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.

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

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.

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

GIAGA 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.2 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.3,4 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
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. While this abnormal protein makes up a small proportion of circulating IgA molecules, it preferentially deposits in the mesangium in IgA nephropathy. 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. 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.

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 and kidney donors 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 and the complexing of circulating IgG or other autoantibodies with (gal)-deficient IgA, which deposit in glomeruli and lead to clinical disease.

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.

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. 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). Other nonimmunosuppressive treatments for IgA nephropathy, such as fish oil and tonsillectomy, remain controversial. 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. A recent meta-analysis by Lv et al 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, 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 been shown added benefit to corticosteroids in a larger study. Mycophenolate mofetil (MMF) use in IgA nephropathy has been explored in 4 randomized controlled trials with mixed results. 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. 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.

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.
with FSGS and clinical improvement after plasma exchange therapy, which presumably removes the factor. Savin et al. described a 50-kDa permeability factor that was identified in patients with recurrent FSGS after kidney transplantation and that increased glomerular permeability to albumin in vitro. Moreover, the injection of plasma supernatant from such patients into rats results in proteinuria. Cardiotrophin-like cytokine 1, a 30- to 50-kDa molecule, has been identified in the sera of some patients with recurrent FSGS after transplantation, suPAR levels decreased in parallel with proteinuria when patients underwent plasma exchange therapy. In an analysis of 2 cohorts of patients with steroid-resistant FSGS, suPAR levels were found to be elevated in 84% of patients from the National Institutes of Health Clinical Trial (NIH CT) group and 55% of patients from the National Institutes of Health Clinical Trial (PodoNet, a European cohort). Moreover, in the NIH CT group, reduction in suPAR levels with treatment was associated with proteinuria reduction and odds of complete remission. This was the first study that associated immunosuppressive treatment with suPAR levels. However, elevated suPAR levels have also been found in patients with secondary FSGS, as well as with chronic kidney disease and in septic patients with kidney injury. Moreover, the true sensitivity and specificity of suPAR in FSGS may be influenced by the assay and the relative concentration of different suPAR isoforms. Although an exciting discovery, whether suPAR will be a reliable diagnostic or prognostic biomarker in idiopathic FSGS awaits further study.

Corticosteroid therapy is considered first-line treatment for idiopathic FSGS based on retrospective studies. However, because steroid-dependent, glomerular diseases, such as minimal change disease, membranous nephropathy, and pre-eclampsia. In recurrent FSGS after transplantation, suPAR levels decreased in parallel with proteinuria when patients underwent plasma exchange therapy. In an analysis of 2 cohorts of patients with steroid-resistant FSGS, suPAR levels were found to be elevated in 84% of patients from the National Institutes of Health Clinical Trial (NIH CT) group and 55% of patients from the National Institutes of Health Clinical Trial (NIH CT).

