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Atypical Hemolytic Uremic Syndrome (aHUS): Treating the Patient

Plus: A Review of Case Studies

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Abstract: The 3 major thrombotic microangiopathies (TMAs) are thrombotic thrombocytopenic purpura (TTP), atypical hemolytic uremic syndrome (aHUS), and Shiga toxin–producing *Escherichia coli* (STEC)-HUS. These conditions are often clinically identical, but they require different treatment. The TMAs can be distinguished based on factors such as presenting platelet count and serum creatinine level, assessment of ADAMTS13 activity and inhibitor assays, and evaluation for STEC if diarrhea is present. aHUS is a chronic, genetic disorder that is based, in most cases, on an inability to regulate the alternative complement pathway. In the absence of appropriate therapy, up to 50% of aHUS patients progress to end-stage renal disease within a year, and 25% die during the acute phase. Patients who present with clinical and laboratory evidence of a TMA should begin immediate treatment with plasma therapy, but there is no role for plasma infusion or plasma exchange in the long-term management of aHUS. Eculizumab is a potent inhibitor of the terminal complement pathway. It was recently approved by the US Food and Drug Administration for the treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy, including adverse effects on renal function. Eculizumab should be initiated as early as possible after making the diagnosis of aHUS, in order to attempt optimal recovery of renal function and prevent an ongoing TMA with extrarenal manifestations.

Introduction

One year ago, I wrote a primer for distinguishing among the 3 major thrombotic microangiopathies (TMAs): thrombotic thrombocytopenic purpura (TTP), atypical hemolytic uremic syndrome (aHUS), and Shiga toxin–producing *Escherichia coli* (STEC)-HUS.[1] These conditions are often clinically identical. A further impediment to reaching an accurate diagnosis is that they are ultra-rare. The incidence of TTP and aHUS is approximately 2 to 4 per million, and STEC-HUS is recognized primarily in outbreaks of variable expression. Yet the high morbidity and mortality associated with untreated TTP and inappropriately treated aHUS, and the divergent treatments they require, mandate 3 steps:

- First, recognition of the existence of a TMA.
- Second, the ability to distinguish between aHUS and TTP.
- Third, rapid institution of appropriate therapy.

This review, the second of a 2-part series on aHUS, briefly summarizes how the different TMAs are diagnosed, and then describes advances in the treatment of aHUS.

Distinguishing Among the TMAs: Review of Current Diagnostic Criteria

Initiation of appropriate treatment for aHUS requires an accurate diagnosis. Up to 50% of aHUS patients progress

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to end-stage renal disease (ESRD) within a year, and 25% die during the acute phase in the absence of appropriate therapy.[2] In this context, it is particularly important to distinguish aHUS—a chronic, genetic disorder that is based, in most cases, on an inability to regulate the alternative complement pathway—from a clinically related but pathologically distinct condition, TTP. The latter is, in virtually all instances, an acute, acquired disease, characterized by severe deficiency (<5% of normal activity levels) of the von Willebrand cleaving protease ADAMTS13, secondary to an immunoglobulin G (IgG) autoantibody against this enzyme.[3-5]

There are 5 critical steps to reaching a specific TMA diagnosis: documentation of the TMA, documentation of clinical involvement, investigation of any diarrhea, ordering of an ADAMTS13 activity and inhibitor assay before initiating plasma therapy, and understanding the components of response to plasma therapy in the TMAs.

Document a TMA

TMAs present with 2 main features: thrombocytopenia and a microangiopathic hemolytic anemia, characterized by fragmented red blood cells (schistocytes) on peripheral blood smear, low haptoglobin levels, a decline in baseline hemoglobin, an elevated lactate dehydrogenase (LDH), and a negative direct Coombs assay. However:

- Although schistocytes are the *sine qua non* of a TMA, they may be infrequent on initial presentation, particularly in aHUS, occurring at less than 1 per high-power microscopic field.
- An elevated LDH is typical of any hemolytic anemia, but isoenzyme analysis documents that a substantial portion of the increase in LDH in the TMAs reflects its release from ischemic tissues.[6]
- In terms of the thrombocytopenia, a platelet count higher than 30,000/mm^3 at presentation almost eliminates a diagnosis of TTP.[4,5,7,8] The adjusted odds ratio for aHUS vs TTP is 23.4 in the setting of a platelet count exceeding 30,000/mm^3.[4] Near normal platelet counts occur in up to 20% of aHUS cases at presentation.[9]

Document Clinical Involvement

The above laboratory abnormalities must be accompanied by disruption of at least 1 organ system. The most commonly involved systems in any TMA are renal, neurologic, and gastrointestinal. However, neurologic symptoms occur in 48% of aHUS cases,[1] and 4 recent studies have shown that a serum creatinine level higher than 1.7 to 2.3 mg/dL (150-200 µmol/L) is unusual in TTP.[4,5,7,8] The adjusted odds ratio for aHUS vs TTP is 9.1 with serum creatinine levels that exceed this range.[4] Conversely, in approximately 20% of initial aHUS presentations, serum creatinine levels are normal,[10] whereas classic TTP involves the kidneys in more than 50% of cases (although with lower serum creatinine levels than in aHUS).

The one possible exception to the rule that any organ or tissue can be involved in any TMA is the lung. Although severe cardiovascular or renal involvement can lead to pulmonary symptoms in all TMAs, the vascular endothelium of the lungs is not involved in TTP, whereas pulmonary pathology is frequent in untreated aHUS.[11] For example, in one large autopsy series, the lung was not involved in TTP,[12] whereas 3 of 3 cases of aHUS had pulmonary microthrombi.[13] Premortem, pulmonary involvement was seen in 2.2% of a series of 46 children,[14] and in 5% of children and adults[10] with aHUS.

Investigate Any Diarrhea

In the presence of diarrhea, STEC-HUS must be excluded. It is diagnosed by polymerase chain reaction or culture-based assays for Shiga toxin–producing *E. coli*, using stool or a rectal swab. Gastrointestinal signs and symptoms cannot be relied upon to distinguish among the TMAs. Prodromic diarrhea, particularly bloody diarrhea, is a classic sign of STEC-HUS. However, up to one-third of aHUS cases involve diarrhea, which can be bloody, and it is also not uncommon in TTP.[15] This again highlights the importance of rapidly assessing both Shiga toxin and ADAMTS13 activity in a TMA accompanied by diarrhea.

Order an ADAMTS13 Activity and Inhibitor Assay Before Initiating Plasma Therapy

The vast majority of TTP cases can be distinguished from aHUS on the basis of an ADAMTS13 activity lower than 5% in the presence of an anti-ADAMTS13 inhibitor, usually an IgG autoantibody. Both tests should be ordered. The incidence of autoantibodies to ADAMTS13 in the healthy population is only 4%, and they are usually of a low titer.[3] In addition, a myriad of conditions apart from the TMAs, including malignancy, hepatic and renal disease, and systemic infection, may be associated with ADAMTS13 activity levels below the range for healthy controls (which is 67% to 100%). However, in the absence of evidence for a TMA, none of those patients should have activity levels less than 10%, regardless of the occurrence of thrombocytopenia, in clear distinction to acute TTP.[3]

It takes from 2 to 7 days to obtain these test results, which are performed only by specialty laboratories. Given that constraint, the value of reaching a preliminary diagnosis of aHUS vs TTP in a TMA patient based on the presenting platelet count and serum creatinine level must be emphasized.

Understand the Components of Response to Plasma Therapy in the TMAs

In TTP, the platelet count; hemoglobin; haptoglobin; and total LDH, including its isoenzyme subsets, are normalized, and creatinine is normalized or reduced by at least 25% from pretreatment baseline, in more

than 80% of cases following plasma exchange (PEx). These responses should occur, on average, after a mean of 5 to 9 daily plasma exchanges.[1] They should persist for at least 1 month following cessation of PEx to define a complete response to plasma in that disorder.[16] There is sufficient ADAMTS13 enzyme in fresh frozen plasma to effect a complete hematologic and tissue remission in TTP. In addition, pheresis, often used along with immunosuppressive agents (eg, corticosteroids, rituximab), serves to deplete or block the anti-ADAMTS13 autoantibody inhibitor.

