Clinical Grand Rounds: Atypical Hemolytic Uremic Syndrome

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Key Words

Thrombotic microangiopathy • Acute kidney injury •
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Abstract

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening, chronic, genetic disease of uncontrolled alternative pathway complement activation. The understanding of the pathophysiology and genetics of this disease has expanded over recent decades and promising new developments in the management of aHUS have emerged. Regardless of the cause of aHUS, with or without a demonstrated mutation or autoantibody, blockade of terminal complement activation through C5 is of high interest as a mechanism to ameliorate the disease. Eculizumab, an existing monoclonal antibody directed against C5 with high affinity, prevents the perpetuation of the downstream activation of the complement cascade and the damage caused by generation of the anaphylotoxin C5a and the membrane attack complex C5b-9, by blocking C5 cleavage. We report the successful use of eculizumab in a patient after kidney transplantation and discuss the disease aHUS.

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Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening, chronic, genetic disease of uncontrolled alternative pathway complement activation [1]. The understanding of the pathophysiology and genetics of this disease has expanded over recent decades and promising new developments in the management of aHUS have emerged. Eculizumab (Soliris®; Alexion Pharmaceuticals, Cheshire, Conn., USA) is a humanized monoclonal anti-C5 antibody approved by the FDA for use in aHUS on September 23, 2011 [2]. Eculizumab is the first FDA-approved treatment for aHUS, a disease associated with a mortality rate as high as 25% and a 50% rate of progression to end-stage kidney disease (ESKD) [3].

aHUS is a form of thrombotic microangiopathy (TMA). TMA-based syndromes (table 1) are microvascular occlusive disorders that result from aggregation of platelets, thrombocytopenia, and mechanical injury to erythrocytes, ultimately leading to organ dysfunction [4]. A more specific definition of TMA is the activation of the endothelium due to various insults followed by a cascade of pathologic responses, including, among others, platelet and/or complement activation of the terminal (C5b-9) complex, microthrombi formation, thrombocytopenia, and microangiopathic hemolytic anemia [5]. aHUS occurs in both pediatric and adult populations; severe kid-

ney impairment is a prominent but not an essential feature of the disease.

The most common cause of TMA and HUS is associated with Shiga toxin-producing infections (now termed STEC-HUS), including *Escherichia coli* serotype O157:H7 and *Shigella dysenteriae* serotype 1, accounting for more than 90% of HUS cases [5, 6]. Recently, an outbreak in adults was linked to a unique serotype of *E. coli*, O4:H4 [7]. New evidence points to complement activation in STEC-HUS, too [8]. The term aHUS has been used to describe cases of TMA not caused by Shiga toxin-associated microorganisms and bacterial infections in general [6, 9], and in which thrombotic thrombocytopenic purpura has been excluded in the differential diagnosis by demonstrating levels of ADAMTS13 activity above 5–10% [5].

aHUS is caused by uncontrolled complement activation through the alternative pathway. In 50–60% of cases of aHUS, a genetic mutation in complement regulatory proteins and/or autoantibodies against these proteins has been found as an explanation for constitutive complement activation [6]. However, this leaves another 40–50% of patients in whom a mutation or autoantibody cannot be demonstrated, as in our case, but for whom aHUS is the diagnosis. Thus, the ultimate diagnosis of aHUS does not require a formal demonstration of its underlying genetic cause. Less than 20% of aHUS cases are familial, with both autosomal dominant and autosomal recessive inheritance reported [6]. Autosomal recessive cases tend to present in childhood while autosomal dominant cases more typically present in adulthood and prognosis is poor regardless of inheritance [3]. Identification of a genetic mutation, while not required for an individual's diagnosis or management of aHUS, may be helpful for identifying and monitoring disease carriers and for providing genetic counseling.

Regardless of the cause of aHUS, with or without a demonstrated mutation or autoantibody, blockade of terminal complement activation through C5 was of high interest as a mechanism to ameliorate the disease [1]. An existing humanized monoclonal antibody, eculizumab, which had been FDA-approved for the treatment of paroxysmal nocturnal hemoglobinuria, has been evaluated for the treatment of aHUS. Eculizumab binds to human C5 with high affinity, blocking C5 cleavage to C5a and C5b [10]. This blockage prevents the perpetuation of the downstream activation of the complement cascade and the damage caused by generation of the anaphylotoxin C5a and the membrane attack complex C5b-9, responsible for cell lysis [11].

