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IgA Nephropathy: The Renaissance Era of Glomerular Diseases and the New Age of Kidney Care

George Vasquez-Rios MD, MSCR, FASN [1,a,b]

[1] Glomerular and Genetic Diseases Center, Renal Medicine Associates, New Mexico, USA
[a] Director
[b] Co-director, Clinical Trial Research Unit

Chronic kidney disease (CKD) is a leading cause of disability and mortality worldwide, affecting an estimated 800 million individuals according to some reports [(1)]. As a progressive condition, CKD can be life-threatening if left untreated. Among the most common identifiable causes of CKD, glomerular diseases rank just after diabetes mellitus and hypertension. Despite their significant contribution to the CKD burden, glomerular diseases have long been an area lacking effective disease-modifying therapies, with limited treatment options available and a large population size that ultimately suffered from the burden of end-stage kidney disease.

Over the past decade, a surge in translational research has revolutionized this field. Advances have unveiled novel therapeutic targets rooted in the fundamental pathophysiology of these conditions. Bioinformatic approaches have been pivotal in repurposing immunotherapies for rare glomerular diseases, expanding the therapeutic landscape [(2)]. Additionally, a more nuanced understanding of the immune system's role in glomerular pathology has enabled the development of targeted treatments, such as complement inhibitors and monoclonal antibodies. These advances mark a significant shift away from traditional, nonspecific immunosuppressants associated with substantial toxicity, paving the way for more precise and safer interventions. [(3)]

In the field of Immunoglobulin A nephropathy (IgAN)—the most prevalent glomerular disease worldwide—recent guidelines advocate combining immunosuppressive therapies with medications that stabilize glomerular hemodynamics, such as RAAS blockers and SGLT2 inhibitors. Currently, two therapies have received regulatory approval for IgAN management. The first is budesonide, an immunomodulator also used in inflammatory bowel disease, which

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Correspondencia:
George Vasquez Rios
george.vasquez@upch.pe

reduces the production of galactose-deficient IgA, addressing the "first hit" in the IgAN pathophysiologic cascade that initiates kidney inflammation [4]. The second approved therapy is iptacopan, a selective inhibitor of Factor B in the alternative complement pathway, which was previously used in paroxysmal nocturnal hemoglobinuria, a hematological malignancy characterized by premature red blood cell hemolysis and hemoglobinuria [5]. By limiting C_3 cleavage, iptacopan disrupts the terminal complement pathway activation, targeting the "third hit," where inflammation and injury perpetuate kidney damage.

In addition to the above-mentioned advances, promising therapies targeting the "second hit" of the disease are nearing market approval. These include novel B-cell immunomodulators, such as those aimed to block APRIL (A proliferation-inducing ligan) and TACI (transmembrane activator calcium modulator and cyclophilin ligand interactor) activation pathways, which play a critical role in B cell maturation, and antibody-mediated cytotoxicity. These treatments, currently in phase III trials, are poised to further expand the therapeutic options for IgAN, addressing unmet needs in this complex disease. Several newer therapies are in the pipeline in phase I and II, and they are expected to transform the landscape of opportunities for IgAN patients.

The implementation of genetic testing has highlighted a critical challenge in kidney diseases: the identification of genetic mutations that render podocytes vulnerable to physiological stress, leading to podocytopathy and more severe proteinuria. In IgAN, some patients exhibit focal and segmental lesions that cannot be fully explained by hemodynamic factors or injury, suggesting an underlying genetic predisposition. Mutations in key genes such as COL4A, previously recognized in Alport syndrome, have now been identified in subsets of IgAN patients. These genetic alterations may contribute to unique glomerular basement membrane abnormalities and are associated with potentially distinct clinical outcomes compared to non-carriers. While these discoveries underscore the importance of integrating genomics into the study and management of IgAN, they represent only the beginning. We are merely scratching the surface of the genomic landscape in IgAN, paving the way for deeper insights and personalized approaches to care.

Several critical questions remain unanswered before these newer therapeutic options can be seamlessly integrated into clinical practice, particularly regarding patient selection and therapy suitability. IgAN clinical trials often enroll patients with urine-to-protein creatinine ratio (UPCR)<1 and estimated glomerular filtration rate (eGFR)>30 mL/min/1.73 m^2, enabling broader generalization of findings. However, this approach has raised concerns when thinking about individualizing treatment, as certain clinical scenarios might alter the risk-benefit profile and steer clinicians away from specific therapies. For instance, iptacopan, a long-term therapy with an undefined duration, has been associated with infectious complications despite appropriate vaccination and prophylactic measures. On the other hand, while budesonide minimizes infectious risks by bypassing first-pass metabolism, some patients experience peripheral effects such as hypertension and edema, likely influenced by individual steroid sensitivity. Additionally, the controlled environment of clinical trials—characterized by intensive monitoring, frequent visits, and proactive side effect management—differs significantly from real-world practice, where resource constraints and limited infrastructure can hinder close patient oversight.

Nonetheless, the era of reliance solely on RAAS blockers or oral prednisone is coming to an end. Addressing these remaining questions is essential to ensure optimal outcomes while minimizing safety concerns as we transition into this new chapter in IgAN management. However, the expanding therapeutic armamentarium introduces new challenges for nephrologists, requiring them to stay informed and adept in navigating the increasingly complex landscape of treatment options. Recognizing this need, select training programs have begun offering dedicated curricula in glomerular and genetic diseases, underscoring the growing demand for subspecialists with deep expertise in these areas. Such efforts highlight the importance of preparing the next generation of nephrologists to lead in the era of precision medicine.

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