Immunonephrology—innovations that (will) improve clinical practice

Hans-Joachim Anders

Division of Nephrology, Department of Medicine IV, Hospital of the Ludwig-Maximilians University, Munich, Germany
Correspondence to: Hans-Joachim Anders; E-mail: Hans-Joachim.Anders@med.uni-muenchen.de

Immune-mediated kidney diseases are an exciting domain of progress in diagnosis and immunotherapy. Established diagnostic pathways undergo revision, e.g. in ‘membranous nephropathy’, a descriptive term relating to a typical histopathological lesion pattern caused by diverse disorders but always autoimmune. The phospholipase A2 receptor (PLA2R) antibody assay illustrates how the management of this disease can shift from clinical manifestations and proteinuria levels to a serum biomarker-driven approach. However, in many disorders such elegant biomarkers of immunological disease activity are not yet available although they are urgently needed given the approaching wave of novel (costly) immunomodulators. Although patients keep being recruited to trials on C3 glomerulopathy or immunoglobulin A (IgA) nephropathy based on proteinuria levels, there is a hesitance to use such drugs without being clear whether proteinuria really relates to immunological activity or to persistent scarring. For example, a kidney biopsy years ago may define the diagnosis of an IgA nephropathy but does not specify whether the persistent proteinuria should be treated with an immunomodulatory or a therapy targeting the mechanisms of glomerular hyperfiltration in chronic kidney disease. In this setting, advances in immunotherapy reveal the unmet medical need to dissect immunological activity from chronicity, something that has been established for lupus nephritis for decades but not so for IgA nephropathy, C3 glomerulopathy or membrano-proliferative glomerulonephritis.

Another important development in immune-mediated disorders is the availability of specific (biological) drugs that give definitive answers regarding human pathophysiology. The classical bench-to-bedside approach has become less appealing in this regard because the pathophysiology of animal models and human disease categories rarely match as long as human diseases remain defined by histological lesion patterns. The lack of efficacy of anti-interleukin-17 in human lupus nephritis is only the latest example illustrating how the classical bench-to-bedside approach can be misleading. In addition, we learned that the cytokine tumour necrosis factor, even though it is strongly upregulated in kidney biopsies and involved in most inflammatory kidney injury models, is not a valid treatment target for immune-mediated kidney diseases. Vice versa, we have now learned that complement blockade, although absent in kidney biopsy transcriptome analyses, is potent in abrogating immune-mediated kidney injury. Indeed today, ‘experiments’ are carried out directly in human trials using target-specific (biological) drugs. For example, the high response rate of anti-CD20 in steroid-sensitive nephrotic syndrome or membranous glomerulonephritis ultimately proves that B cells are essential in the pathogenesis of human disease, i.e. responders have an autoimmune disease. Indeed, CD20 is also mostly absent in the kidney but we have to control autoimmunity from where it originates, i.e. in the lymphoid organs. The reported complete response of lupus nephritis to anti-CD19 chimeric antigen receptor-T cells ultimately proves that B cells are the key mediators and hence attractive therapeutic targets in human systemic lupus erythematosus, a finding documented by the efficacy of anti-BAFF-IgG (belimumab) in lupus nephritis.

This supplement of Nephrology Dialysis Transplantation highlights how the upcoming availability of novel and very specific drugs has the potential to change how we understand and manage kidney diseases. These drugs will give clear answers about what matters in human kidney disease. In this supplement, Romagnani et al. start out by proposing a new classification for glomerulonephritis based on the underlying immunopathogenesis to define the type of immunotherapy, the immunological activity to define the intensity of immunotherapy, and disease chronicity to define the intensity of chronic kidney disease (CKD) management. Stefan et al. characterize the circulating complement cleavage factor Bb as a biomarker of alternative pathway activation and its role to predict vascular lesions and long-term outcomes of IgA nephropathy.

Odler et al. analyse the increasing number of immunomodulatory drugs being developed for non-kidney disorders and speculate which ones may have a potential in immune-mediated kidney diseases. Wooden et al. explore the potential of complement inhibitors for kidney diseases and review the ongoing trials for the various forms of immune-mediated kidney diseases. Windpessel et al. review all the different means to protect patients with kidney diseases from infections, the second most common cause of death in these patients. They analyse the potential of vaccines as well as protocols for antimicrobial prophylaxis.

Finally, Floege et al. comment on the role of CKD therapy as part of the management of immune-mediated glomerular diseases, a topic recently empowered by the renoprotective effects of sodium-glucose transporter 2 antagonists in patients with non-diabetic kidney diseases.
We hope that the readers of NDT appreciate this article collection mirroring some of the progress in immunonephrology. Supplements on other dynamic areas of kidney medicine will be produced in 2024.

CONFLICT OF INTEREST STATEMENT
H.-J.A. received consulting and lecture fees from Novartis, Boehringer-Ingelheim, Bayer, GSK, Vifor, Otsuka, Stada and AstraZeneca.

REFERENCES