IgA Nephropathy: Core Curriculum 2021

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Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide. The diagnostic histologic hallmark is dominant or codominant IgA staining on kidney biopsy; however, patients may present with various clinical syndromes ranging from asymptomatic abnormalities noted on urinalysis to rapidly progressive glomerulonephritis. Given substantial heterogeneity in the clinical course of disease, online risk calculators are available that may assist in prognostication and inform discussions with patients. Comprehensive supportive treatment is central in the initial therapy of IgAN; the additive benefit of currently available immunosuppressive agents remains an area of controversy. Although proteinuria is attenuated by the use of corticosteroids, the long-term benefits have been questioned, and the use of corticosteroids is associated with severe adverse effects, notably infection. Recent advances in our understanding of mucosal immunity and the role of the complement system in IgAN pathogenesis are leading to development of novel therapeutic options, which are being evaluated in ongoing clinical trials. In this installment of the *AJKD* Core Curriculum in Nephrology, IgAN pathogenesis, clinical manifestations, histology, prediction tools, and treatment are reviewed, and case examples are presented to illustrate the approach to the management of patients with IgAN.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Immunoglobulin A nephropathy (IgAN) is the most prevalent primary glomerulonephritis (GN) worldwide, with an overall incidence of at least 2.5 per 100,000. Estimation of the true incidence is challenging primarily due to variations in biopsy practice patterns, and it is likely that IgAN is more common than appreciated. Notwithstanding differences in screening and biopsy practice, the geographic variation in prevalence highlights the likely contributions of both genetics and environment to IgAN susceptibility and risk of disease progression. The incidence of IgAN is reported to vary from 0.2 to 5 per 100,000 individuals per year, with a lower prevalence in North America and Europe and highest prevalence in East Asian countries. This closely mirrors geographic patterns in asymptomatic IgA deposition rates. Latent mesangial immunoglobulin A (IgA) deposition is detected in 6.8% of forensic necropsies in Finland compared with 16.1% of kidney allograft donors in Japan. Although IgAN is a dominant cause of kidney failure in East Asian countries, representing up to half of cases of primary GN in China, a lower frequency is observed in European and North American centers where diabetes dominates as a cause of kidney failure. Up to 20% to 40% of patients with IgAN develop kidney failure within 10 to 20 years after diagnosis.

Additional Readings

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Pathogenesis

The widely accepted framework for understanding of the steps involved in the pathogenesis of IgAN is known as the "multi-hit hypothesis" (Fig 1). Genome-wide association studies and experimental models have provided insights that expand upon this framework, highlighting a confluence of genetic and environmental influences that modulate mucosal immune function and lead to IgAN. The seminal observations supporting the multi-hit hypothesis include the following:

1. **Patients with IgAN have increased circulating levels of galactose-deficient IgA1.** Patients with IgAN have elevated levels of circulating IgA1 characterized by

