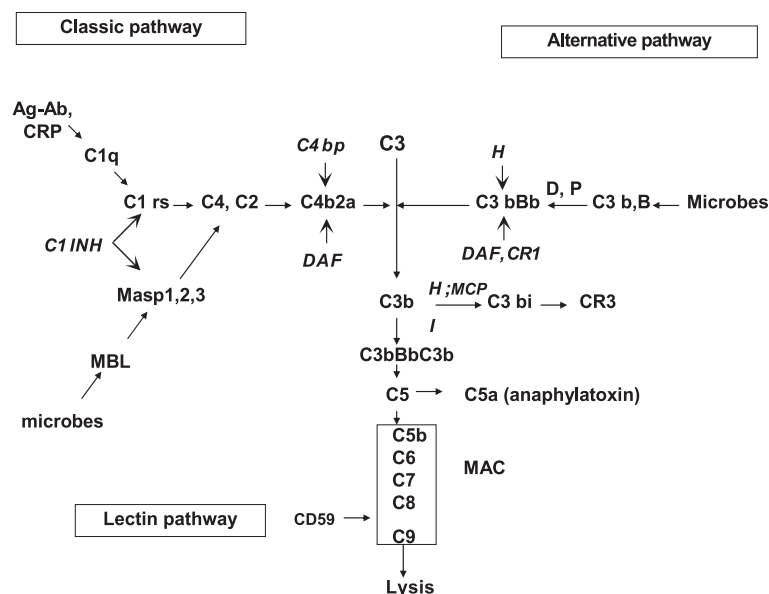


FIGURE 1

The 3 pathways of complement lead to C3 activation followed by the formation of the membrane attack complex (MAC). Note that C3b escapes to inactivation by regulatory circulating (as factor I and factor H) or anchored in cell membranes (as MCP) proteins.

CASE REPORT

A previously healthy 8-year-old boy of Nigerian origin was admitted to our hospital with a 2-day history of abdominal pain, vomiting, 1 episode of bloody diarrhea, and macroscopic hematuria starting 24 hours after a fast food meal.

The patient presented with anemia, thrombocytopenia, and oligoanuria. Three days later, hemodialysis was started (plasma creatinine: 12.1 mg/dL [1070 μ mol/L]; blood urea nitrogen: 329 mg/dL [117.4 mmol/L]). On admission, laboratory data also showed hypocomplementemia (C3: 0.54 g/L [normal range: 0.9–1.8 g/L]). Blood and stool investigations were negative for Shiga toxin–producing bacteria (anti-Shiga toxin antibodies, stool culture, and polymerase chain reaction). On day 7 after admission, the child presented with vomiting, confusion, delirium, agitation, and decreased osteotendinous reflexes, without hypertension. The cerebral MRI revealed multifocal hypersignals of the white matter (bilateral cerebellum, subcortical

parietal, and left frontal lesions) compatible with ischemic lesions. Plasma therapy was therefore started on day 8 for 3 weeks, with plasma infusions (6 sessions) alternately with plasma exchanges (PE; 1.5 $\times$ patient's volume; fresh-frozen plasma; 10 sessions), resulting in an improvement of neurologic symptoms within 48 hours and markedly reduced lactate dehydrogenase plasma levels. However, the patient remained oligoanuric, became hypertensive, and psycho-cognitive function did not recover completely.

Between day 20 and 22, the boy exhibited progressive respiratory distress, persisting despite a marked reduction in weight obtained with fluid management and hemodialysis. Cardiac investigations revealed a left ventricle dilation (ultrasound), repolarization anomalies (electrocardiogram [ECG]), and high troponin T levels (111 ng/L; normal: <14 ng/L) complicated 1 week later by myocardial function degradation (ejection fraction: 37% [normal range: 56%–78%]) and transient pericardial effusion, elements together pointing toward a TMA

ischemic myocardial dysfunction. Because of the cardiac degradation and persistent oligoanuria, PE was intensified from day 31 (daily sessions). After 1 week of this regimen, respiratory symptoms resolved, but the patient remained asthenic and dependent on dialysis.

Because of the patient's allergic reactions on plasma, persistent oligoanuria, and ischemic myocardial dysfunction, eculizumab (Soliris, Alexion Pharmaceuticals, Cheshire, CT) was started after *Streptococcus pneumoniae* and *Neisseria meningitidis* vaccination and initiation of penicillin prophylaxis. The first dose (600 mg, intravenously) was administered on day 37, with the patient weighing 29.9 kg. The next day, the patient underwent his last hemodialysis session. Within 1 week, urine output normalized, proteinuria decreased and eventually disappeared (protein/creatinine ratio: 2.75 g/g before eculizumab; 0.79 g/g and 0.38 g/g after the first and second eculizumab infusion, respectively), plasma creatinine levels decreased to 1.7 mg/dL (150 μ mol/L), his well-being improved markedly, and psycho-cognitive functions recovered completely. After 15 days, left ventricular volume and myocardial function came back to normal. However, repolarization anomalies were persistent, although the patient had already been euvolemic for >10 days. The second dose of eculizumab was administered on day 45. The boy was discharged on day 48 with normalized hematologic values, normal urine output, no proteinuria, and ongoing improvement in renal function; plasma creatinine was 1.6 mg/dL (141 μ mol/L) and blood urea nitrogen was 61 mg/dL (22 mmol/L) (Fig 2).