Table 1. Pending Randomized Trials for Immunosuppression in IgAN Nephropathy

<table>
<thead>
<tr>
<th>NCT Identifier (acronym)</th>
<th>Status</th>
<th>Country</th>
<th>Interventions</th>
<th>Primary Outcome(s)</th>
<th>Est Enrolment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00301600</td>
<td>Completed</td>
<td>China</td>
<td>MMF; IV cyclophosphamide</td>
<td>Efficacy and safety of treatments</td>
<td>40</td>
</tr>
<tr>
<td>NCT00318474</td>
<td>Completed</td>
<td>US</td>
<td>MMF; placebo</td>
<td>Decrease in proteinuria</td>
<td>184</td>
</tr>
<tr>
<td>NCT00863252</td>
<td>Completed</td>
<td>Germany</td>
<td>MMF; conservative management</td>
<td>24-h urinary protein excretion</td>
<td>40</td>
</tr>
<tr>
<td>NCT01224028</td>
<td>Completed</td>
<td>Korea</td>
<td>Tacrolimus; placebo</td>
<td>Percent change in albuminuria</td>
<td>40</td>
</tr>
<tr>
<td>NCT0004448</td>
<td>Completed</td>
<td>US</td>
<td>Prednisone; omega-3 fatty acids</td>
<td>Not listed</td>
<td>123</td>
</tr>
<tr>
<td>NCT00554502 (STOP-IgAN)</td>
<td>Ongoing</td>
<td>Germany</td>
<td>Corticosteroids (GFR &gt; 60); cyclophosphamide + prednisolone, then azathioprine + prednisolone (GFR &lt; 60); supportive care</td>
<td>Full clinical disease remission; GFR loss of 15 mL/min/1.73 m²</td>
<td>148</td>
</tr>
<tr>
<td>NCT01738035</td>
<td>Recruiting</td>
<td>Multicenter (Europe)</td>
<td>Nefecon (PL-56); placebo</td>
<td>Change from baseline in urine protein-creatinine ratio</td>
<td>90</td>
</tr>
<tr>
<td>NCT01758120 (TOPplus-IgAN)</td>
<td>Recruiting</td>
<td>China</td>
<td>Prednisone + IV cyclophosphamide; prednisolone</td>
<td>Change in kidney function; doubling of creatinine or ESRD</td>
<td>120</td>
</tr>
<tr>
<td>NCT01269021</td>
<td>Recruiting</td>
<td>China</td>
<td>MMF; prednisone</td>
<td>Safety and efficacy of treatments</td>
<td>50</td>
</tr>
<tr>
<td>NCT00657059</td>
<td>Recruiting</td>
<td>China</td>
<td>Prednisone; MMF; MMF + prednisone</td>
<td>Remission of proteinuria</td>
<td>150</td>
</tr>
<tr>
<td>NCT01560052 (TESTING)</td>
<td>Recruiting</td>
<td>China</td>
<td>Oral methylprednisolone; placebo</td>
<td>Composite: 50% decrease in eGFR, ESRD, or death due to kidney failure</td>
<td>1,300</td>
</tr>
<tr>
<td>NCT00498368</td>
<td>Recruiting</td>
<td>US</td>
<td>Rituximab; conservative management</td>
<td>Change in proteinuria and eGFR at 12 mo</td>
<td>54</td>
</tr>
</tbody>
</table>

Note: Information obtained from www.clinicaltrials.gov in May 2013.

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IgA, immunoglobulin A; IV, intravenous; MMF, mycophenolate mofetil; STOP-IgAN, Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy; TESTING, Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study; TOPplus-IgAN, Treatment of Prednisone Plus Cyclophosphamide in Patients With Advanced-Stage IgA Nephropathy; US, United States.
steroid-resistant, and relapsing diseases remain common, a demand exists for novel FSGS treatments. The currently recommended next-line therapy for FSGS is a calcineurin inhibitor. The efficacy of cyclosporine in reducing proteinuria in FSGS has been demonstrated in observational and randomized controlled trials. Tacrolimus use in FSGS has been reported in observational studies and is considered by many experts to be interchangeable with cyclosporine.

The efficacy of MMF compared to cyclosporine in steroid-resistant FSGS was evaluated in the NIH CT, in which 138 patients with steroid-resistant FSGS were treated with prednisone (up to 15 mg/d) plus cyclosporine or MMF/dexamethasone pulses for 12 months. Higher cumulative remission (46% vs 33%) and relapse rates (33% vs 18%) were observed in the cyclosporine group, but these results were not statistically significant. Despite low enrollment and low response rates in both arms, the NIH trial suggests that mycophenolate may be a viable therapeutic option for steroid-resistant FSGS.

The role for rituximab in FSGS is unclear because the published experience is composed of case reports and case series with significant heterogeneity of patient populations (adults and children), histology (minimal change disease and FSGS), steroid-response category (steroid-dependent, frequently relapsing, and steroid-resistant disease), and past and concurrent immunosuppression. A recent small controlled trial in children with steroid-resistant nephrotic syndrome could find no benefit of rituximab in proteinuria reduction at 3 months or reduction of the dose of prednisone or calcineurin inhibitor use. Clearly a larger trial will be needed to clarify the role of rituximab in FSGS.

