Can Urinary Complement Proteins Stratify Patients to Therapeutic Complement Inhibitors?

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Targeted complement system inhibition is becoming a therapeutic option for patients with autoimmune kidney diseases. The recent explosion of research into therapeutic complement inhibitors in kidney diseases has been built on key basic science, translational research, and clinical trial discoveries. Inappropriate and deregulated alternative and terminal complement pathway activity was shown to be essential in the pathogenesis of 2 rare, severe, and progressive kidney diseases, atypical hemolytic uremic syndrome and C3 glomerulopathy. This was supported by the demonstration that alternative pathway inhibition by the anti-C5 monoclonal antibody, eculizumab, provided marked clinical benefit for atypical hemolytic uremic syndrome and C3 glomerulopathy. This was supported by the demonstration that terminal complement pathway inhibition by the anti-C5 monoclonal antibody, eculizumab, provided marked clinical benefit for atypical hemolytic uremic syndrome. The demonstration that complement activation mediates kidney pathology and complement inhibition can provide clinical benefit has been followed by impressive growth in complement therapeutic development. For example, research that identified a role for the terminal pathway in anti-neutrophil cytoplasmic autoantibody–associated vasculitis has been followed by clinical trial evidence of benefit from the C5a inhibitor avacopan in anti-neutrophil cytoplasmic autoantibody vasculitis. The arsenal of available medicinal products that inhibit complement is likely to expand imminently as clinical trials report outcomes for severe diseases that currently lack targeted and effective therapies. Regardless of the agent, complement inhibition is associated with important adverse effects. Consequently, understanding which patients and kidney diseases are likely to respond to specific complement protein inhibition is of paramount importance.

Each therapeutic agent targets a specific protein and mechanism in the complement activation pathway. The complement system is a complex network of self-amplifying reactions that, as part of the innate immune system, are important to a number of homeostatic systems, including cancer surveillance, prevention of autoimmunity, and defense from infection, particularly by encapsulated bacteria. The complement system can be initiated by 3 pathways—the classical, lectin, and alternative pathways of complement activation (Figure 1). The pathways are differentiated by the proteins involved in triggering complement activity. The classical pathway is activated by the C1q complex of C1q, C1r, and C1s that binds immunoglobulin. The lectin pathway is activated by mannose-binding lectin-associated serine protease in complex with pattern recognition molecules, such as mannose-binding lectin, that bind carbohydrate molecules. Both the classical and lectin pathways lead to complement activity by C4-dependent convertases. The alternative pathway is constitutively activated by tick-over C3 hydrolysis and depends on the C3 convertase to propagate complement activation. The 3 initiating pathways converge at the C3 amplification loop that leads to C3a release and, if inadequately regulated, terminal pathway activation with the production of C5a and the membrane attack complex, C5b-9.

Autoimmune glomerular diseases are characterized by significant differences in immunohistologic and serum markers of complement activity. This indicates that the nature of complement activation differs between glomerulopathies. For example, glomerular deposition of C1q, immunoglobulin, and C3 activation fragments are diagnostic of lupus nephritis and evidence of classical complement pathway activity. Systemic lupus erythematosus activity correlates with the degree of systemic complement...
activity, detected by low intact serum C3 and C4 levels. In contrast, glomerular deposition of activated C3 is common in IgA nephropathy and often accompanied by C4 activation fragments but not C1q. This pattern indicates alternative and lectin, but not classical complement, activity. Evidence of activation of multiple complement pathways can often be detected in autoimmune kidney diseases. Furthermore, the nature and extent of complement activation vary with disease severity and differ between patients with the same glomerular diagnosis.

The combination of variable complement activation and the availability of targeted complement pathway inhibitors gives the identification of specific complement pathway activity in autoimmune glomerulonephritis (GN) clinical relevance. How can we stratify individual patients with GN to clinical trials and treatments with targeted complement inhibitors? This motivates the research presented by Genest et al. in this issue of the *KI Reports*. The paper presents comparative urinary complement protein levels from patients with 5 autoimmune kidney diseases. With the aim of identifying the pathogenically dominant pathway in each GN, the authors attempted to select points of maximal and minimum clinical activity with proteinuria, at which point urinary markers were measured. The analyzed proteins represented the alternative, lectin, classical, and terminal complement pathways (Figure 1).

The findings are, on the face of it, unexpected. Urinary levels of terminal pathway proteins were highest in focal segmental glomerulosclerosis and membranous nephropathy, even after correcting for differences in proteinuria. Furthermore, markers of C3 convertase (C3a) and classical complement pathway (C1q) activity were lowest in lupus nephritis. Urinary sC5b-9, a terminal pathway marker, was similar to a control cohort of patients with diabetic nephropathy. Given these findings, it is important to highlight limitations to the research methods. First, the study was...
observational. Second, although proteinuria was used to standardize the timing of complement quantification, without paired histology, it is unclear whether proteinuria was a valid biomarker of maximal and minimal disease activity. Third, the comparison of different GN, some of which were treated with immunosuppression, makes the effect of nontargeted immunosuppression on complement markers difficult to interpret. In general, the assessment of urinary complement proteins is complicated by the potential contribution to complement activity from multiple kidney compartments. Urinary complement proteins could be influenced by glomerular inflammation, nephrotic loss of circulating complement proteins, tubular cell recycling of filtered proteins, and the contribution of urinary pH, glucose, and other proteins to complement activation in the urinary space. Furthermore, the lack of matched histology samples makes understanding the pathogenesis of urinary complement levels impossible. For example, we do not know whether low urinary complement protein levels are the result of glomerular complement inactivity or activation with sequestration and clustering of complement activation fragments at nidi of inflammation.

Acknowledgment of the limitations, however, does not mean that these data should be dismissed. The results are noteworthy for a number of reasons. First, high urinary complement activation proteins have previously been detected in samples from patients with focal segmental glomerulosclerosis and diabetic nephropathy. Second, the potential to utilize urine as a biomarker seems tantalizingly close. However, we must consider that urinary levels of complement proteins may inversely correlate with disease activity, and the development of biomarkers is likely to necessitate significant basic and translational research efforts. Furthermore, these data are a reminder that autoimmune GN is diagnosed on the basis of histology and immunostaining for a limited number of proteins. Classification is not based on the presence or nature of complement activation. It is therefore not surprising that comparison of urinary complement proteins by histologic classification yields apparently incongruent results. The imminent era of specific complement protein and pathway inhibition may necessitate the recategorization of glomerulopathies based on evidence of complement pathway activity. Overall, the study demonstrates the current lack of understanding of glomerular complement activation in autoimmune kidney diseases, particularly at points of maximal inflammation and disease activity.

Biomarkers will have significant clinical impact if they stratify patients to receive specific complement inhibitors of benefit and avoid the adverse effects of agents unlikely to be effective. However, translation to clinical use will depend on describing and better understanding the specific complement pathways and mechanisms that contribute to autoimmune glomerular diseases. These mechanisms may not segregate with the current morphologic classification of GN. Similar to understanding the impact of the terminal complement pathway in atypical hemolytic uremic syndrome and the role of alternative pathway complement activation in C3 glomerulopathy, the effective and appropriate use of complement inhibitors will depend on basic science and translational research unpicking the mechanisms of complement activity in autoimmune kidney diseases.

**DISCLOSURE**

The author declared no competing interests.

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