Factors Influencing Treatment of Atypical Hemolytic Uremic Syndrome

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On the Verge of a Revolution

Over the past 2 decades, tremendous strides have been made in our understanding of the ultra-rare disease atypical hemolytic uremic syndrome (aHUS). At the center of this progress has been the discovery that the majority of patients with aHUS (>50%) carry causative DNA variants in alternate complement pathway (AP) genes (1–4). In another approximately 10% of patients, the disease is driven by antibodies to factor H, the major regulator of the AP, triggering acquired complement–mediated hemolytic uremic syndrom (HUS) (2,5,6). The clinical consequence of these discoveries has been the successful implementation of focused efforts to block the terminal complement cascade as a practical approach to targeted therapy for patients with aHUS. With the adoption of targeted therapy has come the recognition of new challenges. In this editorial, we address factors that may influence treatment of aHUS, a number of which are highlighted by Chinchilla *et al.* in this issue of *CJASN* (7).

Chinchilla *et al.* present a comprehensive genetic assessment of a cohort of patients with aHUS (83 of 275) aged <2 years and negative for autoimmune-mediated HUS (7). The authors aimed to determine the contribution of diacylglycerol kinase ε (DGKε) mutations to aHUS in this Spanish population. DGKε is the most recent gene causally related to aHUS (8–10). The novelty of this discovery resides in the presumed mechanism by which DGKε causes aHUS. As an intracellular protein without an overt association with the complement cascade, DGKε is hypothesized to cause aHUS by promoting a prothrombotic state, which has implications for treatment.

An Imprecise Nomenclature

At the heart of defining factors that influence treatment of aHUS is the nonspecific nature of the term aHUS. Created as a foil to "typical" HUS (HUS associated with shiga-toxin carrying bacteria), the adjective "atypical" was never meant to imply a cause. At best, this term encompasses a group of diseases that share in common the clinical features of a microangiopathic hemolytic anemia associated with thrombocytopenia and renal failure. At its worst, however, aHUS lumps together a group of diseases with very different underlying pathologies. In practice, there is little agreement on what defines or limits classifying someone as an aHUS patient.

The disparate definitions of aHUS are illustrated by the reports of two of the larger aHUS cohorts. Fremeaux-Bacchi *et al.* use the term aHUS to designate HUS after all secondary forms had been excluded (1). By contrast, Noris *et al.* adopted a broader definition (2) and included all patients with HUS, excluding only those with thrombotic thrombocytopenic purpura or those associated with shiga toxin–carrying bacteria. In this issue of *CJASN*, Chinchilla *et al.* define their aHUS cohort as patients with microangiopathic hemolytic anemia with thrombocytopenia and renal failure in whom autoimmunity has been excluded (7). The finding that 5% of their aHUS cohort carries recessive mutations in DGKε is considerably lower than the 27% reported in the French cohort (1). Given the differences in inclusion criteria, it remains possible that these results reflect enrollment criteria and not ethnic-specific genetic differences.

Strict definitions of aHUS based on a mechanistic understanding of disease are essential for well designed clinical trials. An optimal therapeutic approach should target the primary pathology and if the primary pathology is appropriately targeted, a disease response should be seen. At the simplest level, if the term aHUS is applied too broadly, it becomes difficult to determine whether an apparent lack of response relates to an ineffective treatment or an inappropriate treatment. Similarly, lumping different pathologies together may hide treatment successes.

Matching Pathology to Treatment

An example within the aHUS group demonstrates how unique, pathology-related factors influence the treatment of aHUS in these relative settings. As mentioned previously, at the genetic level, a *CFH* mutation may be transcribed into a nonfunctional protein leading to aHUS. However, loss of factor H function can also be the consequence of autoantibodies to this protein. Although the phenotypic consequence is dysregulation of the alternate pathway of complement and aHUS, different targeted treatments are possible because the pathophysiology is fundamentally different. Certainly, anticomplement therapy appears to work for both types of aHUS. However, in patients with autoimmune-mediated HUS, a more direct therapy

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would target the antibody and not the terminal complement pathway. This tenet is the basis for considering anticellular immune suppression to reduce antibody titer and limit risk for exacerbation without compromising complement activity in this select patient cohort.

The study by Chinchilla *et al.* highlights other factors that may influence the treatment of aHUS (7). In their cohort, Chinchilla *et al.* identified four patients that carried mutations in DGKε. Of particular interest is that three of these four patients also carried complement mutations, the significance of which is 3-fold. First, it mandates screening of the complement genes in patients with DGKε mutations. Second, their findings suggest that segregating both complement mutations and DGKε mutations alters the disease phenotype. Third, response to anticomplement therapy is affected by mutational analyses.

Lemaire *et al.* first reported DGKε-mediated HUS, noting that this type of HUS did not respond to plasma therapy or eculizumab, a reasonable expectation given the presumption that DGKε mediates HUS through a different mechanism (8). Importantly, neither of their patients had complement mutations. By contrast, Chinchilla *et al.* observed a clinical response with either plasma therapy or eculizumab in the three patients carrying both DGKε mutations and complement mutations (7). The overriding message is that response to therapy depends on the mechanism of disease. As such, a complete genetic workup may influence treatment choices.

Treatment When the Pathophysiology Is Uncertain

Although a comprehensive understanding of the primary pathophysiology underlying aHUS is critical to informing treatment, it is also possible that by defining secondary pathology, alternative therapeutic targets may be identified. Over 30% of patients with aHUS do not have an identifiable mutation in the complement genes currently screened in most clinical laboratories. Yet many of these patients are treated empirically and appear to respond to either plasma exchange or eculizumab. Multiple research centers are studying these cases to identify disease drivers that include pathways that interact with the complement cascade (1–6,8,10–39). It is now understood, for example, that there is crosstalk between the complement system and the coagulation pathway, but the precise relationship between the two pathways and how that relationship could affect a disease like aHUS is unclear. In the absence of a more complete pathologic understanding, as an interim step, it may be reasonable to use biomarkers as indices of disease activity. For example, most patients with aHUS do not have a low C3. Perhaps a low C3 during disease exacerbations, even in the absence of explanatory genetic or acquired factors, should be enough to label the process as "complement associated" and initiate anticomplement therapy.

Chinchilla *et al.* teach us an important lesson: A comprehensive understanding of the genetic and acquired drivers of aHUS is necessary to understand the predisposing pathology and to guide appropriate diagnosis and effective treatment. Patients respond to therapies that are appropriate to the cause of their disease. Until we define the underlying pathology, treatment regimens remain empirical. As currently used, the term aHUS includes diseases of differing causes. It remains a major task to identify the additional pathologic drivers in this group of diseases and to refine our treatment protocols on that basis. Perhaps the generic term aHUS has outlived its usefulness and a more informative nomenclature should be adopted?

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