Although corticotropin was used first for nephrotic syndrome in the 1950s, it was abandoned when prednisone appeared to be an easily administered oral alternative therapy. In the last decade, corticotropin has seen a resurgence in the treatment of nephrotic syndrome, mostly in patients with membranous nephropathy (discussed later). There are no controlled trials using corticotropin in FSGS. The largest experience in using natural corticotropin gel (median dose, 80 units injected subcutaneously twice weekly) for FSGS is a case series of 24 patients with mostly steroid-resistant or steroid-dependent disease (mean of 2.2 prior immunosuppressive medications used). The cumulative remission rate was 29% (partial remission, n = 5; complete remission, n = 2). Serious adverse events were rare, and no serious infections were reported. Although the mechanism of action of corticotropin in FSGS is unknown, because all patients with remissions had steroid-dependent or steroid-resistant disease, these results imply that corticotropin is acting beyond a steroid effect, possibly by direct interaction with podocytes by the melanocortin-1 receptor. The effect of corticotropin on permeability factor levels has not been reported. However, particularly given the high cost of treatment, controlled trials comparing corticotropin with other therapies for resistant FSGS are warranted.

In 2008, Savin et al demonstrated that adding galactose to sera of patients with FSGS attenuated the in vitro glomerular permeability to albumin. In the same report, the authors described the normalization of in vitro glomerular permeability of serum obtained from a patient with recurrent FSGS after transplantation who was treated with both intravenous and oral galactose. Subsequently, 3 case reports have been published that described patients with recurrent FSGS who achieved improvement in proteinuria with oral galactose therapy. Its effect on permeability factor levels has not been evaluated. Galactose, in addition to other therapies, is being evaluated as treatment for FSGS in randomized trials (Table 2).

Table 2. Pending Randomized Trials for Immunosuppression in FSGS

<table>
<thead>
<tr>
<th>NCT Identifier (acronym)</th>
<th>Status</th>
<th>Country</th>
<th>Interventions</th>
<th>Primary Outcome(s)</th>
<th>Target Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT0081463</td>
<td>Completed</td>
<td>China</td>
<td>Tripterygium wilfordii + low-dose prednisone; T wilfordii + high-dose prednisone</td>
<td>Efficacy and safety</td>
<td>67</td>
</tr>
<tr>
<td>NCT00814255 (FONT II)</td>
<td>Active, not recruiting</td>
<td>US</td>
<td>Adalimumab; galactose; conservative management</td>
<td>Protein reduction with stable GFR</td>
<td>179</td>
</tr>
<tr>
<td>NCT01665391</td>
<td>Recruiting</td>
<td>US</td>
<td>Fresolimumab (1 mg/kg); Fresolimumab (4 mg/kg); placebo</td>
<td>Percentage of patients achieving complete or partial remission; no. of patients experiencing adverse events</td>
<td>88</td>
</tr>
<tr>
<td>NCT01451489</td>
<td>Recruiting</td>
<td>China</td>
<td>IV cyclophosphamide; tacrolimus</td>
<td>Rate of complete remission</td>
<td>130</td>
</tr>
</tbody>
</table>

Note: Information obtained from www.clinicaltrials.gov in May 2013.

Abbreviations: FONT II, Novel Therapies in Resistant Focal Segmental Glomerulosclerosis; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; IV, intravenous.
**C3 GLomerulopathies**

Membranoproliferative GN (MPGN) historically has been classified according to glomerular morphology seen on light and electron microscopies, rather than according to disease pathogenesis. In the last decade, the discovery of the C3 glomerulopathies, diseases that result from dysregulation of the alternative complement pathway, has refocused the classification of MPGN to one based on immunofluorescence patterns and disease pathogenesis.\(^6\)\(^2\)\(^6\)\(^3\) This underlying pathophysiology has been established in dense deposit disease (DDD; formerly called MPGN type II), C3 GN, and a group of related glomerular disorders has resulted in the reclassification of many MPGN cases. These diseases are now grouped together as the C3 glomerulopathies.\(^6\)\(^4\)\(^6\)\(^6\)