In contrast, the vast majority of aHUS cases involve familial, germline mutations in complement or complement regulatory proteins. Functional alterations in these factors permit chronic amplification of the alternative complement pathway. This potentiates platelet activation, platelet aggregation, and terminal complement complex–mediated endothelial cell injury throughout the microvasculature.[1,9,17-19] The platelet count, haptoglobin, and hemoglobin may transiently normalize and LDH levels may dramatically decline in 30% to 80% of aHUS patients treated with PEx alone. This wide variability in initial response rates is dependent upon the nature of the complement-related mutation involved in a particular patient.[17] There is sufficient complement factor H (CFH), complement factor I (CFI), and thrombomodulin (which can inactivate C3a and C5a) in fresh frozen plasma to effect those changes, including transient restoration of functional CFH activity in CFH-deficient patients.[20] In contrast to the use of PEx in TTP, however, the LDH and creatinine rarely normalize, and the risk of ESRD and death is not significantly affected. Maintenance of even those initial LDH responses requires continued PEx.[17]

This failure to effect a meaningful clinical response with PEx in aHUS is reflected in persistent platelet activation, as assessed with flow cytometry for P-selectin on platelet membranes,[21] and by continued decline in estimated glomerular filtration rates (eGFR).[22] Approximately 30% to 80% of these patients advance to ESRD or death despite hematologic responses to plasma. This outcome is described in detail in the section on aHUS treatment.

Distinguishing Among the TMAs: Additional Considerations

Evaluating Components of the Alternative Complement System

Overt signs and symptoms of aHUS can occur at any age, despite the fact that the genetic predisposition is present at birth. Events that superactivate the alternative complement pathway and/or cause microvascular endothelial cell injury may be required to unmask the inability to control the alternative complement system. These events can include infection, pregnancy, surgery, autoimmune disease, malignancy, and the use of certain drugs, such as cocaine, cancer chemotherapeutics, and calcineurin inhibitors. With this background, one might anticipate that measuring terminal complement components in the circulation, or screening for mutations in complement and its regulators, would aid in distinguishing aHUS from TTP. As previously described in depth,[1] this is not the case, for the following reasons:

Altered levels of circulating complement components are not useful in diagnosing aHUS. Both the classic and alternative complement systems activate C3, converting it to C5, which is then broken down into the terminal complement components C5a (anaphylatoxin) and C5b-9 (membrane attack complex [MAC]). The importance of the alternative pathway, and its relevance to aHUS, is that as part of the innate immune system, it is always activated, at low levels, and ready to be amplified by a myriad of stressors, such as those listed above. C5a and MAC, produced at markedly elevated levels when so induced, will affect the integrity of cell membranes of normal cells as well as of pathogens unless checked by complement regulatory factors. Measurement of circulating C3, C5a, and MAC might therefore appear to be a logical part of a diagnostic workup for aHUS.

However, a pathognomonic finding of C3 consumption with maintenance of proximal complement proteins, as reflected by a low C3 level accompanied by a normal or elevated C4, is seen in less than 20% of aHUS cases. In several reviews, serum C3 was normal in up to 80% of aHUS patients.[9,15,23] In one report of 19 cases occurring in the presence of identifiable CFH mutations, 11 patients did have very low to moderately low circulating C3 levels. But 8 (42%) of the clinically identical patients with mutations had normal C3 levels.[23] Complement pathways, including suppressed C3 and elevated C5b-9, can also be activated in classic TTP.[24]

Assessment of complement regulatory protein activity, mutations, or autoantibodies is not useful to the diagnosis of aHUS in the majority of cases. To prevent the panoply of activities related to unchecked activation of the alternative pathway, most mammalian cells have membrane-bound regulators that block complement activation. Their highest concentration is on microvascular endothelial cells. They function in concert with the soluble complement regulators.[9,17,25,26] Soluble CFH and CFI, and the membrane-bound proteins MCP (CD46) and CD55, regulate conversion of C3 to C5. Membrane-bound CD59 regulates C5b-9. However, identifiable mutations in 1 or more of these proteins, along with the related molecules complement factor H-related proteins 1 and 3 (CFHR1, CFHR3), C3, complement factor B, and thrombomodulin, account for disease susceptibility in only half of cases.[23,27] Thus, they are an unreliable means of excluding an aHUS diagnosis. In addition, such testing takes

months, and is not generally available.

It is hypothesized that more extensive, genome-wide sequencing will eventually reveal complement-related abnormalities in most aHUS patients. Such analyses will be complicated by the fact that nonsynonymous mutations involving amino acid substitutions in CFH, the most frequently involved protein in aHUS, are present in 0.5% to 5% of healthy controls who have no family history of aHUS.[28] Genetic testing can be useful, however, in the counseling of family members of an affected proband. Carriers might be closely monitored when experiencing events that trigger marked complement activation. Clearly, there is room to improve gene-based diagnostics in this disorder.

In terms of measuring activity of circulating CFH, the soluble protein responsible for more than 30% of adult aHUS cases, other problems arise. More than 90% of CFH-related aHUS cases involve heterozygous, monoallelic mutations. Reduction in expression of even 50% of normal activity levels is sufficient to affect vulnerability to aHUS during events such as infection, pregnancy, and surgery.[10,29] Measurements of circulating CFH protein are available but not useful in most cases, given the wide range considered normal—265 µg/mL to 684 µg/mL[20]—and the fact that functional activity, not antigen concentration, is usually involved. A small pilot study suggested that assessment of CFH by a functional assay can be used to monitor aHUS and, by implication, diagnose cases of CFH-related aHUS.[30] However, normal ranges have not been established for clinically relevant functional activity, and there is no standard assay for its assessment.

Autoantibodies to CFH have also been described in 6% to 10% of aHUS patients, leading to decreased factor H function, at least as assessed in vitro.[25,31] The clinical relevance of these autoantibodies, and the need to suppress them, is controversial. Virtually all patients with aHUS and the anti-CFH autoantibody also have a deficiency of CFHR1/CFHR3 or abnormalities in other complement regulatory genes.[31-33] This issue is considered in depth in the section on treatment.

Intercurrent Disorders May Obfuscate the Diagnosis of aHUS

An additional confounding factor in reaching a diagnosis of a TMA, and specifically aHUS, is the failure to consider that myriad disorders, particularly autoimmune diseases—such as systemic lupus erythematosus (SLE) and systemic sclerosis—can present with signs and symptoms similar to any TMA. In turn, aHUS can occur in the setting of SLE and related conditions, as these disorders are potent activators of the alternative and classic complement pathways. As noted above, such complement activation also occurs in STEC-HUS[34] as well as during pregnancy, organ and tissue transplantation, cancer and its chemotherapy, and following the use of certain drugs.[1,35] A list of the most common coexisting conditions that can mask a diagnosis of aHUS in a patient with a defect in regulation of the alternative complement pathway is presented in Table 1. Unless a TMA distinct from the intercurrent disorder is considered, and the appropriate diagnostic procedures described above are undertaken, accurate treatment decisions cannot be made. This issue is revisited in the section on treatment.

Utility of a Tissue Biopsy

Historically, biopsies were rarely performed to distinguish TTP from aHUS. They were of little clinical relevance, as the US Food and Drug Administration (FDA) had not approved a therapy specific for aHUS until September 2011. However, biopsies may now be important in difficult diagnostic situations.[36] Gingival tissue, skin, or bone marrow are suggested sites to sample, regardless of whether there is an apparent lesion.[37] Because the TMAs, both primary and secondary, are systemic disorders, a kidney biopsy is rarely required unless anti-body-mediated rejection is suspected.

Table 1. Disorders Associated With Secondary Thrombotic Microangiopathies That May Obscure the Diagnosis, and Thus Delay Effective Treatment, of aHUS

Autoimmune disorders, including systemic lupus erythematosus, systemic sclerosis, and catastrophic antiphospholipid syndrome
Bone marrow, peripheral blood stem cell, and organ transplantation, including transplant complications such as graft-vs-host disease
Pregnancy, including preeclampsia and postpartum HELLP
Cancer chemotherapy (particularly gemcitabine and mitomycin C)
Calcineurin inhibitors
Cocaine and certain opiates
Malignant hypertension

aHUS, atypical hemolytic uremic syndrome; HELLP, hemolysis with elevated liver enzymes and low platelets.