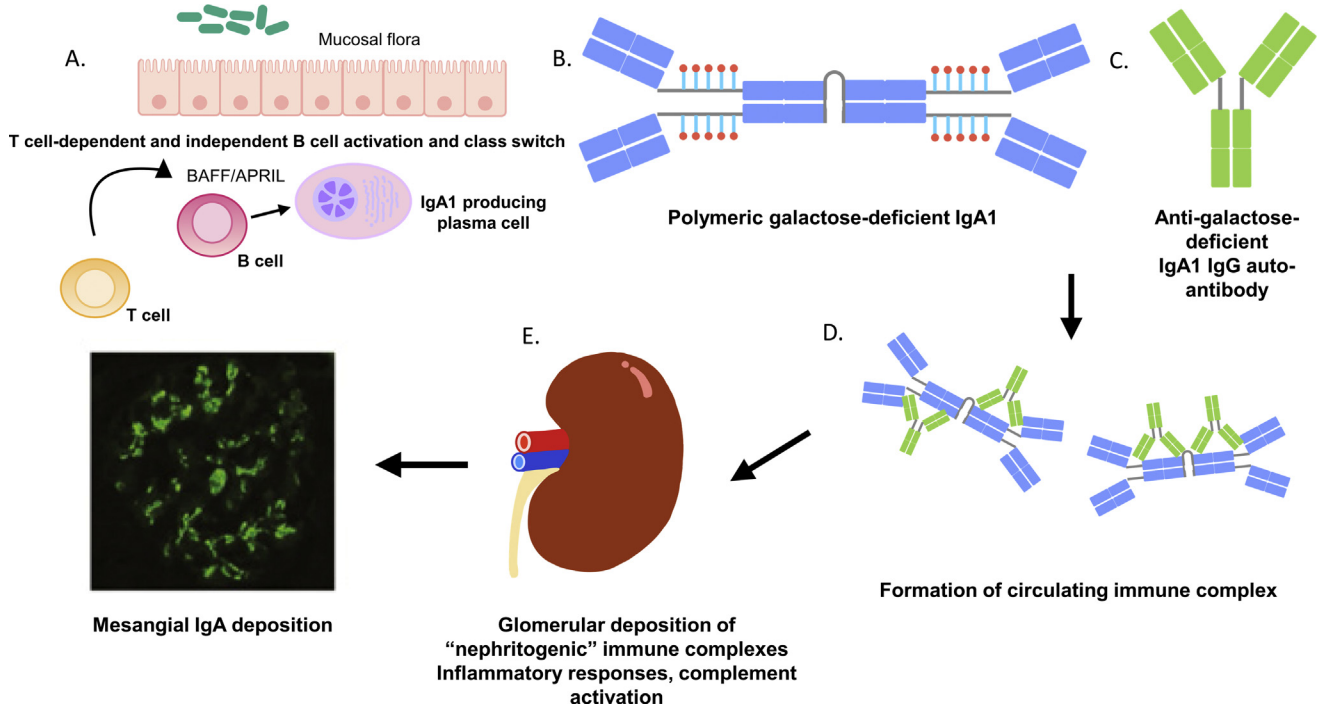

Figure 1. The multi-hit model of immunoglobulin A nephropathy (IgAN). (A) The source of pathogenic IgA is unknown but is hypothesized to originate from IgA1-producing plasma cells located in the mucosal associated lymphoid tissue. B cells are activated and undergo class switch via T-cell dependent mechanisms as well as T-cell independent pathways. The tumor necrosis factor–related cytokines BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand) are central to T-cell-independent induction of B cells and class switch to IgA-producing plasma cells. (B) Patients with IgAN have increased levels of galactose-deficient IgA1 antibodies; these are detected in circulated polymeric form. (C) Antiglycan IgG autoantibodies form immune complexes detected in the circulation and kidneys. These "nephritogenic" immune complexes may activate complement and trigger glomerular inflammatory responses. Based on information in Suzuki et al, 2011 (*J Am Soc Nephrol.* https://doi.org/10.1681/asn.2011050464).

the presence of galactose-deficient O-glycans in the hinge region of IgA1 (Gd-IgA1). Aberrant IgA glycosylation is a heritable trait but is not sufficient to cause disease; similar defects are observed in unaffected relatives of patients with familial and sporadic disease. The trigger, site, and source of pathogenic IgA production remain an active area of investigation. The level of Gd-IgA1 in circulation correlates with disease severity and outcome.

2. **Antiglycan autoantibodies target Gd-IgA1.** The abnormalities in O-glycan biosynthesis result in exposure of terminal N-acetylgalactosamine (GalNAc) residues. The galactose-deficient hinge region with terminally exposed GalNAc residues acts as a neoepitope, promoting the formation of antiglycan immunoglobulin G (IgG) autoantibodies.
3. **Circulating immune complexes contain Gd-IgA1.** Circulating immune complexes can be detected in patients with IgAN. Although IgA does not commonly activate complement, these immune complexes are composed of Gd-IgA1 (often polymeric), antiglycan IgG autoantibodies, and complement C3.
4. **The Gd-IgA1-antiglycan IgG immune complexes deposit in the mesangium.** A recent study has confirmed the presence of Gd-IgA1 and IgG autoantibodies targeted against Gd-IgA1 in the mesangium of kidney biopsies from patients with IgAN. These "nephritogenic" complexes activate inflammatory and cellular proliferative signaling cascades, contributing to local inflammation, mesangial matrix production, and mesangial cell proliferation. The end product of unchecked inflammation (facilitated by mediators such as interleukin 6 [IL-6] and transforming growth factor β [TGF-β]) is glomerular and interstitial fibrosis.