The distinction between classic MPGN (associated with infections, autoimmune disease, and dysproteinemias and with glomerular staining for C3 and immunoglobulin) and C3 GN is important because patients with C3 GN should be evaluated for dysregulation in the alternative complement pathway. Some patients with these disorders have genetic mutations in alternative complement pathway regulatory proteins, including inhibitory factors such as factor H, factor I, and membrane cofactor protein. Others have autoantibodies that either target these inhibitory factors (as in autoantibodies to factor H and factor I) or stabilize the C3 convertase (as in C3 nephritic factor), leading to overactivation of the alternative complement pathway and glomerular complement deposition. This activation may be reflected by elevated serum levels of the soluble membrane attack complex, the terminal component of the complement cascade, and low serum total complement and C3 levels. Although some assays used in evaluating patients with C3 GN currently are available only in research laboratories, others, such as C3 levels, are commercially available, and still others should be available in the near future.

Treatment of C3 GN and DDD in the past has been attempted with blockers of the renin-angiotensin-aldosterone system; immunosuppression with corticosteroids, cyclosporine, and alkylating agents; and plasma exchange therapy.\(^5\)\(^7\)\(^8\) None has given satisfying long-term results. However, new insight into the C3 glomerulopathy pathogenesis has led to targeted treatments for these diseases. Eculizumab is a humanized monoclonal antibody directed against the fifth component of complement (C5). It already is approved by the US Food and Drug Administration for use in 2 rare disorders of the alternative complement pathway, atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria. Four recent case reports describe the successful use of eculizumab in patients with DDD, MPGN 1, and C3 GN.\(^6\)\(^9\)\(^7\)\(^1\) We recently described treatment of 6 patients with C3 glomerulopathy (3 with C3 GN and 3 with DDD) with intravenous eculizumab every 2 weeks for 1 year.\(^7\)\(^2\) Four patients showed signs of improvement: 2 patients had improved serum creatinine levels, one had improved proteinuria, and one had marked improved histology on repeat biopsy with stable kidney function at 1 year of follow-up. Repeat biopsies showed the persistence of C3 deposition (because eculizumab works downstream from this complement component), but improvement in glomerular inflammation and fading of dense deposits with continued use of eculizumab.\(^7\)\(^3\) However, careful consideration of eculizumab use is warranted due to the extremely high cost of treatment, as well as the potential necessity for lifelong therapy. Although a controlled trial clearly is needed studying eculizumab in the treatment of the C3 glomerulopathies, the hope is that targeting therapies for these disorders in the future will prove to be both safe and effective.

**MEMBRANOUS NEPHROPATHY**

Membranous nephropathy is the most common primary cause of nephrotic syndrome in Caucasians.\(^7\)\(^4\) The diagnosis of membranous nephropathy is made with a kidney biopsy showing capillary wall thickening and normal cellularity on light microscopy, granular capillary wall staining for immunoglobulins and complement on immunofluorescence, and subepithelial electron-dense deposits on electron microscopy. Clinical and histologic features may aid in distinguishing between primary (idiopathic) and secondary forms of the disease due to malignancy, autoimmune disease, and infections.\(^5\)\(^7\)\(^6\)\(^7\) This distinction is important in both guiding diagnosis and directing treatment. Until recently, when the pathogenesis in the majority of cases of idiopathic membranous nephropathy was elucidated, there was no highly predictive method to distinguish primary from secondary forms of membranous nephropathy.