Treatment with eculizumab was continued, but the dosage was increased from 600 to 900 mg every 2 weeks because of incomplete suppression of the complement hemolytic activity in vitro

(as monitored by using CH50 levels). A follow-up MRI performed 3 months after discharge showed a complete regression of the bilateral cerebellum and left frontal lesions present on the first image; residual bilateral hyper-signals of the subcortical parietal white matter were still noted.

After 6 months of iterative treatment with eculizumab, the patient's general condition was excellent (he is a very sportive student, doing regular football and long distance running activities.), serum creatinine was stabilized at 0.8 mg/dL (71 μ mol/L), cardiac function and ECG were normal, and blood pressure with antihypertensive bitherapy was normal. He had findings positive for anti-FH antibodies (1800 AU/mL [positive threshold: 100 AU/mL]). Mutations of *CFH* and *MCP* were not found, and the screening of other genes was not yet completed at publication of this case report.

DISCUSSION

Traditionally, the presence of bloody diarrhea at presentation oriented the diagnosis of HUS toward the typical form. Contrarily, low C3 plasma levels and the evidence of a genetic mutation on the complement alternative pathway steered the diagnosis toward aHUS.

Recent literature has blurred this clear diagnostic distinction.⁷ The diagnosis at presentation of aHUS is actually mainly based on the exclusion of an STEC infection because diarrhea is observed in up to 20% of patients (possibly even more in cases presenting with anti-FH antibodies), complement activation through the alternative pathway is often observed in STEC-HUS, systemic complement activation is often missing in patients with aHUS, and no genetic cause is detected in approximately one-half of the latter cases.⁸ Our reported case illustrates that the correct diagnosis and resulting

choice of treatment can be complex and sometimes delayed by accessibility to specific investigations. Our patient presented with bloody diarrhea after a fast food meal, but results of all investigations toward verotoxin-producing bacteria remained negative, orienting the diagnosis toward aHUS. Evidence of high anti-FH antibodies was only obtained 6 months after instauration of eculizumab.

HUS patients with no evidences of STEC infections should be promptly tested for other possible causes (eg, pneumococcal infection, HIV, anomalies of the alternative complement pathway, ADAMTS13 deficiency). In terms of disorders of complement activation, the following investigations are recommended: plasma levels of C3, C3d, C4, FH, factors I, factor B, and CD46 concentrations, as well as the screening of anti-FH antibodies. Genetic analyses of complement factors should also be realized, although the results are generally not rapidly available. Because all plasma factors of the complement system can remain normal in aHUS, and because complement activation may take place only at the endothelial surface and therefore might not be detectable in the whole blood, eculizumab should be started before availability of the results of genetic investigation even in the absence of systemic complement abnormalities in case results of the first diagnostic screening remain negative.

The use and benefit of eculizumab on aHUS associated with anti-FH antibodies have been recently reported in 2 patients: as a maintenance treatment in a plasma therapy-dependent patient, and more acutely in a plasma-allergic patient.⁹ Our article confirms these observations and, to the best of our knowledge, shows for the first time the use and benefit of eculizumab on the extrarenal symptoms of aHUS associated with anti-FH antibodies.