Recent experimental and genetic studies have elucidated some of the pathogenic processes that initiate disease activity and underlie disease susceptibility. These include insights into the role of the mucosal immune system and complement activation in disease pathogenesis.

The classic manifestation of gross hematuria, which occurs concurrently with mucosal infection, has long suggested a role for aberrant mucosal immune responses to perturbations in microbiota in IgAN. This has been affirmed by observations in an experimental IgAN model.

Mice overexpressing the cytokine BAFF (B-cell activating factor), a member of the tumor necrosis factor family, develop IgAN exclusively in the presence of commensal microbial colonization; this phenotype does not develop in mice reared in germ-free conditions. Subsequent to this observation, the APRIL (a proliferation-inducing ligand) locus was linked to IgAN susceptibility in genome-wide association studies. Because APRIL and BAFF share common receptors, the BAFF/APRIL axis has been implicated in IgAN pathogenesis. These cytokines play a key role in promoting class switch of mucosal B cells into IgA-producing plasmablasts and plasma cells, after priming by exposure to mucosal bacteria. Several susceptibility loci identified in IgAN are also known to confer risk for development of inflammatory bowel disease as well as maintenance of the intestinal epithelial barrier and response to mucosal pathogens.

A role for complement activation in the pathogenesis of IgAN was suggested by the finding of products of the complement cascade in IgAN immune complexes. Components of the alternative pathway such as C3 and complement factor H (CFH) are found in glomerular immune deposits. In a subset of individuals, products of the mannose-binding-lectin (MBL) pathway are also detected, including MBL-associated serine proteases and C4d (without C1q). Perhaps the most compelling evidence for a contribution of the alternative pathway (AP) of complement activation in IgAN is the association of a variant in the genes encoding the CFH-related proteins (CFHRPs); deletions of these genes confer "protection" against IgAN. One of the key negative regulators of the alternative pathway is CFH; the CFHRPs are competitors of CFH function, and titrate CFH activity. It is hypothesized that the protective association of *CFHR1,3* deletion reflects competing roles of CFH and CFHR proteins, such that loss of CFHR1 enhances CFH effects, and protects against AP-mediated injury.

Several systemic conditions are associated with development of histologic and clinical manifestations of IgAN, and these conditions are listed in Table 1. Kidney disease in this context is often referred to as "secondary IgAN," and it is postulated that shared pathophysiologic processes underlie this association. In cirrhosis, patients with and without clinically evident IgAN have IgA1 glycosylation patterns that are distinct from healthy individuals, which has been attributed to impaired hepatic clearance of abnormally glycosylated IgA. Unlike primary IgAN, both O-linked and N-linked glycans are affected, creating distinct effects on mesangial cell proliferation. In inflammatory bowel disease, the increased incidence of IgAN could be explained by mucosal inflammation and increased numbers or activity of IgA1-secreting cells. Gastrointestinal disease activity has been reported to correlate with progression or regression of IgAN, and tumor necrosis factor α (TNF-α) inhibitors have been documented to be able to successfully treat inflammatory bowel disease and induce remission of IgAN. Recent studies have confirmed the presence of Gd-IgA1 in plasma and kidney biopsy tissues from a spectrum of patients with secondary IgAN that are indistinguishable from patients with primary IgAN. It is important to note that a number of patients with these conditions have only "lanthanic" mesangial IgA deposition with little or no clinical evidence of glomerular injury.

Table 1. Causes of Secondary IgAN

Group	Disease
Gastrointestinal and liver diseases	Inflammatory bowel disease[a] (Crohn disease, ulcerative colitis), celiac disease,[a] cirrhosis[a]
Infection	HBV,[a] HCV,[a] HIV,[a] tuberculosis, leprosy
Autoimmune diseases	Ankylosing spondylitis, rheumatoid arthritis, Sjögren syndrome
Malignancy	Lung cancer, renal cell carcinoma, non-Hodgkin and Hodgkin lymphoma, IgA myeloma
Respiratory tract	Sarcoidosis, bronchiolitis obliterans, pulmonary hemosiderosis, cystic fibrosis, pulmonary fibrosis
Skin	Dermatitis herpetiformis, psoriasis

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus, HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy.
[a]Diseases with relatively more frequent association.