In an important discovery, Beck et al demonstrated that the M-type phospholipase A2 receptor (PLA2R), a podocyte protein, is a major disease antigen in the immune subepithelial deposits of patients with idiopathic membranous nephropathy. IgG4 antibodies (anti-PLA2R) colocalize with PLA2R in membranous nephropathy immune deposits. Follow-up studies in multiple populations have confirmed that circulating anti-PLA2R antibody is present in 70%-80% of patients with idiopathic membranous nephropathy.\(^7\)\(^8\)\(^7\)\(^9\) Although the PLA2R antibody appears to be specific for idiopathic membranous nephropathy, some PLA2R antibody–positive patients with secondary causes have been identified. It is unclear whether
these cases are truly secondary membranous nephropathy or these patients have 2 distinct diseases (ie, malignancy and idiopathic membranous nephropathy).79 This will need to be evaluated in larger membranous nephropathy cohorts. Subsequent genetic studies have demonstrated PLA2R polymorphisms and risk alleles in idiopathic membranous nephropathy.80–82 Importantly, increased staining for the PLA2R antigen on kidney biopsy specimens correlates with increased serum PLA2R antibody levels and may be a useful clue for the diagnosis of PLA2R-related idiopathic membranous nephropathy.83–85

Increased serum PLA2R antibody levels have been associated with disease activity, disease severity, and renal outcomes in membranous nephropathy,84–88 as well as disease recurrence after transplantation.84,89 The hope is that serum PLA2R antibody levels will help guide decisions in treating membranous nephropathy and assessing clinical and immunologic response to therapy. Serum PLA2R antibody levels already have been shown to parallel disease activity after treatment with MMF and prednisone, cyclophosphamide and prednisone,85 and rituximab.87,90 Aldolase reductase, superoxide dismutase 2, and alpha-enolase may be additional podocyte antigens in patients with idiopathic membranous nephropathy who are PLA2R antibody negative or whose PLA2R IgG4 level and clinical disease do not respond to treatment.91 Commercial testing for circulating PLA2R IgG4 is not yet available for clinical use in the United States, but in the near future, circulating PLA2R IgG4 levels and kidney biopsy staining for the PLA2R antigen may help guide the diagnosis and treatment of idiopathic membranous nephropathy, as well as in making idiopathic membranous nephropathy a definitive diagnosis rather than one of exclusion.92

Given the slowly progressive course and substantial spontaneous remission rate of untreated membranous nephropathy, immunosuppressive therapy is recommended only for patients who are at high risk of disease progression or complications of nephrotic syndrome, such as infections and thromboembolic events.19 In patients with preserved kidney function and significant proteinuria despite 6 months of conservative therapy with renin-angiotensin-aldosterone system blockade with ACE inhibitors or ARBs, the KDIGO clinical practice guideline for GN recommends alternating months of glucocorticoids and a cytotoxic agent as first-line immunosuppressive therapy,19 which has achieved cumulative (partial + complete) remission in up to 70%-90% of patients.92,93 A calcineurin inhibitor may be used in patients who do not tolerate or elect not to take cytotoxic agents with similar remission rates, but they should be used with extreme caution in patients with decreased kidney function.94 MMF been used to treat idiopathic membranous nephropathy in a number of small uncontrolled trials since 1998.95–99 Similar efficacy of MMF with corticosteroids compared with alternating months of corticosteroids and a cytotoxic drug then was demonstrated in small randomized controlled,100 randomized open-label,101 and historically controlled experiences.102 However, the enthusiasm generated by these results was tempered by high relapse rates with MMF and one randomized controlled trial that showed no difference in remission rates with the use of MMF monotherapy versus conservative treatment.103 Most recently, a meta-analysis of studies conducted in Chinese adults with membranous nephropathy found a significant association of MMF treatment with cumulative remission.104 The mixed results have prevented the designation of MMF as first- or second-line therapy in membranous nephropathy,19 but in our experience, it is still a useful and well-tolerated therapy in patients with membranous nephropathy who want to avoid the side effects of cytotoxics and for whom there is concern about kidney toxicity with calcineurin inhibitors.

