AJKD

Narrative Review

Diagnostic Tests and Treatment Options in Glomerular Disease: 2014 Update

Jonathan Hogan, MD, Prince Mohan, MD, and Gerald B. Appel, MD

Glomerular diseases historically have been challenging disorders to comprehend and treat for patients and physicians alike. Kidney biopsy is the gold standard of diagnosis, but the link between pathophysiology and the histologic representation of kidney injury has remained elusive in many of these diseases. As a result, treatment of glomerular disease usually involves therapies that are not specific to disease pathogenesis, such as blockade of the renin-angiotensin-aldosterone system and various immunosuppression regimens. Recent research has resulted in greater insight into some glomerular diseases, leading to the hope that new diagnostic tests and treatments targeting disease-specific mechanisms are on the horizon. We review recent progress on the understanding, diagnosis, and treatment of 4 glomerular diseases: immunoglobulin A nephropathy, focal segmental glomerulosclerosis, the C3 glomerulopathies, and idiopathic membranous nephropathy.
Am J Kidney Dis. ■(■):■-■. © *2013 by the National Kidney Foundation, Inc.*

INDEX WORDS: Immunoglobulin A (IgA) nephropathy; membranous nephropathy; focal segmental glomerulosclerosis; C3 glomerulopathies; glomerular disease.

Gerald B. Appel, MD, was the Donald W. Seldin Distinguished Award recipient at the 2012 National Kidney Foundation Spring Clinical Meetings. This award was established to recognize excellence in clinical nephrology in the tradition of one of the foremost teachers and researchers in the field, Dr Donald W. Seldin.

Hematuria and proteinuria are the most widely used and accepted biomarkers for glomerular disorders, but they cannot supplant the kidney biopsy for diagnosis. In the last decade, groundbreaking research has attempted to bridge the knowledge gaps between the mechanisms of glomerular diseases, their clinical and histologic phenotypes, and their responses to treatment. These new insights have redefined certain glomerular diseases and have led to the anticipation of new diagnostic tests that reflect underlying disease pathogenesis. During the same period, multiple new therapies have become available for these diseases, some of which have been evaluated in randomized controlled trials in the hope that nephrologists will be able to target pathophysiology while minimizing side effects. In this review, we focus on new diagnostic testing and treatment for 4 glomerular diseases: immunoglobulin A (IgA) nephropathy, idiopathic focal segmental glomerulosclerosis (FSGS), the C3 glomerulopathies, and idiopathic membranous nephropathy.

IGA NEPHROPATHY

IgA nephropathy is the most common idiopathic glomerulonephritis (GN) worldwide, with higher prevalences in Asia and Europe.[1] It progresses to end-stage renal disease (ESRD) in 15%-20% and 30%-40% of patients at 10 and 20 years after diagnosis, respectively. IgA nephropathy presents as recurrent gross or microscopic hematuria, with or without significant proteinuria. Presently, IgA nephropathy can be diagnosed only with a kidney biopsy in which immunofluorescence microscopy demonstrates dominant or codominant glomerular IgA deposition (predominantly in the mesangium) along with electron-dense deposits on electron microscopy.[1]

Clinical predictors of worsened long-term renal outcomes have included older age, hypertension, decreased estimated glomerular filtration rate, and higher amounts of proteinuria at the time of diagnosis.[2] Recently, a risk score for progression (based on a review of 619 Chinese patients with IgA nephropathy) demonstrated that in addition to these factors, lower hemoglobin and serum albumin levels increased the risk for ESRD.[3] Biopsy features also have been used to predict renal outcomes in IgA nephropathy. The Oxford Classification is the newest histologic scoring system, and found worsened renal outcomes with increased mesangial hypercellularity, endocapillary proliferation, segmental sclerosis, and tubular atrophy/interstitial fibrosis on biopsy.[4,5]

Significant progress in understanding the pathophysiology of IgA nephropathy has been made in the last few decades, with a particular focus on the structure of the IgA molecule itself. Patients with IgA

From the Division of Nephrology, Department of Medicine, Columbia University Medical Center, New York, NY.

Received May 21, 2013. Accepted in revised form September 19, 2013.