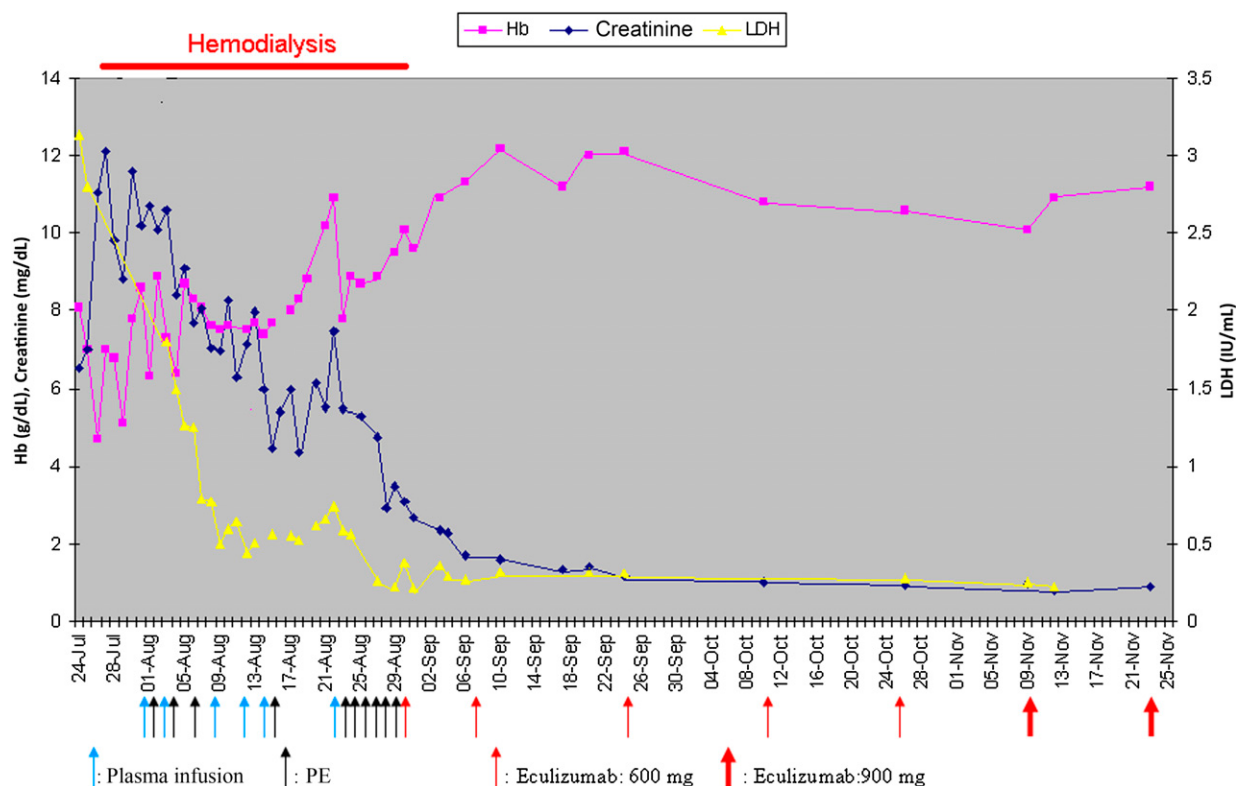


FIGURE 2

Clinical course and laboratory findings. Four months of biological evolution from admission illustrating hemoglobin (Hb), creatinine, and lactate dehydrogenase (LDH IU/mL) changes according to treatments.

The neurologic and cardiac complication features of our patient suggest multisystemic TMA. In typical HUS and aHUS, neurologic symptoms can be due to hypertension, but blood pressure was normal when neurologic symptoms developed in our patient. The diagnosis of cardiac TMA can be challenging because HUS-associated cardiac dysfunction may result from several etiologies: electrolytic disorders, systemic hypertension, fluid overload, and TMA-associated myocarditis.¹⁰ The ejection fraction reduction, transient pericardial effusion, and increases in troponin levels and ECG repolarization anomalies seen in our patient are not pathognomonic of ischemic cardiac involvement. However, the persistence of cardiac abnormalities despite complete correction of cardiovascular overload and the normalization of cardiac function and of the ECG observed after eculizumab

initiation strongly points toward aHUS-related cardiac TMA. Noteworthy, among cardiac signs, repolarization abnormalities persisted the longest, possibly reflecting the duration of the repair process of the heart vasculature to be completed.

Eculizumab has already been shown to be an effective therapy in aHUS with neurologic complications and renal failure.^{6,11} In our patient, a complete recovery of neurologic functions followed eculizumab treatment, while only a partial restoration was achieved with plasma therapy, which is considered the empiric first-line treatment of aHUS.^{12–15} The observed immediate and persistent recovery from dialysis after starting eculizumab confirms the efficacy of this drug in aHUS with severe renal involvement. In addition, the gradual improvement and finally the complete normalization of heart function after eculizumab initiation in our

patient also suggests a beneficial effect on the aHUS cardiac complications. This finding is a particularly relevant observation, given that aHUS-related myocardial involvement, described in ~10% of the autoimmune forms of aHUS,^{16,17} is presumed to be the cause of reported episodes of sudden death.^{17,18} We also show how the efficacy of eculizumab is highly dependent on the dose and frequency of administration. The incidence of ischemic heart involvement in aHUS has rarely been reported up to now, perhaps because of a lack of attention due to the common opinion that the kidney is the only organ affected by the TMA process in aHUS. Given the possible deleterious cardiac evolution resulting from hypertension, fluid overload, and electrolyte unbalance combined with heart TMA, close monitoring of cardiac function is mandatory in any case of aHUS. In addition, the use of eculizumab might

be considered as first-line treatment without delay in cases of a cardiac condition not responding rapidly to supportive measures.

PE associated with immunosuppression has been shown to be beneficial in the treatment of aHUS associated with anti-complement FH antibodies.¹⁶

In the present case, intolerance to plasma contraindicated this treatment association. However, an immunosuppressive drug should still be considered in our case patient for long-term management, with the goal of sufficiently reducing the plasma level of anti-complement FH antibodies to allow

for interruption of the eculizumab infusions. Our observation suggests that eculizumab might contribute to the recovery of neurologic and cardiac function, and demonstrates its ability to restore a prolonged normal renal function without plasma therapy and immunosuppressive drugs.

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