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Clinical Manifestations

In its primary or secondary form, IgAN can present with a spectrum of clinical syndromes, as detailed in the following sections.

Asymptomatic Hematuria, Varying Degree of Proteinuria, With or Without Progressive Kidney Disease

The most common presentation of IgAN in adults is asymptomatic hematuria with varying degrees of proteinuria, with or without progressive kidney disease. Routine screening urinalysis in healthy individuals is not part of most health check guidelines, so IgAN may be more frequently detected early in the countries that have national screening programs such as the urinary screening programs for school-age children in Japan, South Korea, and Taiwan. Follow-up evaluation of individuals with abnormal urinalysis is essential because decreases in kidney function can be progressive over the course of disease.

Synpharyngitic Macroscopic Hematuria

In synpharyngitic macroscopic hematuria, patients develop gross hematuria with concurrent upper respiratory tract infection or less commonly gastrointestinal tract infections. Hematuria is typically visible at the same time as symptoms of infection (synpharyngitic), compared with the 2- to 3-week gap between the onset of infection and gross hematuria seen in postinfectious glomerulonephritis (postpharyngitic). Although this is a classic clinical syndrome prompting patients to seek medical attention, it occurs in only 10% to 15% of adult patients with IgAN, most commonly in patients under 40 years old. This phenotype is associated with a favorable prognosis, in part due to early detection of gross hematuria. However, a subset of patients with isolated hematuria will develop persistent proteinuria and hypertension, placing them at risk of progressive kidney disease. Thus, long-term follow-up observation is required.

Rapidly Progressive Glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome characterized by a ≥50% decline in estimated glomerular filtration rate (eGFR) over 3 months or less, where reversible causes have been excluded. This syndrome can occur at presentation or during the course of IgAN and may occur in the absence of any clinical features of IgA vasculitis. It is frequently associated with the histologic finding of crescents in ≥50% of glomeruli. The term RPGN describes a clinical syndrome, and crescentic GN describes a histologic finding. Crescents are commonly observed in patients with IgAN and are not necessarily accompanied by RPGN. As such, the presence of rare crescents does not itself mandate use of immunotherapy in the absence of other high-risk clinical features. RPGN portends a poor kidney prognosis. In one study 42.5% of patients developed kidney failure within 1 year of diagnosis despite immunosuppression.

Nephrotic Syndrome

Nephrotic syndrome is a rare presentation of IgAN. Patients exhibiting the clinical features of nephrotic syndrome (including hypoalbuminemia) are indistinguishable from those who present with minimal change disease. Kidney biopsy demonstrates mesangial deposition of IgA and extensive foot process effacement. Other histologic features of IgAN (ie, mesangial cell proliferation) may or may not be present. In the presence of histologic features of IgAN, one can postulate the coexistence of 2 glomerular disorders: IgAN and a "podocytopathy." The treatment approach for this condition is typically akin to other forms of nephrotic syndrome. Given its distinct presentation and treatment approach, this rare clinical entity should be distinguished from the more common presence of "nephrotic-range" proteinuria observed in some patients with IgAN who typically do not exhibit hypoalbuminemia.

Acute Kidney Injury in IgA Nephropathy

Decreases in kidney function in IgAN are usually chronically progressive. If IgAN patients develop acute kidney injury (AKI), there are 2 specific causes related to IgAN that should be taken into consideration: RPGN and acute tubular injury from red blood cell cast obstruction and/or heme toxicity. In patients with AKI after gross hematuria, improvement of kidney function usually occurs within 1 to 2 weeks after the disappearance of gross hematuria. However, if there is no improvement in this time frame, a repeat kidney biopsy should be considered to rule out alternative diagnoses, including acute tubular necrosis or evolution of IgAN to RPGN with new crescent formation.

AKI and hematuria from concurrent anticoagulant-related nephropathy can be the initial presentation of IgAN if patients are taking anticoagulants. In contrast to vitamin K antagonists, many cases of dabigatran-induced anticoagulant-related nephropathy have been found in patients with underlying IgAN, suggesting a predisposition to this type of injury.

Patients with underlying comorbid conditions such as diabetes may present with AKI due to a postinfectious proliferative GN dominated by IgA deposits (rather than the typical IgG). Although beyond the scope of this review, it should be noted that these patients typically have a poor kidney prognosis.