Adapted from Coppo P, Veyradier A. *Cardiovasc Hematol Disord Drug Targets.* 2009;9:36-50.[35]

The thrombi of TTP are typically "white clots," composed of platelets, with only small amounts of fibrin present. Immunohistochemical staining will show entrapped von Willebrand factor (vWF).[38] This finding reflects its pathophysiology, in particular the inability to cleave ultra-large molecular weight multimers of vWF, which form massive platelet tethers in the face of a deficiency in ADAMTS13 activity. Vascular and perivascular inflammatory cell infiltrations are minimal or absent,[38] consistent with the fact that endothelial cell damage in TTP is apoptotic in nature, and such programmed cell death, as opposed to necrosis, typically lacks an inflammatory component.[11]

In contrast, biopsy of similar sites in aHUS typically reveals "red clots," or microthrombi in which fibrin dominates, and an inflammatory infiltrate may be seen.[12,38] Deposits of terminal complement components C5a and

MAC are classically present in involved vessels, and are detectable by immunohistochemistry or immunofluorescence on fresh or fixed tissues.[36,39]

It must be emphasized that the sensitivity and specificity of such biopsy results in distinguishing TTP from aHUS, or from TMAs arising in the setting of conditions that can unmask an underlying inability to control complement activation, have not been authenticated in clinical trials. Tissue-based testing should not be done routinely, but rather on a case-by-case basis. Prospective studies are needed to define and standardize such an approach.

Treating aHUS

There Is No Role for Plasma Infusion or Plasma Exchange in the Long-Term Management of aHUS

A new patient presenting with clinical and laboratory evidence of a TMA should immediately begin treatment with plasma therapy while awaiting the results of the tests described above to distinguish among TTP, aHUS, and STEC-HUS. Testing should include evaluation of the presenting platelet count and serum creatinine level, assessment of ADAMTS13 activity and inhibitor assays, and evaluation for STEC if diarrhea is present. PEx rather than plasma infusion is the initial standard of care for such an undifferentiated TMA. If an apheresis station is not immediately available, and renal function permits, then fresh frozen plasma infusions (40-60 mL/kg body weight daily) may instead be initiated while awaiting PEx.

Mortality from TTP declined from more than 90% to less than 10% with institution of PEx,[16] but the outcome is highly unfavorable in aHUS patients treated with PEx alone. As noted above, most patients will experience ongoing tissue injury, as evidenced by platelet activation and failure to normalize the LDH, and discontinuing PEx is associated with high relapse rates and progression to ESRD.[19,40,41] Delay in confirming an aHUS diagnosis and instituting appropriate therapy often results in ESRD or death within a year, regardless of whether PEx had induced a transient hematologic remission. The incidence of ESRD or death within a year varies somewhat according to the mutation responsible for disease susceptibility, but it is always high. Rates are 60% to 80% with CFH, CFI, complement factor B, and TM deficiencies; 30% to 40% with CFHR1/CFHR3 changes; and less than 20% with MCP mutations.[17]

If a putative TTP or other TMA patient is not responding to PEx according to generally accepted measures of hematologic, clinical, and organ system changes, or if he or she requires prolonged PEx to effect and/or maintain a remission, it is then important to reevaluate the diagnosis and consider aHUS. Response to PEx in TTP may be defined in terms of the amount of plasma usually required to induce a complete response. The first randomized study of PEx vs plasma infusion in TTP that was defined clinically and without the benefit of ADAMTS13 testing demonstrated the superiority of PEx over plasma infusion.[16] Forty-seven percent of patients receiving PEx had a complete response after the first treatment cycle, which involved an average of 21.5 L ± 7.8 L of fresh frozen plasma exchanged over 9 days. In an additional 31% of patients, 1 or 2 further cycles of PEx were required to effect a complete response.[16] These findings are similar to those in many later trials of PEx, in which complete remissions were obtained with a mean cumulative infused plasma volume of 43 L ± 77 L.[42] Each exchange involves 40 to 60 mL/kg of plasma, or 1 to 1.5 plasma volumes, which can be infused within 5 to 9 days. If the patient has not responded as defined by all of the parameters listed above, then the clinician should reevaluate the diagnosis and therapy.

Use of Hepatorenal Transplantation in aHUS

Supported by the knowledge that the major source of CFH is the liver, Remuzzi and colleagues performed the first successful combined orthotopic split liver and kidney transplant for an infant with aHUS and CFH mutation.[43] However, these procedures were highly problematic, given that surgery itself is a key activator of the alternative complement pathway. Complement activation occurs in the graft organ during this procedure, and vascular injury, thrombosis, or death occurred in 90% of cases.[44,45]

A modified procedure involves providing large quantities of plasma before and during the transplants in conjunction with heparin, aspirin prophylaxis, and ongoing immunosuppressive agents. This approach dramatically reduced morbidity and mortality and preserved organ function.[44] It led to a Consensus Study Group statement, published in 2009, that "patients who have ESRD and a CFH or CFI mutation should be considered for combined liver-kidney transplantation because of the high risk for graft loss to disease recurrence."[45] However, the group added a critical warning: "The gravity of risk associated with the procedure has not been eliminated."[45]

In fact, of the first 15 aHUS patients treated with this protocol, 12 achieved long-term remissions and were considered cured. But 3 died from surgical complications (Julien Zuber, MD, PhD, personal communication, August 2013). Of practical importance, the liver is rarely involved significantly in aHUS; the likelihood that most aHUS patients will have a Model for End-Stage Liver Disease (MELD) score sufficiently high to position themselves on a liver transplant list is low. With the approval of anticomplement therapy, this mode of treatment is rarely indicated.

Use of Anticomplement Therapy With Eculizumab in the Control of aHUS

Eculizumab (Soliris) is a recombinant, fully humanized monoclonal antibody that binds with high affinity to human

C5.[46] It is thought to prevent entry of C5 into the C5 convertase, thereby inhibiting its cleavage and subsequent release of C5a (anaphylatoxin) and recruitment of C5b, blocking formation of the terminal membrane attack complex, MAC (C5b-9).[46] It preserves the proximal parts of the complement cascade, which are crucial for opsonization of most microorganisms and the clearance of immune complexes. However, in blocking C5 activation, it impedes immune responses to certain encapsulated bacteria. In adults, these are mainly the *Neisseria* species, meningococcus, and gonococcus. Vaccination and prophylactic antibiotic strategies to mitigate this potential problem are described later in this section.

Eculizumab is a hybrid of 2 IgG subtypes 2 and 4 and was designed to minimize development of autoantibodies and Fc receptor–mediated functions.[40,46] It is administered as an intravenous infusion over 30 minutes, and has an estimated half-life of 11 to 12 days. In an adult weighing more than 40 kg, therapy is initiated with 4 weekly doses of 900 mg, followed by a biweekly maintenance phase of 1200 mg. This schedule usually maintains drug trough levels of 50 to 100 µg/mL, which is sufficient to achieve complete terminal complement blockade, as assessed by hemolytic complement CH_{50} activity.[40]

Minimal drug is detectable in cord blood samples from pregnant women receiving eculizumab. At least 23 live births have been recorded in the 11 years during which eculizumab has been used in the treatment of paroxysmal nocturnal hemoglobinuria (PNH), with no evidence of fetal deformities.[47]

Until recently,[19,41] the majority of published data with eculizumab in aHUS came from case reports and industry-sponsored prospective trials that had been released only in abstract form.[15,18,29,48-52] Those results, which led to the approval of eculizumab for the treatment of aHUS by the FDA and by the European Medicines Agency (EMEA), are now available in complete articles.[41]

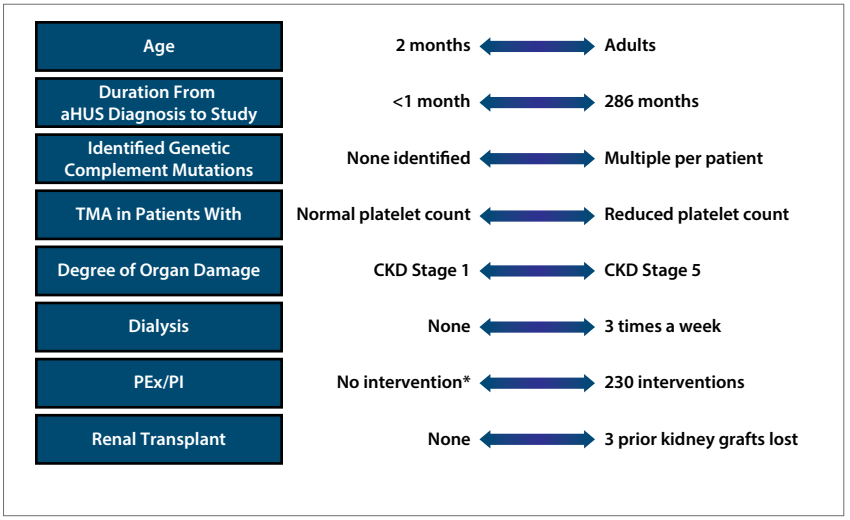

Figure 1. Characteristics of aHUS patients enrolled in prospective and observational studies of eculizumab. *Based on study definition. aHUS, atypical hemolytic uremic syndrome; CKD, chronic kidney disease; PEx/PI, plasma exchange/infusion; TMA, thrombotic microangiopathy.

