Proteinuria in Nephrotic Syndrome: Mechanistic and Clinical Considerations in Optimizing Management

James A. Tumlin^a Kirk N. Campbell^b

^aDepartment of Medicine, UT College of Medicine, University of Tennessee, Chattanooga, TN, USA;

^bDivision of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Nephrotic syndrome (NS) is comprised of constellation of symptoms that may be due to a primary kidney disorder or may be secondary to systemic disease. When left untreated or when resistant to treatment, the glomerular damage associated with NS may be accompanied by progressively declining kidney function, including end-stage renal failure. There is a strong need to identify and manage early stages of kidney disease to prevent substantial morbidity and mortality. The presence of proteinuria serves both as a diagnostic marker of NS as well as a factor affecting the progression of kidney disease. Optimizing treatment of proteinuria in NS (PNS) may lead to improvements of symptoms and systemic sequelae, and may also have a renoprotective effect. However, development of standardized treatment guidelines has been complicated by factors that include a lack of adequately powered randomized clinical trials and heterogeneity of disease types, etiologies, and outcome measures.

Advances in basic science research have enhanced our understanding of disease types and have also elucidated common mechanisms underlying varied presentations. Increasing knowledge of podocyte biology and the interplay of immunological, inflammatory, and physiological

processes holds the potential for optimizing therapeutic interventions. Use of such information must be aligned with the clinical data and real-world evidence to provide guidance on treatment considerations, including the course and timing of response, risks and benefits of therapy, and accurate patient identification for optimal customization of treatments.

We convened a group of experienced nephrologists with a wide array of research and clinical interests at a roundtable meeting on October 22, 2016, to discuss the mechanistic and clinical considerations in optimizing the management of PNS. Some of our goals were to link our understanding of the pathogenesis of PNS to treatment mechanisms, to critically assess treatment regimens within the context of mechanistic processes and to identify factors impacting individualized treatment regimens. The articles in this supplement review the presentations and discussions from this meeting.

The first article, “A Review of Podocyte Biology”, Garg [1] sets the foundation for discussion. It explores the pathogenesis of PNS with a focus on pathways that involve podocyte epithelial cells. Greater knowledge of podocyte biology offers the promise of improved understanding of

the glomerular filtering process and the mechanistic nature of multiple diseases associated with PNS, and offers the potential for new targets for treatment.

Continuing with the critical role of the podocyte in maintaining normal glomerular function, our article, “Protecting Podocytes: a Key Target for Therapy of Focal Segmental Glomerulosclerosis” [2], focuses on damage to the podocyte and the consequences of other structural changes in patients with focal segmental glomerulosclerosis (FSGS). It is increasingly recognized that FSGS is not a disease itself but, rather, a histologic pattern of injury that can arise from diverse causes and mechanisms. As such, several classes of treatments have been shown to be effective in treating FSGS, as well as having protective effects on podocytes. We expect continued growth in our understanding of the pathogenesis of FSGS to result in the development of new treatment approaches tailored to suit the underlying pathology as well as the clinical features.

In contrast to the varied causes of FSGS, the majority of patients with membranous nephropathy have antibodies directed against identified podocyte antigens, most commonly M-type phospholipase A₂ receptor. In “Membranous Nephropathy: Approaches to Treatment,” Bomback and Fervenza [3] discuss initial conservative treatment as well as approaches for those patients who are not responsive. Furthermore, they discuss the variability in clinical progression and the potential use of anti-phospholipase A₂ receptor antibodies along with proteinuria as markers for both prognosis and response to therapy, enabling a more personalized treatment approach.

Finally, in “Immunoglobulin A Nephropathy: Advances in Understanding of Pathogenesis and Treatment,” Lafayette and Kelepouris [4] address the challenges around managing the most common form of primary glomerulonephritis, that is, immunoglobulin A nephropathy. They describe the wide variability in clinical course and outcomes, and the limited treatment options that tend to focus on arresting disease progression rather than treating the primary defect. They end with a discussion on investigations into novel interventions based on the inflammatory nature of the disease and its “multi-hit” pathogenesis.

It has been a pleasure to work with this group of esteemed colleagues who brought their experience, research, and points of view to life through discussion at the roundtable meeting and in the writing of the articles in this supplement. It is our hope that the articles will serve not only as references about mechanistic and clinical considerations in optimizing the management of PNS, but as starting points for further research.

Disclosure statement

K.N.C. and J.A.T. received honoraria from IQVIA (formerly QuintilesIMS) for their participation in a roundtable meeting supported by a grant from Mallinckrodt Pharmaceuticals. J.A.T. is a consultant for Mallinckrodt and has received previous research funding. K.N.C. has served as a consultant for Mallinckrodt and serves on the Medical Advisory Board of the National Kidney Foundation of Greater New York.

References

- 1 Garg P: A review of podocyte biology. *Am J Nephrol* 2018;47(suppl 1):3–13.
- 2 Campbell KN, Tumlin JA: Protecting podocytes: a key target for therapy of focal segmental glomerulosclerosis. *Am J Nephrol* 2018;47(suppl 1):14–29.
- 3 Bomback AS, Fervenza FC: Membranous nephropathy: approaches to treatment. *Am J Nephrol* 2018;47(suppl 1):30–42.
- 4 Lafayette RA, Kelepouris E: Immunoglobulin A nephropathy: advances in understanding of pathogenesis and treatment. *Am J Nephrol* 2018;47(suppl 1):43–52.