IgAN may occur in the context of systemic IgA vasculitis (Henoch-Schönlein purpura). This is often considered to be a secondary form of IgAN. The extrarenal manifestations include palpable purpura, arthralgia/arthritis, and gastrointestinal vasculitis. Although this condition is more

commonly found in children, adults are more likely to have more severe kidney disease with lower eGFR at the time of kidney biopsy. Further details regarding IgA vasculitis are beyond the scope of this review.

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Pathology

Kidney biopsy demonstrating dominant or codominant mesangial IgA staining is required for definitive diagnosis of IgAN. Light microscopy may reveal a variety of morphological changes, including mesangial matrix expansion, mesangial or endocapillary hypercellularity, and fibrous or fibrocellular crescents. Segmental or global glomerulosclerosis, tubular atrophy, and interstitial fibrosis are often seen, representing the chronicity of the disease. Examples of these lesions are illustrated in Figure 2. In the presence of predominant crescents without mesangial cell proliferation, antineutrophil cytoplasmic antibody (ANCA) serology to rule out the coexistence of ANCA vasculitis should be considered. Microangiopathic changes are reported in 2% to 53% of IgAN patients, a range reflecting patient selection and histologic definition. Although a large proportion of patients with this finding have severe hypertension, the presence of

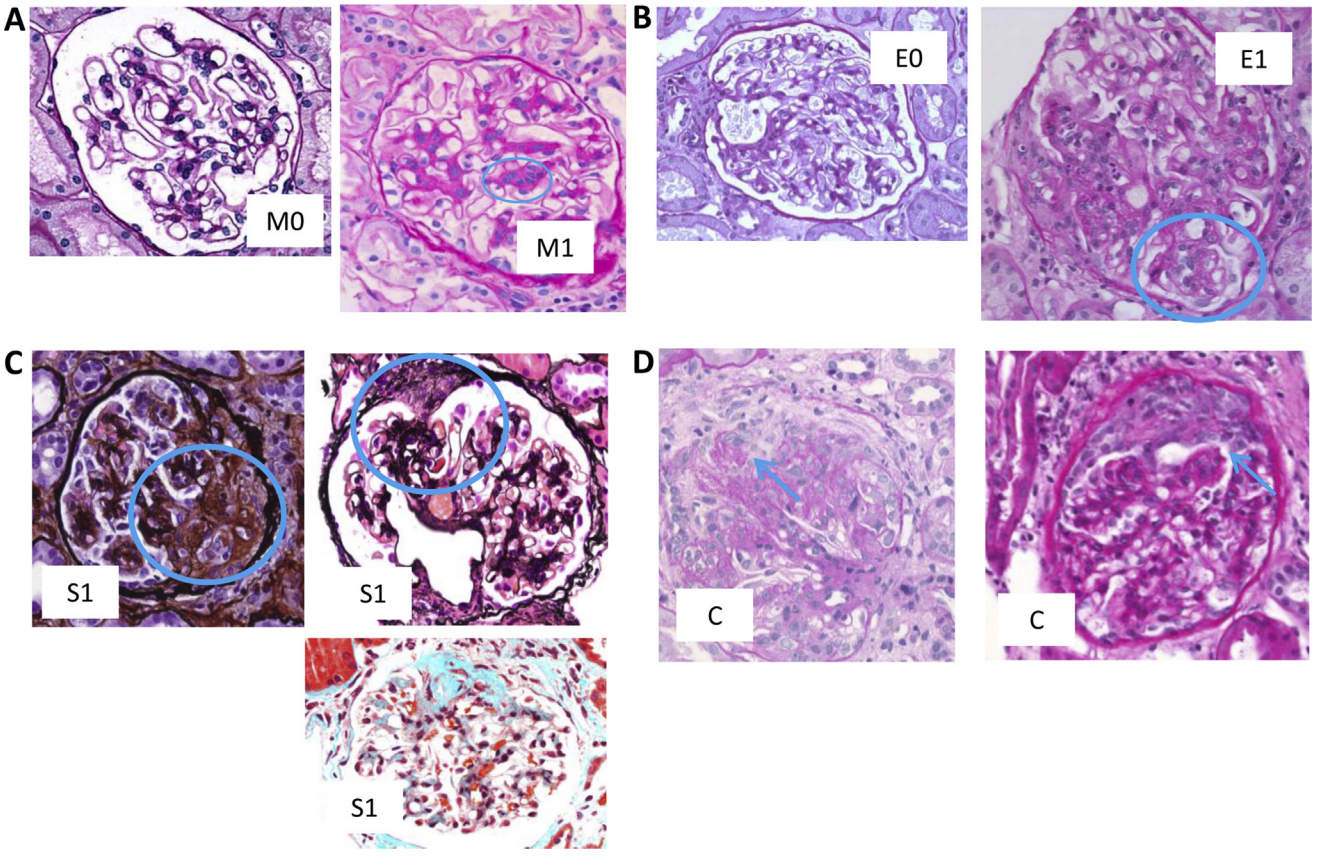

Figure 2. Histologic lesions observed in immunoglobulin A nephropathy (IgAN). Light microscopy illustrating key histologic findings observed in IgAN. For all images, original magnification is ×40. (A) Mesangial changes (M), periodic acid–Schiff stain (PAS). (B) Endocapillary proliferation (E), PAS stain. (C) Segmental sclerosis (S), silver and trichrome stains. (D) Crescents (C), PAS stain.