Prospective data have been derived from 2 phase 2 trials, one involving patients with recently diagnosed, progressing aHUS (trial 1, also known as C08-002; N=17), and another recruiting patients with long-term disease receiving prolonged PEx or plasma infusions (trial 2, also known as C08-003; N=20). A third study was a retrospective, observational survey of aHUS patients younger than 18 years (Medical Practice Setting C09-001; N=30). As shown in Figure 1, these 3 trials included a broad range of patients, from age 2 months to adults, with disease duration from less than 1 month to more than 2 decades, and across broad stages of chronic kidney disease. The studies were not controlled for 2 reasons: because there was no clearly established effective reference treatment for aHUS and because of the rarity of the disease. (Controlled trials with eculizumab were undertaken, however, for an equally rare condition, PNH.)

In trial 1, which involved cases of recent onset, progressive disease, platelet counts were normalized in 82% of patients, and all hematologic values were normalized in 76% by week 26 of treatment.[41] Normalization of both platelet counts and all hematologic values occurred in 88% of these patients by week 64.[41] Normalization of LDH occurred in 82% of patients at week 26 and 88% by week 64.[41] These changes were reflected in clinical response: 88% remained free of TMA events at weeks 26 and 64, serum creatinine declined by at least 25% in 76% by week 64, and 4 of 5 patients on dialysis discontinued the procedure, all without plasma therapy.

Trial 2 results, with patients on long-standing plasma therapy, were also impressive. As shown in Figure 2, initiation of eculizumab led to a TMA event-free status in 80% of patients at 26 weeks and 85% at 1 year of treatment. Furthermore, there was a continuous decline in mean eGFR for the entire pre-eculizumab observation period of 420 days, despite the treating physician's best application of plasma therapy (Figure 3).[22] Institution of eculizumab resulted in significant (P<.01) increases in mean eGFR, beginning within 2 to 4 weeks of therapy and extending throughout the 504-day observation period.[22] These data support the conclusions of one recent review that "eculizumab appears to be becoming the treatment of choice for aHUS without initial plasma therapy."[31]

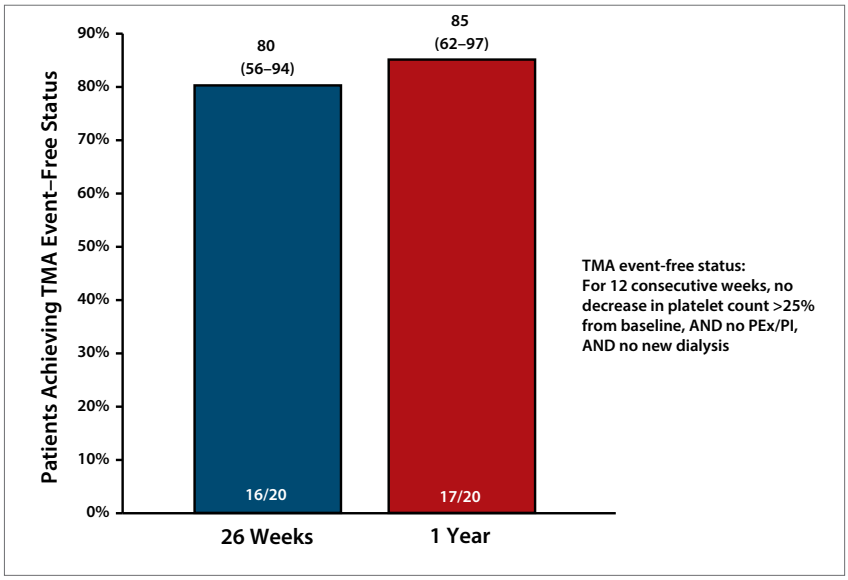

Figure 2. TMA event-free status was achieved in 80% of patients at 26 weeks, and 85% of patients at 1 year, with eculizumab therapy. PEx/PI, plasma exchange/infusion; TMA, thrombotic microangiopathy. Data from Licht C et al. ASH Abstract 985. *Blood*. 2012;120(21).[22]

There were no complement-related genetic mutations or CFH autoantibody detectable in 24% of patients in trial 1 and 30% of patients in trial 2, but the presence or absence of these abnormalities had no impact on clinical response to drug.[41] This finding is consistent with earlier case series[19,33] as well as several studies showing that mortality or progression to ESRD are identical whether or not patients have a complement-related mutation.[2,9]

The Extent and Kinetics of Clinical and Laboratory Responses to Eculizumab

Following a recognized episode of aHUS, 90% of adults relapse within 1 year absent appropriate treatment.[40] Beyond the first year, the risk of relapse is approximately 25%.[40] These rates are almost certainly underestimates; prior to the availability of eculizumab, most patients with severe aHUS progressed to ESRD with their first episode. Clearly, eculizumab should be initiated as early as possible after the diagnosis of aHUS is made. This is of most importance when attempting to realize maximal recovery of renal function.

For example, in one series, 13 renal transplant recipients were given eculizumab for posttransplant aHUS recurrence.[53] A complete reversal of ongoing TMA activity was obtained in all of these patients, and the interval between onset of the aHUS episode and drug initiation inversely correlated with the degree of recovery in renal function.[53] In a more recent review of 11 pediatric and 13 adult patients with aHUS treated with eculizumab, hematologic recovery occurred in 100%.[19] Creatinine declined by at least 25% in 90% of the pediatric cases but in only 69.2% of adult cases. Again, the shorter the interval between onset of clinical symptoms and eculizumab therapy, the better the response.[19]

It is presently unclear whether there is an outer limit, related to time on hemodialysis or extent of sclerosis on kidney biopsy performed prior to initiating eculizumab, when dialysis cannot be successfully discontinued with the drug. In the 2 prospective studies described above, some recovery of renal function was seen across all CKD stages. But the numbers were relatively small; the fact that the longest duration for which eculizumab enabled discontinuation of hemodialysis was 4 months should not be seen as a limit to the potential for complete renal recovery.

In terms of other laboratory parameters consistent with a TMA, platelet counts should normalize, or at least increase significantly, by weeks 1 to 2 of treatment (after 1 or 2 doses of eculizumab), in concert with cessation of all plasma therapy and no need to initiate new dialysis. By week 4, there should be continued increases in platelet counts; normalization of the haptoglobin; and a normalization, or at least a marked decrease, in LDH.

Monitoring plasma levels of the drug does not appear to be helpful, at least in adults. One measure of drug activity may be obtained through a simple CH_{50} assessment; it should be completely suppressed within a day of initiating eculizumab. But it is clear, from my own experience and that of several colleagues, that certain patients may not maintain a clinical or laboratory response via the standard biweekly dosing schedule. They may require adjustment to every 10 to 12 days to maintain a stable course.

There is generally no role for PEx after initiation of eculizumab. However, if PEx is continued during the 4-week treatment induction period, a supplemental dose of 600 mg of eculizumab must be administered within 60 minutes after each PEx. Dosage adjustment for hemodialysis has not been determined, but in my experience, supplemental doses have not been given.