Case Presentation

Our patient is an African-American female who presented in June 2000 at 1 year of age with azotemia, microangiopathic hemolytic anemia, thrombocytopenia, schistocytosis, cardiomyopathy, and severe hypertension. C3 levels were persistently low. She was diagnosed clinically with aHUS in the face of a normal ADAMTS13 activity (78%). She had no known family history of kidney disease or aHUS. Attempted treatment with therapeutic plasma exchange failed to result in reversal of the TMA and progressive CKD. She developed ESKD and was started on peritoneal dialysis in February 2001. The patient's course on dialysis was complicated by hypertension requiring multiple hospitalizations and episodes of peritonitis including fungal peritonitis with an interval change to hemodialysis in August 2002.

She received a deceased donor kidney transplant on March 24, 2005. Immunosuppression was initiated with CellCept and Rapamune (using a prednisone-free protocol). Postoperatively, the patient's serum creatinine decreased from 16 mg/dl to a nadir of 0.3 mg/dl; her serum creatinine subsequently stabilized between 0.5 and 0.6 mg/dl (fig. 1). She received three sessions of prophylactic plasmapheresis on days 1 through 4 after the transplant. Her platelet count abruptly decreased to 8,000/ μ l on postoperative day 4 and her hemoglobin declined gradually to 7.2 mg/dl by postoperative day 7, though there were no other signs of TMA and she responded to platelet and red blood cell transfusions, respectively. Transplant kidney biopsies on postoperative days 7 and 18 showed an eosinophilic lymphocytic infiltrate that lessened between the biopsies, but neither biopsy demonstrated any evidence of TMA. C3 at the time of transplant was reduced, at 38.6 mg/dl, but normalized by 1 month after transplantation. Plasma complement factor H (CFH) level sent at the time of transplant was normal at 310 μ g/ml.

The patient remained well for over 4 years following transplantation. Her nutritional status improved significantly as did her statural growth.

On September 4, 2009, she presented with a recurrence of aHUS at 10 years of age. She reported several days of nausea, vomiting, diarrhea, and fatigue prior to presentation to the hospital in oliguric acute kidney failure. Her initial laboratory studies were notable for a blood urea nitrogen of 117 mg/dl, serum creatinine of 8.5 mg/dl, platelet count of 35,000/ μ l, hemoglobin of 9.4 g/dl, peripheral blood smear positive for 3+ schistocytes, and C3 of 67.8 mg/dl. She received one session of plasma exchange as well as two sessions of hemodialysis through a temporary catheter. She required several blood transfusions coordinated with the dialysis sessions. A kidney ultrasound on admission showed increased size and echotexture of the transplanted kidney and elevated resistive indices within the transplant kidney. An evaluation for the cause of aHUS was completed and was unrevealing (table 2). Plasma concentrations of CFH, complement factor I (CFI), and complement factor B (CFB) were normal; expression of membrane cofactor protein (MCP) on leukocytes was normal, no anti-factor H antibodies were found, and no mutations in the genes for CFH, CFI, or MCP were identified. Due to her presentation with aHUS recurrence and acute failure of the transplant graft, and given her previous and current failed response to plasma exchange, an intravenous dose of eculizumab 900 mg was administered on September 6, 2009. The patient had received the meningococcal vaccine 1 day beforehand,

Fig. 1. Time course of selected parameters in the reported patient. The figure demonstrates the actual levels of serum creatinine (**a**), hemoglobin (**b**), and platelet count (**c**) for the patient from 2002 and through the latest data set in 2012. The first arrow represents the kidney transplant in 2005, and the second arrow represents the recurrence and administration of eculizumab.

in anticipation of initiating therapy with eculizumab, and she was started on penicillin prophylaxis.

After the first dose of eculizumab, the oliguria reversed within hours, and she did not require subsequent hemodialysis or undergo further plasma exchange. Her platelet count remained between 30,000 and 40,000/ μl but normalized by 1 week after the

first dose of eculizumab. Her serum creatinine steadily trended downward until it stabilized at around 0.6 mg/dl 1 month after initiation of eculizumab. She received eculizumab infusions of 900 mg weekly for 4 weeks (days 0, 6, 12, and 19) after which she has been maintained on 1,200 mg every 2 weeks. 28 months after her presentation with recurrence of aHUS, the patient has stable

kidney function on eculizumab and no further indication of recurrence of aHUS. Selected laboratory measurements for the patient from 2002 through the latest data of 2012 are shown in figure 1.