Address correspondence to Gerald B. Appel, MD, 622 W 168th St, PH 4-124, New York, NY 10032. E-mail: nephroman@msn.com

0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2013.09.019

nephropathy and their family members have elevated circulating levels of IgA1 molecules that lack the galactose residues normally present at the antibody's hinge region.[6] While this abnormal protein makes up a small proportion of circulating IgA molecules, it preferentially deposits in the mesangium in IgA nephropathy.[6,7] This (gal)-deficient IgA molecule has been found in both IgA nephropathy and Henoch-Schönlein purpura, in adults and children, and in patients from diverse geographic and ethnic backgrounds.[8] Moreover, although the majority of IgA nephropathy cases (90%) are sporadic, genome-wide association studies have discovered genetic loci that explain 4%-5% of cases.[9,10]

The discovery of elevated levels of circulating (gal)-deficient IgA in relatives of many patients with IgA nephropathy has led to the development of a 2-hit hypothesis. The first hit is the presence of the abnormal (gal)-deficient IgA molecule, which causes either minimal or asymptomatic disease. Such subclinical IgA deposition is present in 4%-16% of patients in autopsy series[11-13] and kidney donors[14] and also is found in some kidney transplant recipients whose transplant biopsies show IgA deposition without clinical disease. Potential second hits include the induction of mesangial oxidative stress with (gal)-deficient IgA deposition[15] and the complexing of circulating IgG or other autoantibodies with (gal)-deficient IgA, which deposit in glomeruli and lead to clinical disease.[7,16]

The (gal)-deficient IgA antibody and anti-IgA autoantibodies are the focus of new research testing, with the hope that high levels of these molecules could help distinguish IgA nephropathy from other causes of microscopic hematuria and proteinuria, such as thin basement membrane disease. Prognostically, higher levels of (gal)-deficient IgA and anti-IgA autoantibodies have both been associated with more progressive courses to ESRD.[7,16]

Treatment options for IgA nephropathy currently are limited. Nonimmunosuppressive treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have been shown to slow the progression of IgA nephropathy independently of their effect on blood pressure.[17,18] Their importance is reflected in the recent KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for glomerulonephritis, which recommends using ACE inhibitors or ARBs to decrease proteinuria and attain a goal blood pressure dependent on the level of proteinuria (<125/75 mm Hg if initial proteinuria has protein excretion > 1 g/d, and <130/80 mm Hg if initial protein excretion is <0.5 g/d).[19] Other nonimmunosuppressive treatments for IgA nephropathy, such as fish oil and tonsillectomy, remain controversial.[20-22] Corticosteroids remain the first-line immunosuppressive therapy in patients who have preserved kidney function and significant (protein excretion > 1 g/d) proteinuria after 6 months of conservative therapy.[23-27] A recent meta-analysis by Lv et al[28] demonstrated a relative risk of 0.32 for developing kidney failure in steroid-treated versus non–steroid-treated IgA nephropathy (95% confidence interval, 0.15-0.67; $P = 0.002$), as well as a decrease in proteinuria with steroid therapy. There also is interest in the role of enteric nonabsorbable corticosteroids in the treatment of IgA nephropathy,[29] one of which is being evaluated in a phase 2 clinical trial in Europe (www.clinicaltrials.gov identifier NCT01738035). Results of multiple randomized trials will shed further light on the role of systemic corticosteroids in the treatment of IgA nephropathy (Table 1).

There is limited experience using other immunosuppressive agents in patients with IgA nephropathy. Although a short course of oral cyclophosphamide followed by azathioprine has been effective in one small randomized trial, azathioprine use has not shown added benefit to corticosteroids in a larger study.[30,31] Mycophenolate mofetil (MMF) use in IgA nephropathy has been explored in 4 randomized controlled trials with mixed results.[32-36] Although favorable outcomes have been demonstrated in Chinese studies only, our clinical experience supports using MMF in selected patients in whom steroid therapy has failed or who are intolerant of steroid therapy (grade 2D evidence). Published data on newer therapies such as rituximab and corticotropin gel have been limited to case reports and case series.[37-39] However, a number of important trials will further define the role of immunosuppression for IgA nephropathy (Table 1).

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Idiopathic FSGS remains a challenging glomerular disease to understand and treat, and treatment-resistant FSGS often progresses to ESRD. The FSGS lesion itself is a common histologic end point for many underlying diseases, such as hypertension, low nephron mass, and reflux nephropathy. FSGS is characterized as idiopathic/primary and secondary to a genetic or otherwise identifiable cause such as those listed previously.[40]

Multiple different pathogenic mechanisms result in proteinuria and the FSGS lesion on kidney biopsy. One possible cause in a subset of patients is the presence of a circulating permeability factor that results in the FSGS lesion on light microscopy, podocyte foot-process effacement on electron microscopy, and nephrotic syndrome. Clinical evidence for the involvement of such a permeability factor includes the recurrence (sometimes immediate) of nephrotic syndrome after kidney transplantation in patients