Adverse Events

In the previously described trials, the most frequently reported adverse events (≥15% per patient incidence) were hypertension, upper respiratory tract and urinary tract infections, diarrhea, headache, anemia, emesis, nausea, and leukopenia.[41] None of these events were severe enough to require cessation of therapy or dose modification. No patients experienced infusion reactions

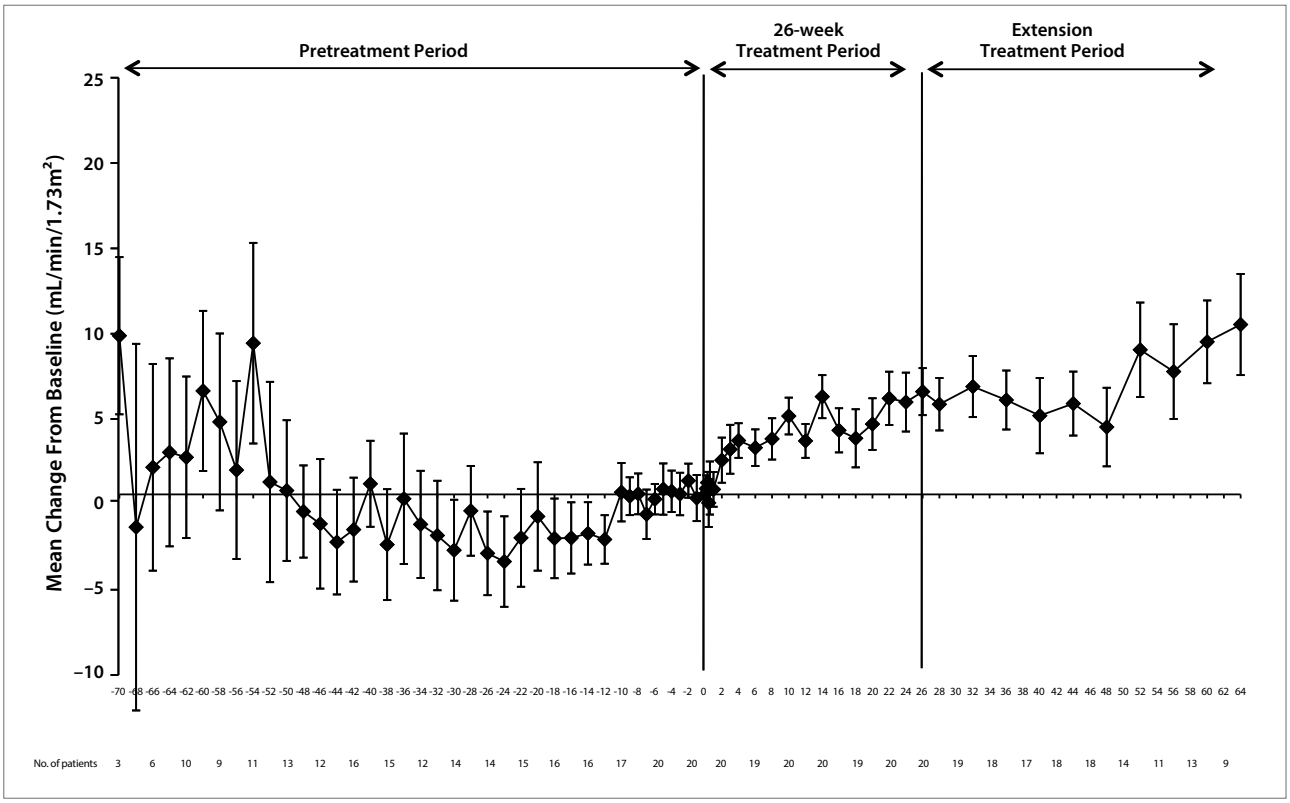

Figure 3. Estimated glomerular filtration rates continue to improve following initiation of eculizumab in patients with chronic atypical hemolytic uremic syndrome. The pretreatment period includes use of plasma and plasma exchange. Adapted from Licht C et al. ASH abstract 985. *Blood.* 2012;120(21).[22]

that required discontinuation. However, severe infusion reactions are a risk attendant upon administration of any foreign protein, and if they occur, the drug should be stopped and appropriate medical therapy provided.

Severe and fatal meningococcal infections have occurred in patients treated with eculizumab, primarily in the setting of PNH. As described earlier, this reaction relates to the drug's potent inhibition of terminal complement components. Patients must be immunized with a meningococcal vaccine, preferably the tetravalent preparation, at least 2 weeks prior to administration of the first dose of eculizumab. In acute aHUS, the risk of delaying anticomplement therapy often outweighs the risk of acute meningitis. It is thus standard practice to vaccinate and simultaneously start a 2-week course of prophylactic antibiotics. I have used 3 oral agents: ciprofloxacin at 500 mg twice daily, rifampin at 600 mg orally twice daily, or penicillin VK at 250 mg 4 times daily. It is also good practice to check antimeningococcal antibody titers if the patient has an underlying immune deficiency. Finally, recall that current trivalent and tetravalent vaccines do not protect against meningococcal serotype B. That serotype is of very low prevalence in the United States but common in Europe. Therefore, outside of the United States and Canada, prophylactic antibiotics, usually penicillin, are often continued for the duration of eculizumab treatment.

The importance of this information is reinforced by the fact that eculizumab is available only through a Risk Evaluation and Mitigation Strategy (REMS) program that prescribers must enroll in. It is a simple procedure, with details available by telephone (888-765-4747).

One should use caution when administering eculizumab to patients with any systemic infection. However, if a patient develops a meningococcal or other infection while taking this drug, it should not be discontinued. Recall that infection is one of the major activators of the alternative complement pathway, and the consequences of an infection would appear to outweigh any immune benefit achieved by stopping the drug in that setting.

Defining Treatment Duration With Eculizumab

The duration of treatment with eculizumab is an unresolved issue. One might hypothesize that if the original condition(s) that unmasked the disease was removed, then extended therapy with the drug would be unnecessary until and unless the unmasking factor recurred. For example, in a study of 30 index cases with aHUS and identified

mutations in CFH, CFI, and/or MCP, there was a 67% clinical penetrance as assessed by renal disease by age 40 years, and 100% by age 65 years.[54] Yet in 30 relatives of those index cases, who bore identical mutations, there was only an 11% penetrance in terms of onset of renal disease by age 40 years; one such relative did not develop overt renal disease until age 88 years.[54]

That being said, it is clear that in most instances, eculizumab cannot be stopped after the 4-week induction. For example, among the 67 patients treated in the 2 prospective (N=37) studies and one observational (N=30) study reviewed above, clinical deterioration and laboratory signs of TMA were observed in 27% of patients who discontinued therapy or dose-interrupted within the first year. Five of the patients who did not receive the recommended dose or duration of eculizumab developed reactions such as changes in mental status, seizures, angina, thrombosis or dyspnea, thrombocytopenia, elevated LDH, and elevated serum creatinine following the first missed dose. Of the 4 patients who were then immediately restarted on the drug, 3 were able to regain normal renal function. The fourth patient progressed to ESRD despite intensive eculizumab therapy.

Relapse has been reported in several case studies of patients who discontinued eculizumab within a year of initiating therapy.[19,29,39,48,50,55] For example, clinical relapse occurred after eculizumab was discontinued in 2 patients with classic CFH mutations: a 20-year-old woman with postpartum aHUS relapsed within 6 months of stopping the drug, which had maintained her in complete remission for 9 months,[55] and one of our own early patients, a 28-year-old man with postinfection aHUS, relapsed within 30 days of stopping the drug that had maintained a complete remission for 2 months.[39] According to the package insert for eculizumab, after stopping treatment, patients should be followed closely for clinical signs of a TMA as well as any changes in hemoglobin, LDH, and creatinine for at least 12 weeks. However, based upon my own experience, clinical case reports, and the opinions of other experts,[40] I would recommend that such close follow-up evaluation take place twice a month for the first 2 months and then monthly for a year. Data gathered through prospective studies are clearly needed. In one attempt at obtaining such information, our group is following the terminal complement component (C5a and MAC) staining patterns of patients who have had serial biopsies (skin, ileum) performed as part of their clinical assessment over the course of 1 to 2 years. It appears that 1 to 1.5 years of therapy are necessary to resolve MAC deposition in tissue microvasculature, despite the fact that the patients are in clinical and laboratory remission while on the drug (unpublished data). This finding is consistent with the turnover rate of microvascular endothelium, which is in the range of 100 to 1000 days, varying by tissue lineage. However, it does not imply that alternative complement pathway activation itself would be terminated in the absence of drug maintenance, nor are there any controlled trials to relate such preliminary biopsy observations to the clinical course while off of eculizumab.