Summary of Case Reports in the Literature for Eculizumab Therapy in aHUS (table 3)

Including our patient, to date we found 21 cases reported in the literature of aHUS treated with eculizumab (table 3) [12–33]. Patients range in age from 1 month to 50 years at the time of treatment with eculizumab. 10 cases involved aHUS occurrence in native kidneys, 8 cases involved aHUS recurrence in a transplanted kidney, and 3 cases involved prophylactic treatment after kidney transplant. In 1 case of aHUS diagnosed in an adolescent male, a single dose of eculizumab led to resolution of hematologic disease markers and transient improvement in kidney function (serum creatinine decreased from 7.8 to 5.2 mg/dl). aHUS recurred and, despite three more doses of eculizumab, the patient progressed to ESKD and eculizumab was discontinued [14]. A second case reports an adult with aHUS recurrence after a third kidney transplant who developed ESKD despite treatment with eculizumab, although the authors report that kidney function had already declined significantly by the time treatment was attempted [28]. In a third case, a female child with aHUS with ESKD for 5 months was treated with eculizumab due to the development of distal extremity ischemia and gangrene; eculizumab halted the progression of ischemia but did not reverse her ESKD [30]. The remaining 18 cases report complete or partial recovery of kidney function with no need for subsequent renal replacement therapy. The longest period of remission from literature case reports appears to be our patient, who has been treated with eculizumab for 28 months with no evidence of aHUS recurrence.

In addition to the above case reports, two prospective clinical trials have been conducted to evaluate the safety and efficacy of eculizumab use in aHUS. These studies are not yet published, but their preliminary results, as reported by the FDA, are promising [34]. In one study, 17 patients with aHUS resistant to or intolerant of plasma therapy were treated with eculizumab for a minimum of 26 weeks. The median age was 28 years (range 17–68). These patients showed decreased signs of TMA activity including improvement in platelet counts and eGFR. In a second study, 20 patients with aHUS undergoing chronic plasma exchange or plasma infusion therapy were treated

Table 1. TMA-based diseases

TTP
Congenital ADAMTS13 deficiency
Antibody-mediated ADAMTS12 deficiency
HUS
STEC-HUS
Pneumococcal HUS
aHUS
TMA associated with
Medications
Hypertension
Pregnancy/HELLP syndrome
Solid organ transplantation
Stem cell transplantation
Malignant solid tumors
HIV and other viruses

TTP = Thrombotic thrombocytopenic purpura; HELLP = hemolysis, elevated liver enzymes, low platelet count.

with eculizumab for a minimum of 26 weeks. The median age was 28 years (range 13–63). These patients also showed decreased signs of TMA activity with maintenance of platelet counts and eGFR off plasma therapy.

Discussion

aHUS is a challenging disease process to manage with a relatively poor prognosis, as many patients develop ESKD or die within the first year of diagnosis [6, 9]. Mutations have been described in CFH, CFI, MCP, CFB, C3, and thrombomodulin [6, 9]. In addition, autoantibodies to CFH can cause aHUS and are commonly associated with deletions of CFH-related proteins CFHR1 and CFHR3 [6].

Mutations in either CFH, CFI, MCP, thrombomodulin, and/or CFHR1/3 with autoantibodies to CFH are associated with loss of regulatory control of the alternative pathway of the complement cascade. Mutations in CFB and C3 are gain-of-function mutations leading to complement overactivation. Loss-of-function mutations in CFH are most common and have the worst prognosis based on registry data, with 60–70% of patients progressing to ESKD or death within a year of disease onset [9]. The prognosis for patients with CFI mutations appears slightly better, followed by patients with MCP mutations, of whom 20% require renal replacement therapy [9]. However, patients without demonstrated mutations have similar dire outcomes, raising the idea that the presence

Table 2. Evaluation of complement, complement regulatory proteins, and complement regulatory genes in the patient

	C3	CFH	CFI	CFB	MCP	Anti-FH Ab
Antigen level ^a (normal range)	1,040 mg/l ^b (660–1,250 mg/l)	144% ^c (65–140%)	132% ^c (70–130%)	283 mg/l ^a (90–320 mg/l)		
CD46 expression					1,180 ^d	
Antibody presence						not detected
Gene mutation analysis		negative	negative		negative	

^a Results expressed as percentage of mean values obtained with a reference plasma prepared from 100 healthy blood donors. ^b Determined by nephelometry. ^c Determined by ELISA. ^d Mean of fluorescence intensity: membrane expression of PBMC determined by cytometry.