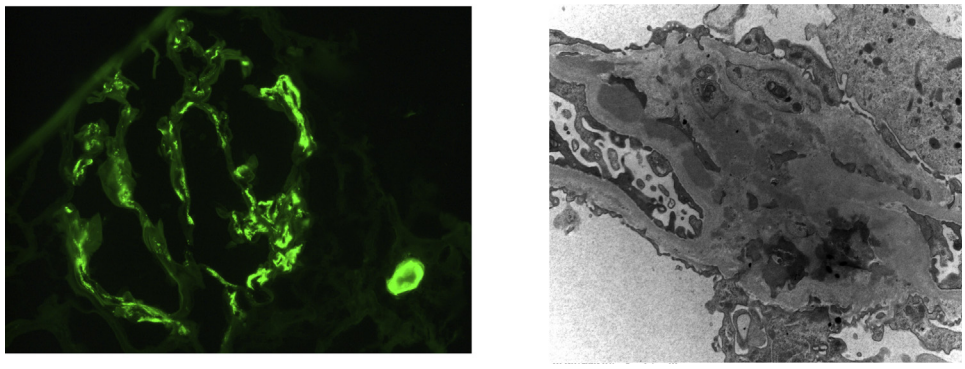

Figure 3. Pathology: immunofluorescence and electron microscopy. Left panel shows mesangial immunoglobulin A staining by immunofluorescence. Right panel shows characteristic mesangial electron-dense immune deposits.

microangiopathic changes in the absence of hypertension highlights a gap in our understanding of the pathogenesis of this finding in IgAN.

Immunofluorescence must reveal dominant or codominant mesangial IgA deposits with or without capillary loop staining. This is accompanied by a variable degree of IgG and IgM staining by immunofluorescence, often more prominent in sclerotic areas. Complement C3 is present in up to 90% of cases. Hump-shaped subepithelial immune complexes characterize IgA-dominant postinfectious GN, usually accompanied with more prominent C3 staining and occasional neutrophil infiltration. Electron microscopy should confirm the immunofluorescence findings with immune-type electron-dense deposits in the mesangium with or without subendothelial deposits (Fig 3).

The original Oxford histologic classification (known as the MEST score) proposed in 2009 is composed of 4 histologic features: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T). This scoring system is highly reproducible among pathologists. The details of the Oxford classification are illustrated in Table 2, and examples are provided in Figure 2. Each element independently shows a correlation with kidney failure, 50% decrease in eGFR, and rate of deterioration of kidney function. This score has been extensively validated with largely consistent demonstration of the correlation between the M, S, and T scores and prognosis. It should be noted that patients with rapid loss of kidney function were not included in the original study, a very small number of patients had crescents, and a large proportion of the patients who had evidence of crescents or endocapillary proliferation received corticosteroid therapy.