After eculizumab has been discontinued, it is important to consider the likelihood of aHUS relapse if the event that unmasked the disease is expected to recur. Prophylactic administration of eculizumab may then be indicated. Likely scenarios could include a second pregnancy in a patient with a prior pregnancy-related aHUS, and renal transplantation, particularly in patients with a high risk of another TMA manifestation. But again, this is highly speculative.

Treating aHUS Associated With CFH Autoantibody

The 2 prospective, industry-sponsored trials of eculizumab in aHUS described above found no difference in response to therapy based upon the presence of anti-CFH autoantibodies.[41] In the vast majority of instances, such patients have germline mutations in complement regulatory proteins, so it is unclear what role, if any, the autoantibody has in their disease. However, some investigators have raised the issue of whether immunosuppression alone, using steroids and pulses of high-dose cyclophosphamide, might be effective. Such a protocol induced sustained remissions in 4 pediatric aHUS patients, only 1 of whom required maintenance prednisone, after follow-up periods of 4 months (1 patient), 4 years (2 patients), and 6 years (1 patient).[31] This scenario, which represents 6% to 10% of aHUS cases in children (but, in my experience, far fewer in adults), suggests the need for further study of the treatment options in CFH autoantibody–associated disease.

Treating aHUS Arising in the Context of Other Conditions

As summarized in Table 1, many conditions linked to activation of the alternative complement pathway can themselves present with signs and symptoms of a TMA. Unless the occurrence of aHUS as a secondary disorder in such settings is recognized, appropriate therapy will not be initiated. Noris and colleagues found that 25% (47 of 191) of patients with aHUS have coexisting disorders, regardless of whether a known mutation in a complement regulatory pathway could be identified.[19] These disorders included malignant hypertension (30%); posttransplant TMA, including use of calcineurin inhibitors (23%); and pregnancy-related conditions (21%).[17] As mentioned, eculizumab is indicated only for the treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy. Appropriate use of eculizumab in these settings may demand more than just documenting a TMA with altered platelet count, hemolysis, schistocytes, serum complement abnormalities, and organ involvement in conjunction with

normal ADAMTS13 activity. Adjustments may be necessary for patients with such conditions as:

Autoimmune disease. SLE may manifest as a lupus nephritis with altered creatinine; schistocytes as a consequence of renal injury; elevated LDH; hemolysis, which may be Coombs negative; and a low C3 level. ADAMTS13 activity should be greater than 5% to 10%. However, aHUS arising from alternative complement activation as a consequence of SLE could look the same. Kidney biopsy may be necessary to distinguish the vasculitis typical of lupus, which may occur along with deposition of immunoglobulin and proximal complement components C4 and C1q, from the TMA, pauci-inflammatory response, and deposition of terminal complement components (C5a and MAC) that are consistent with aHUS.

Catastrophic antiphospholipid syndrome (CAPS) is a prothrombotic disorder involving multiple small vascular beds and activation of terminal complement components. It can also present with signs and symptoms of a TMA that are indistinguishable from those in aHUS.[56] If CAPS does not respond to appropriate therapy, one should rule out the existence of underlying aHUS, which could respond to eculizumab as illustrated in a recent case report.[57]

STEC-HUS. Eculizumab is not approved or indicated for the treatment of STEC-HUS. However, Shiga toxin is a potent diarrhea-associated infection, and related disorders can trigger endothelial complement deposition.[58] If a patient had an underlying inability to regulate complement, then classic aHUS, and not just STEC-HUS, could develop. Indeed, eculizumab has been used in this setting when supportive care and PEx were ineffective.[34]

TTP. As emphasized above, TTP is generally an acquired, not familial, disorder related to an inability to regulate platelet thrombus formation rather than to regulate complement. It is completely distinct from aHUS and usually responds to PEx or second-line immunosuppressive therapies. However, the massive platelet thrombi generated as a consequence of severe ADAMTS13 deficiency in TTP does activate the alternative complement pathway,[58] as does free heme, which is released as a consequence of any hemolytic anemia, including that associated with TTP.[59] With a coexistent complement regulatory defect, aHUS might then develop. This scenario appeared to be the case in a young man we treated who presented with a TMA characterized by a platelet count less than 20,000/mm^3 and ADAMTS13 activity less than 5% with a classic IgG ADAMTS13 inhibitor. He remained comatose, with recurrent grand mal seizures, for 22 days despite receiving plasma exchange of more than 220 L, as well as rituximab, vincristine, and steroids. He woke from the coma when eculizumab was initiated.[36] Workup revealed MAC deposition in the microvasculature on skin biopsy.[36] An initial attempt to identify a complement regulatory mutation through available commercial channels was negative[36]—recall that such platforms will not recognize at least 30% of known aHUS-linked mutations—but a subsequent, extensive genetic analysis in the laboratory did reveal a CFH mutation consistent with aHUS.[39]

Similarly, thienopyridines (ticlopidine and clopidogrel) can cause a TMA characterized by an ADAMTS13 of less than 5% with an ADAMTS13 inhibitor, which would be appropriately classified by these criteria as TTP. This disorder, however, is usually resistant to PEx. We reported CFH mutations in 4 of 4 cases of thienopyridine-linked TTP resistant to PEx.[60] The role of eculizumab in these thienopyridine-induced TMAs is unknown.

Pregnancy, malignancy, chemotherapy, medications, and transplantation. Mutations linked to complement control and thought to be etiologic in aHUS have also been identified in patients with pregnancy-related HELLP (hemolysis, elevated liver enzymes, low platelet count) and preeclampsia, history of stem cell and organ transplantation, graft-vs-host disease, and gemcitabine-associated TMA. As one might anticipate, patients who have TMAs associated with those conditions and diagnosable as aHUS per the criteria outlined at the beginning of this review are generally unresponsive to PEx but have been successfully treated with eculizumab.[61-65]

As noted above, transient responses to PEx in aHUS vary from 30% to 80%, depending upon the mutations implicated. Different complement-linked mutations may also be critical in determining susceptibility to a complement-linked TMA in certain settings, such as stem cell transplants. Mutations common in aHUS outside the stem cell transplant setting are much rarer than in TMAs following such transplants, so it is important to establish careful monitoring of how these patients respond to C5-targeted intervention with eculizumab.[66]

When treatment with eculizumab is unclear. There are minor subsets of aHUS patients, diagnosed as described above, in whom the disease is genetically based but does not involve complement. Therefore, these patients would not necessarily be expected to respond to eculizumab. One recently identified such syndrome involves mutations in *DGKE*, a gene encoding diacylglycerol kinase-ε. Mutations are cosegregated with clinical aHUS in 9 unrelated kindreds.[67] The mechanism of how pathologic thrombosis and aHUS develop in this setting, and how it might be treated, is unclear.[67]

The Cost of Treating aHUS

On a per weight basis, eculizumab is the ninth most expensive drug in our pharmacy. The cost may be a factor prompting clinicians to prematurely discontinue the drug, or to prefer initiating treatment with PEx. In a pediatric population, where drug dosing is weight-based, cost should not be

an issue. As one group emphasized, in these cases "the cost is significantly less than that of dialysis and regular PEx."[68] It is a concern with hospitalized adult patients, however, among whom drug cost affects DRG-based reimbursements. (Most insurance plans cover its use in the outpatient setting.) Zuber and colleagues have analyzed the expense of aHUS inpatient treatment. They took into account the cost of plasma—approximately $4200 for a single PEx—as well as charges related to factors such as personnel, equipment amortization, arteriovenous catheterization, dialysis, extrarenal complications, and vascular catheter infections. Overall, the cost of 3 months of treatment with eculizumab in adults is on the same order of magnitude as the money saved by rescuing a renal allograft from early failure.[53]