Anti-FH Ab = Anti-factor H antibodies.

Table 3. Description of case reports of eculizumab therapy for aHUS

Age range	1 month to 50 years
Gender	
Male	6
Female	12
Not documented	3
Disease occurrence	
Native kidneys	10
Posttransplant recurrence	8
Posttransplant prophylaxis	3
Mutation	
CFH	10
C3	3
CFI	2
None found	5
Not documented	1
Kidney function outcome	
Complete/partial recovery	18 (length of follow-up 2.5–27 months, 2 not documented)
ESKD	3
Eculizumab regimen (outcome)	
Administered 1–4 doses only	3 (2 kidney function recovery for 7 and 8 months, 1 ESKD)
Maintained on recurrent dosing	17 (16 kidney function recovery for 2.5–28 months, 1 ESKD)
Not documented (ESKD)	1

or absence of a given mutation may have limited prognostic value, except for the MCP mutation that may not recur after kidney transplantation.

Until recently, there have been no specific therapies for aHUS. Therapeutic plasma exchange or plasma infusion has generally been the initial approach to disease management, although there are no randomized controlled trials of plasma therapy in aHUS to establish its effectiveness [9]. Plasma exchange may only be beneficial for aHUS in the short term, since long-term kidney outcomes are uniformly poor with a varying short-term response in hematological parameters. Plasma exchange would not be expected to be effective for patients with mutations in MCP, a transmembrane protein. Patients who do respond to plasma exchange frequently become plasma dependent, requiring long-term therapy to maintain remission [9].

Kidney transplantation can be successful for patients with MCP mutations. MCP is cell membrane bound and highly expressed in the kidney; kidney transplant, then, would be expected to halt the disease process [6]. Other mutations or unknown ones have led to high relapse rates of aHUS in the transplanted kidney. CFH and CFI mutations have been studied more extensively. These circulating proteins are primarily synthesized in the liver. Not unexpectedly, aHUS recurs in 80% of patients with CFH mutations and 90% of patients with CFI mutations after an isolated kidney transplant [9]. Living-donor kidney transplantation is contraindicated in patients with aHUS due to mutations in CFH, CFI, C3, and CFB without other therapies concomitantly [35].

Combined liver-kidney transplantation has been attempted for patients with CFH and CFI mutations to address the abnormal protein synthesis in the liver and its downstream effect on the kidney. Simultaneous liver-

kidney transplantation with prophylactic use of plasma therapy has been successful in patients with CFH mutations [11]. However, liver-kidney transplantation is associated with a higher mortality rate than kidney transplantation alone [20]. In the absence of a noted mutation, comprising a sizable fraction of patients with aHUS, liver-kidney transplantation should be avoided [36].

A pathophysiologic-based treatment in aHUS is available now with eculizumab, through inhibiting the formation of the common terminal complement complex (C5b-9). Its recent approval for aHUS in adults and in children represents its first approved use for pediatric patients [2]. Due to the impaired capacity for opsonization and clearance of encapsulated organisms, meningococcal disease is a risk with the use of eculizumab and has been reported among patients given eculizumab for paroxysmal nocturnal hemoglobinuria [10]. Patients must receive the meningococcal vaccine prior to treatment initiation.

Although recovery of kidney function has been variable with eculizumab, most case reports have demonstrated resolution of hematologic disease, and no mortality related to eculizumab use has been described to date [20]. Early initiation of eculizumab, prior to significant kidney injury, has been associated with improved renal outcomes [20]. Our patient, however, who presented in

acute kidney failure, recovered complete transplant graft function with eculizumab.

Further, eculizumab holds potential for prevention as well as treatment of aHUS. Reports of preemptive use of eculizumab in kidney transplant recipients who suffer from aHUS show promising results with sustained aHUS remission after transplantation [31–33].

Conclusion

Eculizumab, recently approved for aHUS, represents the most promising new approach to the treatment of a complex, heterogeneous disease with a high rate of morbidity and mortality. Data from ongoing clinical trials of eculizumab administration in aHUS will likely provide further needed data on its effectiveness and safety. Our patient with aHUS and the absence of a genetic mutation had her transplant kidney function restored to normal and the TMA process halted now after over 2 years of eculizumab therapy.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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