In 2017, a study from an IgAN classification working group sought to clarify the independent relationship between crescents and outcome. Indeed, the proportion of glomeruli with crescents in biopsied tissue correlated with prognosis, and this was incorporated into the MEST score. The presence of cellular/fibrocellular crescents in ≥25% of glomeruli (C2) was associated with poor kidney outcome even with use of immunosuppression. The independent association between C1 (crescents in less than 25% of glomeruli) and poor outcome was confounded, and potentially attenuated by the use of immunotherapy. However, the utility of corticosteroids therapy, simply based on the presence of crescents (independent of clinical features), cannot be determined from this retrospective observational study.

Table 2. MEST-C Score

Pathologic Feature	Definition	Scoring System
Mesangial hypercellularity (M)	≥4 mesangial cells in any mesangial area of a glomerulus	M0: mesangial hypercellularity in ≤50% of glomeruli M1: mesangial hypercellularity in >50% of glomeruli
Endocapillary hypercellularity (E)	An increased number of cells in glomerular capillary lumen	E0: absence E1: presence of any glomeruli showing endocapillary hypercellularity
Segmental glomerulosclerosis (S)	Adhesion or sclerosis that not involving the entire glomerulus	S0: absence S1: presence of any segmental glomerulosclerosis (podocyte hypertrophy/tip lesions should be noted if present)
Tubular atrophy/interstitial fibrosis (T)	The percentage of tubular atrophy/interstitial fibrosis of cortical area	T0: 0-25% T1: 26%-50% T2: >50%
Cellular/fibrocellular crescents (C)	Extracapillary cell proliferation > 2 cell layers thick and < 50% matrix	C0: absence C1: presence of cellular/fibrocellular crescents in <25% of glomeruli C2: presence of cellular/fibrocellular crescents in ≥25% of glomeruli

At least 8 viable glomeruli are required for MEST-C score.
Based on information from Markowitz G, 2017 (*Nat Rev Nephrol.* https://doi.org/10.1038/nrneph.2017.67).

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Prognosis

Case 1: *A 36-year-old man of Chinese ethnicity is found to have hypertension (160/90 mm Hg) and microscopic hematuria during an evaluation for life insurance. Further investigation reveals serum creatinine of 1.4 mg/dL and 0.6 g/d of proteinuria. Kidney biopsy shows IgA nephropathy with MEST-C score M1, E1, S1, T1, C1.*

Question 1: What is your next step in clinical management?

a) Start prednisone because there are crescents (C1), which is considered a high-risk feature on kidney biopsy.
b) Start prednisone because there is endocapillary hypercellularity (E1), which indicates the high likelihood of response to immunotherapy.
c) Recommend no additional therapy because there is irreversible scarring on kidney biopsy with segmental glomerulosclerosis (S1) and tubular atrophy/interstitial fibrosis (T1).
d) Start conservative treatment with renin angiotensin system (RAS) blockade as a first step because he has low-grade proteinuria.

For the answer to the question, see the following text.

There is substantial variability in the clinical course of IgAN. Before deciding on a therapeutic approach, an individualized estimate of a patient's risk of disease progression is essential. Risk assessment helps inform the discussions with patients for collaborative decision making about treatment strategies.

Proteinuria is consistently demonstrated to be a dominant risk factor for disease progression in IgAN. Incremental levels of sustained proteinuria above 1 g/d are associated with marked changes in the risk of loss of kidney function; reduction of proteinuria, ideally to under 1 g/d, is associated with favorable outcomes. Given the close association between incremental proteinuria changes and disease risk, we recommend using 24-hour urine collections to discern smaller gradations of proteinuria. In patients with biopsy-proven GN, urinary protein-creatinine ratio (UPCR) has relatively poor correlation with 24-hour urine protein excretion, particularly when proteinuria is over 1 g/d. This makes distinguishing smaller changes in proteinuria (eg, 1.5 vs 2 g/d) challenging. As a result, most current clinical trials rely on ratios obtained from 24-hour collections. Additional clinical risk factors include decreased kidney function at presentation and hypertension. Obesity and smoking also likely contribute directly and indirectly to kidney risk.

Recently, the International IgAN Prediction Tool was developed to predict the risk of a 50% decline in eGFR or kidney failure, incorporating both clinical and histologic parameters at the time of kidney biopsy. The clinical variables include age, blood pressure, eGFR, proteinuria, and use of immunosuppression, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) before or at the time of biopsy. MEST score is also included in the calculation, but crescents did not meet the threshold for inclusion in the final model (likely because this variable was highly correlated with ethnicity and confounded by the use of immunosuppression). There are 2 models of the International IgAN Prediction Tool, which include or do not include patient's race. Given that this tool was developed and validated in a multi-ethnic international cohort of patients from China, Japan, Europe, and North America, if a patient is not White or of Chinese or Japanese origin, it is suggested to use the model that does not include race.

