ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Diagnosis and Treatment of Atypical Hemolytic Uremic Syndrome

Catherine Broome, MD
Associate Clinical Professor of Medicine
Lombardi Cancer Center
Georgetown University Hospital
Washington, DC

H&O What is atypical hemolytic uremic syndrome?

CB Atypical hemolytic uremic syndrome (aHUS) is a relatively uncommon disorder. It is a disease that primarily affects kidney function, and can occur at any age. It is characterized by 3 main features: microangiopathic hemolytic anemia, thrombocytopenia, and kidney dysfunction. Most cases of aHUS are sporadic. We do not have a good understanding of the prevalence of aHUS primarily because clinically it is very difficult to distinguish from another similar disorder called thrombotic thrombocytopenic purpura (TTP). Treatment for TTP and aHUS has historically been very similar, therefore they are often considered the same/similar conditions. However, the recent approval of a specific and targeted therapy for aHUS has sparked considerable interest in understanding the very subtle differences between these disorders.

H&O How is aHUS distinguished from other similar disorders?

CB We now have a better understanding that aHUS is a complement-mediated disorder. Although there is no specific laboratory test to definitively diagnose aHUS, we do have better laboratory tests to define TTP. Determination of ADAMS TS13 activity, which is a protein that is responsible for regulating the multimeric structure of Von Willebrand factor proteins, should be used to establish a diagnosis of TTP. If a patient has a very low level of ADAMS TS13 activity, the diagnosis is more consistent with TTP. If a patient does not have very low levels of ADAMS TS13 but still has many of the clinical features, this is more consistent with aHUS. aHUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, renal insufficiency, and microangiopathic changes on renal biopsy. There are also neurologic features that can be seen with aHUS, including altered mental status, headaches, and seizures. Although these are not as well characterized, they are certainly being discussed more frequently in relation to an aHUS diagnosis.

H&O What genes are associated with aHUS?

CB Genes that have been associated with aHUS have been much better characterized in the pediatric population. These genes are responsible for encoding for factors that are regulators of complement activation; they include complement factor I, complement factor H, membrane-cofactor protein, and thrombomodulin. These are the 4 most well-described genetic abnormalities that have been evaluated and detected. Not every person who presents with aHUS has these genetic abnormalities, and this may be due to 1 of 2 reasons: we may not have yet discovered some of the other genetic abnormalities seen in aHUS patients, or there may be a population of people who do not have a genetic abnormality but who do develop antibodies to these complement regulatory proteins.

I think that there are multiple forms of this disease. In children, the disease presents at a young age, there are multiple episodes of the disease, and genetic abnormalities have been seen in siblings, strongly suggesting genetic predisposition. In adults, aHUS may represent a slightly different disease; instead of major genetic mutations, patients may have antibody formation perhaps coupled with minor genetic predispositions.

As we learn more about this disorder, we will be able to distinguish the subtle differences in the pediatric form of the disease versus the adult form, and we may uncover new genes and mechanisms implicated in this disease.

H&O What is the current treatment landscape in aHUS?

CB For the last 10–15 years, plasma exchange was the mainstay of therapy for aHUS, regardless of whether it was termed typical or atypical. There is clinical evidence of a subset of patients who have not responded well to therapy, who have required therapy for extended periods of time, and who have gone on to develop permanent renal failure despite plasma exchange therapy.

In the last several weeks, eculizumab (Soliris, Alexion Pharmaceuticals) was approved specifically for the treatment of aHUS. Eculizumab is an anti-C5 antibody that specifically targets the uncontrolled complement activation seen in aHUS. Once it was recognized that aHUS is mediated by complement, blocking the terminal activation of complement appeared to be a logical pharmacologic intervention. Published studies have found that eculizumab is indeed very successful in reversing complement-mediated thrombotic microangiopathy and, in a vast majority of patients, stabilizing and ultimately improving renal function.

H&O What data have led to the approval of eculizumab for patients with aHUS?

CB The US Food and Drug Administration approved eculizumab for aHUS based on data from 2 prospective, phase II, open-label trials of adults and adolescents and 1 retrospective trial of pediatric and adult patients with aHUS.

The first prospective study looked at patients with aHUS who were resistant or intolerant to plasma exchange therapy. The study found that eculizumab led to the elimination of the need for continued plasma exchange and dialysis and sustained improvement in glomerular filtration rate and hematologic parameters (eg, hemoglobin, hematocrit, and platelet count). Hematologic normalization was seen in 76% of patients. The second retrospective trial comprised patients who had either a refractory or a prolonged course of plasma exchange. In this study, 90% of patients maintained a hematologic normalization after discontinuing plasma exchange therapy and had stabilization of renal function. A large percentage of these patients were also able to discontinue dialysis.

The findings from the retrospective trial showed that the outcomes in the pediatric patients were consistent with those seen in the prospective studies. The majority of patients could be weaned off of plasma exchange therapy, and approximately 40% of pediatric patients maintained a normalization of hematologic parameters.

H&O What is the safety profile of eculizumab?

CB Eculizumab has to be administered intravenously. Occasionally, some minor infusion side effects, such as headaches and skin rash or skin reactions, have been observed. Generally, the infusion is very well tolerated, and there have not been any long-term side effects reported to date. Eculizumab interferes with complement, which is an important part of immune regulation; therefore, treatment with eculizumab is associated with life-threatening meningococcal infections. Everyone who receives this medication has to be vaccinated against meningococcal bacteria. Patients are advised to watch for signs and symptoms of meningococcal infections and to monitor for fever, headaches, and other related symptoms. If patients develop any of these symptoms, they should immediately present to a medical facility.

H&O What kind of research is ongoing in aHUS?

CB There are research efforts that are evaluating a variety of issues related to aHUS. There is a registry of data that is being collected to evaluate potential genetic abnormalities that may predispose people to the development of this disorder. The registry is aiming to collect data on all patients with this disorder in order to develop a better understanding of this disease. One of the areas where most clinicians would like to see additional investigation is in diagnosis. Currently, we only have a clinical diagnosis; we do not have a laboratory test that establishes aHUS. Hence, there is a push towards evaluating whether or not there are other markers of dysregulation of complement that may be more clinically appropriate to help diagnose and manage these patients. All these are ongoing efforts to improve characterization, diagnosis, and treatment of this rare disorder.

Suggested Readings

Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol*. 2010;5:1844-1859.

ClinicalTrials.gov. An open-label, multi-center clinical trial of eculizumab in pediatric patients with atypical hemolytic-uremic syndrome (aHUS). http://www.clinicaltrials.gov/ct2/show/NCT01193348?term=NCT01193348&rank=1. Identifier: NCT01193348.

US Food and Drug Administration. Office of Medical Products and Tobacco. Eculizumab (Soliris). http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm273089.htm.