Summary

- Eculizumab (Soliris) is a potent inhibitor of the terminal complement pathway. It is indicated for the treatment of patients with aHUS to inhibit complement-mediated thrombotic microangiopathy, including adverse effects on renal function.
- A new patient presenting with laboratory and clinical signs of a TMA should immediately begin plasma therapy while awaiting the results of tests to distinguish among TTP, aHUS, and STEC-HUS. Evaluation should include ADAMTS13 activity and inhibitor assays, testing for Shiga toxin, and consideration of the likelihood of an aHUS vs TTP diagnosis based on presenting platelet count and serum creatinine level. The relative risk of an aHUS vs a TTP diagnosis in a patient with a TMA is much greater if the presenting platelet count is more than 30,000/mm^3 and the serum creatinine is more than 1.7.
- The clinician should recognize the amount of plasma usually required to effect a complete response in TTP, which typically involves 5 episodes of PEx. There is no role for PEx in aHUS.
- Eculizumab should be initiated as early as possible after making the diagnosis of aHUS, in order to attempt optimal recovery of renal function and prevent an ongoing TMA with extrarenal manifestations.
- Many conditions linked to activation of the alternative complement pathway can themselves present with signs and symptoms of a TMA. Unless the possibility of aHUS occurring in patients with other potential inciting disorders is considered, appropriate therapy cannot be initiated.
- The vast majority of cases of aHUS appear related to germline mutation(s) in 1 or more complement regulatory proteins. Given the current nature of generally available technology to detect these mutations, they cannot be identified in at least 30% of cases. However, disease severity, mortality, and response to eculizumab are equivalent whether or not such mutations can be identified in a given patient.

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Management of Atypical Hemolytic Uremic Syndrome (aHUS): A Review of Case Studies

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Management of atypical hemolytic uremic syndrome (aHUS) poses several clinical challenges. The following published case studies highlight important points concerning events that precipitate aHUS; interpretation of ADAMTS13 activity in the differential diagnosis of aHUS; the overlap in clinical manifestations of the thrombotic microangiopathies, including severe central nervous system disease; use of the anti-complement drug eculizumab in the treatment of aHUS; consideration of therapeutic costs; and treatment duration.

aHUS in an Adult With TMA Presenting With Bloody Diarrhea and Mental Status Changes

Salem and colleagues[1] reported a case of a 66-year-old woman with thrombotic microangiopathy (TMA). She presented to an intensive care unit with nausea, abdominal cramps, and intermittent bloody diarrhea. Nine days earlier, she had eaten a salad at a restaurant. She tested negative for Shiga toxin. The patient was not thrombocytopenic on presentation, but during the 36 hours in which she was hospitalized, her platelet count decreased to 100,000/µL. She had 3+ schistocytes per high-power field. She developed anuria and mental status changes.

She was transferred to the institution of Salem and colleagues, where she was intubated for airway protection. Laboratory studies showed microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. The patient's ADAMTS13 activity level was 68%. She underwent plasma exchange, and on day 3, she developed generalized tonic-clonic seizures and was unresponsive. On day 4, eculizumab therapy was initiated, in a regimen of 900 mg intravenously each week for 4 weeks followed by maintenance therapy at 1200 mg biweekly. After her third weekly infusion of eculizumab, the patient no longer needed hemodialysis, although she was still unresponsive. On week 7, she abruptly awoke from her coma. She gradually improved neurologically and was close to her pre-illness state at the time of the report.

Key Points

There are several important messages raised by this case study. This patient's diagnosis of TMA was made in the traditional manner, based on laboratory findings and a clinical problem. The patient was not thrombocytopenic on presentation, a reminder that patients with aHUS can have normal or near-normal platelet counts on presentation. The median platelet count in an aHUS patient is 30,000/µL to 40,000/µL, and can be near-normal on initial presentation, in distinct contrast to the other major TMA, thrombotic thrombocytopenic purpura (TTP), which is associated with a median platelet count of 20,000/µL or lower.[2] Indeed, this patient's platelet count was normal upon initial hospitalization, declining some 36 hours after admission.

In addition, the patient had prominent central nervous disease and remained in a coma for more than 7 weeks. This point is important because many clinicians erroneously equate severe CNS disease in the presence of TMA with TTP. In fact, almost half of patients with aHUS have prominent neurologic disease.

Another interesting aspect of this case is the way the patient presented. She ate a salad and developed bloody diarrhea. Typically, when patients have bloody diarrhea in association with TMA, the initial thought is Shiga toxin–related HUS or STEC-HUS. The authors appropriately tested for the presence of Shiga toxin, and it was negative. In the vast majority of cases, aHUS results from the genetic inability to control complement activation, and the infections that cause diarrhea—particularly bloody diarrhea—are the most potent activators of the alternate complement pathway. Therefore, it is not uncommon for an aHUS patient to present with diarrhea, and it may be bloody, regardless of Shiga toxin status.

ADAMTS13 activity was also measured. It was 68%, which is in the normal range, but more specifically, it was higher than 5%. aHUS is most commonly distinguished from TTP by an ADAMTS13 activity above 5% to 10%, in the absence of an autoantibody inhibitor. The patient's plasma exchange was stopped when the results of the ADAMTS13 test returned and proved normal, and treatment with eculizumab was initiated. Eculizumab

is the only therapy approved by the US Food and Drug Administration (FDA) for this disease. There is no role for plasma in the therapy of aHUS. All patients with an undifferentiated TMA are usually given plasma until a definitive diagnosis is made. Indeed, there is enough complement regulatory protein in normal, fresh, frozen plasma to tide the patient over in terms of hematologic responses, but plasma will do little to impede ongoing tissue damage.

Not only did the patient have prominent central nervous system disease, but she also had renal disease and was on hemodialysis. Eculizumab is usually administered in a weekly dose for 4 weeks and then in a maintenance dose every other week. At the time of the patient's third weekly dose, her kidney function improved enough to discontinue dialysis. In another 3 weeks, her central nervous system disease improved.

This case highlights a question I am not infrequently asked by physicians: Can a patient who has been in a coma for a few months, and who has been diagnosed with aHUS, still benefit from treatment? This patient was in a coma for 7 weeks, and she still was able to abruptly awake. The level of response to eculizumab can be quite dramatic.

The authors noted that the patient had to be intubated, but they did not provide the reason for the intubation. It may have been due to lung disease, which is a prominent issue in aHUS, whereas in TTP, TMA of the lung is very rare.

The authors did not report on the patient's immune status in terms of *meningococcus,* nor did they indicate whether they gave her prophylactic antibiotics. It should be noted that eculizumab blocks the terminal complement components, which increases the risk for gonorrhea and meningococcemia. It is necessary to vaccinate the patient[3]; we recommend the tetravalent vaccine against *meningococcus*. On the day that the patient is vaccinated, prophylactic therapy with antibiotics should be administered for 2 weeks to allow the vaccine to take effect.

Although it is not necessary to test patients for complement regulatory factor mutations characteristic of aHUS, the authors in this case did so. They found an unusual mutation. Approximately 30% of aHUS patients have a mutation in complement factor H (CFH).[4] This patient's mutation was in a relatively unusual part of the system, complement 3. This mutation does not cause loss of function; it causes a gain of function mutation in the complement system that serves to superactivate the pathway, or heighten the response of complement.

aHUS in an Infant

Kim and coworkers[5] report a case of a previously healthy 7-month-old girl who presented with symptoms of paleness and easy bruising that were preceded by croup. She was anemic and thrombocytopenic, but her kidney function was normal. Six weeks later, she developed dark urine, oliguria, fluid overload, and hypertension. She did not have diarrhea or vomiting. Her hemoglobin was 4.5 g/dL, and her platelets were 72,000/µL. She had microangiopathic hemolytic anemia and elevated urea and creatinine.

The clinical diagnosis of aHUS was made, and hemodialysis was initiated. On the second day of hospitalization, she underwent plasma infusion. On the fourth day, plasma exchange was initiated. She underwent 9 plasma exchange sessions in the first 2 weeks. She then developed hypertensive encephalopathy, which required ventilation, continuous venovenous hemofiltration, and pressors. The encephalopathy resolved after 5 days, and plasma exchange was continued 3 times weekly.

The patient's ADAMTS13 activity was outside the range of normal for a healthy infant or adult at 25%, but was clearly greater than 5% to 10%. The methylmalonic acid level was normal.