Although no randomized controlled trial has been conducted, extensive case series and observational data support the use of rituximab in the treatment of membranous nephropathy.105–108 Recently, Ruggenenti et al109 published the largest experience using rituximab in membranous nephropathy. One hundred patients received rituximab (either 375 mg/m² weekly for 4 doses or the minimal dose required to achieve B-cell depletion) as first- (n = 68) or second-line therapy (n = 32). At an average of 29 months of follow-up after rituximab administration, the cumulative remission rate was 65% (complete remission, 27%; partial remission, 38%), with a median time to remission of 7.1 months and relapse rate of 28% among responders. Similar remission rates were observed for those treated with rituximab as first- (69%) or second-line (56%) therapy. Twenty-eight percent of patients experienced nonserious treatment-related events, and 2 patients died during the follow-up period (n = 3 cardiovascular events and n = 1 lung cancer in a patient who had been treated previously with steroids and cyclophosphamide).

Rituximab also has been shown to be effective in treating patients with calcineurin inhibitor-dependent disease10 and recurrent disease after transplantation.111 Unfortunately, no consistent clinical, laboratory, or histologic predictor of response to rituximab has been identified. The optimal dosing of rituximab in membranous nephropathy is unknown, although prescribing the minimal dose needed to achieve B-cell depletion may be as clinically- and cost-effective as conventionally prescribed doses.112 Adverse events noted in other patient populations
treated with rituximab include infusion reactions, serious infections (observed in 7%-18% of patients treated for antineutrophil cytoplasmic antibody–associated vasculitis),113,114 and progressive multifocal leukoencephalopathy (low incidence in patients treated for rheumatoid arthritis). The drug also is expensive compared to the generic medications recommended by KDIGO as first- and second-line therapies for idiopathic membranous nephropathy.

Corticotropin is available as a synthetic form in Europe and as a natural gel preparation in the United States. The use of synthetic corticotropin in membranous nephropathy has been demonstrated in case series data57,115-117 and a small randomized controlled trial,118 which found no difference in cumulative remission rates in patients treated with corticotropin (94%) versus alternating months of steroids and cyclophosphamide (88%), and with similar long-term remission rates (75% vs 88%; median follow-up, 24 months). The long-term durability of the response of membranous nephropathy to synthetic corticotropin has been reported in abstract form, with 19 of 28 Swedish patients experiencing complete remission, 8 of 28 patients with partial remission, and 2 relapses occurring 36-58 months after stopping corticotropin therapy.119 The use of natural corticotropin gel for membranous nephropathy has been described in 2 case series.37,38 Because corticosteroid monotherapy is ineffective in membranous nephropathy, the effectiveness of corticotropin therapy implies additional mechanisms of actions, possibly by direct podocyte interaction with the melanocortin-1 receptor57 or induction of immunologic remission of the PLA2R antibody.37,120 Steroid-like side effects may occur with corticotropin therapy, but life-threatening infections have not been reported. Although the mechanism of action remains unclear, corticotropin clearly has some place in the treatment of patients with severe and resistant membranous nephropathy. However, given the high cost of treatment, randomized controlled trials to determine the role of corticotropin in the treatment of membranous nephropathy are warranted. Trials currently are recruiting to help define the utility of corticotropin and other immunosuppressives in membranous nephropathy (Table 3).

**CONCLUSION**

There has been great progress in our understanding of the pathogenesis of a number of glomerular diseases. In parallel, a number of promising diagnostic and prognostic tests are being developed at the same time that newer therapeutic agents are being evaluated. Excitement for this recent progress appears justified, with the hope and anticipation that these advances will translate into better outcomes for patients with glomerular diseases.

**ACKNOWLEDGEMENTS**

**Support:** None.

**Financial Disclosure:** Dr Appel has received research grants, consultancies, and/or speaker honoraria from the following companies: Ardea, Alexion, Pfizer, Merck, Genentech, Aspreva (Vifor), Bristol-Myers Squibb, Questcor, FibroGen, Up-to-Date.
Amgen, Centocor Ortho Biotech, Sanoft, Novartis, and Teva. Drs. Hogan and Mohan declare that they have no relevant financial interests.

REFERENCES