Dialysis was initiated to manage her renal failure. Attempts to discontinue plasma exchange were unsuccessful due to hematologic relapses. She received 9 packed red blood cell transfusions in 4 months and blood priming for the plasma exchange sessions. She developed 3 exacerbations of her TMA, all following infections.

Given that the responses to plasma were only partial, eculizumab was initiated 2 weeks after administration of a tetravalent *meningococcus* vaccine. After the first dose, the patient's hematologic abnormalities resolved, and plasma exchange was stopped. One month later, dialysis was no longer needed. At the age of 18 months, her estimated glomerular filtration rate was 42 mL/min/1.73m^2, and her neurodevelopmental progress was excellent.

Key Points

This patient first presented with easy bruising and low counts of platelets and hemoglobin. Her renal function was normal, so she was thought to have an infectious process, possibly viral, which can cause hemolytic anemia or thrombocytopenia. Six weeks later, however, when she became oliguric with persistent thrombocytopenia and elevated creatinine, she was diagnosed with a TMA.

Her ADAMTS13 level was 25%, which can be misleading in terms of distinguishing TTP from aHUS. The authors noted that the normal range for ADAMTS13 activity in their hospital is 55% to 166%. The key point here is that the normal ranges reported by hospitals are for people with healthy kidneys and livers, and no evidence of endothelial cell damage. In the presence of liver and kidney damage, there is an enzyme production problem. Injury to endothelial cells can release von Willebrand factor, which can bind ADAMTS13, altering levels so they do not fall into the normal range. Thus, they must be less than 5% to 10%, not just lower than the reference range, to make a TTP diagnosis. The authors noted that the results of the standard complement tests they ordered, C3 and C4, were normal. It might be expected

that aHUS would lead to a low serum C3 with a normal or high C4, because it is a disease of uncontrolled activation of the terminal complement pathway. However, such a classic pattern is seen in only approximately 15% of cases, and C3 levels are low in less than half of classic aHUS cases.

The authors measured methylmalonic acid levels, a particularly important consideration in infants and children. Vitamin B_{12} deficiency, and particularly pernicious anemia, can rarely mimic the laboratory and clinical signs of aHUS.

This patient received plasma exchanges for 2 weeks and still became encephalopathic. She developed severe central nervous system disease and required ventilation. The tetravalent *meningococcus* vaccine was given to prepare for initiation of eculizumab therapy 2 weeks later. In severe cases such as this one, I favor rapid intervention rather than withholding the drug pending an immune response to the vaccine. Eculizumab can be given at the same time as the vaccine, as long as prophylactic antibiotics are also administered.

The first dose of eculizumab was followed by recovery of hematologic parameters and improvement in renal function. Dialysis was stopped a month after the first dose, and the patient had full neurologic improvement. Plasma had been given because the patient was thought to have TTP. The plasma had some effect on the patient's hematologic parameters, but did not prevent ongoing damage to her brain or her kidneys. When appropriate therapy was started, the recovery was dramatic.

This case raises another point, concerning costs of aHUS therapy. Eculizumab is the only FDA-approved therapy for aHUS, but it is an expensive drug. The authors make the point that in children—or anyone weighing less than 40 kg—dosing is weight-based. For this infant, the cost of eculizumab was significantly less than dialysis and regular plasma exchange. In addition, this patient had to stay in the intensive care unit. When eculizumab is given on a weight-based basis for patients who weigh less than 40 kg, it results in cost savings for the institution.

An aHUS Patient Who Discontinues Therapy

Carr and Cataland[6] describe the case of a 20-year-old woman who developed a TMA a week after delivery of a child. The patient presented with bilateral lower extremity edema, malaise, and bruising. Her hemoglobin was 6.0 g/dL, her platelet count was 28,000/µL, a serum creatinine was 5.27 mg/dL, and her lactate dehydrogenase (LDH) was 2,114 U/L. She had 2+ schistocytes on peripheral smear. ADAMTS13 activity was 100%. A kidney biopsy suggested TMA and acute tubular necrosis. Treatment began with plasma exchange and prednisone. After 7 days, she achieved a partial hematologic response, but her kidney function worsened and she required hemodialysis. Based on her lack of improvement with plasma exchange, her normal ADAMTS13 activity, and findings consistent with a TMA, the diagnosis of aHUS was then made, and treatment with eculizumab was initiated. After 2 weeks, her platelet count and LDH reached normal levels. After 6 weeks, dialysis was no longer needed. Serum creatinine returned to normal levels after 12 weeks of treatment with eculizumab. Testing showed that the patient had a mutant allele for CFH.

After 9 months of treatment with eculizumab, the patient elected to discontinue it. Six months later, she presented with fatigue, facial edema, and easy bruising that occurred after an upper respiratory infection. Her platelet count was 54,000/µL, her serum creatinine was 5.06 mg/dL, and she had 1+ schistocytes. Hemodialysis and eculizumab were initiated. Three weeks later, hemodialysis was no longer required.

Key Points

The first case highlighted the fact that infections, particularly infectious diarrheas, are the most potent activators of the alternate complement pathway. This case highlights the second most potent activator, pregnancy. A TMA that occurs in pregnancy, or one that seems to be associated with the syndrome known as HELLP (hemolysis, elevated liver enzymes, low platelet count), eclampsia, or preeclampsia, may instead be an unmasking of the inability to control complement leading to aHUS. This is particularly important to consider in the postpartum setting, as in this case, because the vast majority of classic HELLP, eclampsia, and preeclampsia syndromes should resolve postpartum.

The authors made the diagnosis relatively quickly, based on a normal ADAMTS13. Because the patient had renal failure, they performed a kidney biopsy. I would argue that based on her other diagnostic indicators—the platelet count of 28,000/µL, elevated LDH, serum creatinine of 5.3 mg/dL, schistocytes in peripheral smear, and ADAMTS13 of 100%—the kidney biopsy was unnecessary. However, the kidney biopsy was consistent with the TMA. Treatment with eculizumab was initiated.

After 9 months, the patient decided to discontinue therapy. She felt perfectly fine, and her kidneys and laboratory findings were normal. Six months later, she returned with complaints of fatigue and easy bruising. Similar to the first case, these symptoms followed a respiratory tract infection that most likely superactivated the alternative complement pathway. The patient was again diagnosed with a classic TMA. She rapidly began hemodialysis and treatment with eculizumab. After 3 weeks, dialysis was no longer needed.

In the vast majority of cases, aHUS is a chronic condition. Patients are born with a predisposition to it, that is, a complement or complement regulatory mutation. However, clinical penetrance varies greatly, and there have been reports in the literature of first clinical presentation at the age of 88 years.[7] Presentation of aHUS may relate to the

particular complement-linked mutation inherited as well as exposure to potent complement-activating events, mainly pregnancy, infection, autoimmune disease, and surgery.

This case also emphasizes that the point at which eculizumab therapy might be discontinued is unknown. This patient stopped therapy after 9 months. The drug package insert recommends close follow-up for at least 12 weeks thereafter,[3] and I would argue for such follow-up to last at least a year and include examination of levels of creatinine, platelets, and LDH.

This case highlights the ability to rescue a patient following serious clinical relapse after stopping eculizumab. The patient relapsed 6 months after she had received 9 months of therapy. Eculizumab was immediately restarted, and she did fine. However, among patients in the 2 prospective clinical trials leading to FDA approval of eculizumab for aHUS,[8] there were 5 patients who had elected to discontinue therapy. All experienced recrudescence of their disease. Eculizumab was restarted in 4, but only 3 could be rescued clinically. The fourth patient developed end-stage renal disease. Published studies, case reports, and my own experience appear to suggest that it might be possible to consider tapering the patient off the drug by lengthening the interval between the recommended biweekly maintenance doses after 12 or 18 months. There is some biologic basis for this suggestion. However, much more information is needed before any such recommendation can be made. The article by Carr and Cataland appropriately concludes that ". . . 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."[6] I absolutely agree with that statement. It may take a while to obtain that information. There are now registries of patients with aHUS; a patient need not be receiving drug therapy to enroll. Information from the registry will help determine the best approach.

Conclusion

These case studies describe the recent and dramatic evolution in the treatment of patients with aHUS. Research is under way to clarify the questions raised by these cases in order to optimize management.

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