This prediction tool, which is available online (https://qxmd.com/calculate/), is not validated for use with clinical variables taken after the time of biopsy. However, it is a valuable starting point for discussions with patients, helping to balance the risks and benefits of various treatment options. It is also extremely informative for design of future clinical trials.

Although several putative serum and urine biomarkers have been tested for prognostication, including serum level of Gd-IgA1 and its autoantibodies, these tests are not clinically available. Proteinuria and eGFR remain the only clinically useful markers at this time.

For the answer to question 1, using the International IgAN Prediction Tool, the risk of a 50% decline in eGFR or progression to kidney failure 5 years after kidney biopsy is 36% for this patient. These are important data to inform shared decision making. The risk of progression is high, but there are insufficient data to support the use of any individual histologic lesion from the Oxford classification to guide decisions on immunosuppression without considering other clinical features. The clinical data (proteinuria, eGFR) remain the primary guide. Until there are more data clarifying the relationship between the histologic finding and likelihood of treatment response, the best answer to this question is (d). Although a crescent is present, this patient has proteinuria ranging between 0.5 and 1.0 g/d and does not have RPGN so RAS blockade is the first appropriate treatment. The additional benefit of immunosuppression after optimization of conservative therapy is discussed in subsequent sections. Close follow-up observation is indicated to ensure that the patient's kidney function remains stable and does not decline rapidly.

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Treatment

Case 2: *A 42-year-old White woman presents with a history of microscopic hematuria and low-grade proteinuria for almost 20 years. For the past 10 years, her blood pressure has become elevated and serum creatinine level has gradually worsened from 0.6 to 1.5 mg/dL (eGFR 43 mL/min/1.73 m^2). Her body mass index (BMI) is 29 kg/m^2, but she does not have other chronic health conditions. The kidney biopsy reveals IgAN with MEST-C score M0, E0, S1, T1, C0. Her proteinuria has recently increased from 0.44 to 1.9 g/d.*

Question 2: What is an appropriate management?

a) Enroll her in a clinical trial or start prednisone because she has proteinuria > 1 g/d.
b) Start a combination of cyclophosphamide and prednisone because her kidney function has deteriorated.
c) Recommend no additional therapy because her eGFR is < 50 mL/min/1.73 m^2.
d) Start RAS blockade and comprehensive supportive treatment.

Case 2 (continued): *After treatment with 16 mg of perindopril for 9 months with adequate blood pressure control, her proteinuria falls to 1.5 g/d and her serum creatinine level is stable at 1.5 mg/dL (eGFR 43 mL/min/1.73 m^2).*

Question 3: What is the next step in her management?

a) Start prednisone.
b) Start a combination of cyclophosphamide and prednisone because her kidney function has deteriorated over the past 10 years.
c) Recommend no additional therapy because her eGFR is already < 50 mL/min/1.73 m^2.
d) Enroll her in a clinical trial.

For the answers to the questions, see the following text.

Conservative Treatment

Supportive care is particularly important in the management of IgAN. The importance of comprehensive supportive care in IgAN is emphasized by the results from the STOP-IgAN study. Approximately one-third of participants completing the run-in phase responded to intensive supportive care and were no longer eligible for randomization. Furthermore, the rate of annual eGFR decline in the supportive arm was only 1.6 mL/min/1.73 m^2, much lower than in other studies. As a consequence, comprehensive supportive care is considered the first-line treatment in the absence of rapidly progressive decline of kidney function. As shown in Box 1, comprehensive supportive care in IgAN includes blood pressure control, use of RAS blockade, treatment of dyslipidemia, low-salt diet, weight reduction, smoking cessation, and avoidance of nephrotoxic drugs.

Meta-analysis of individual data from randomized controlled trials confirms that reduction in proteinuria is associated with reduction in the risk of kidney failure. These studies demonstrate this association independent of the presence of hypertension. The level of proteinuria to target with treatment may be gleaned from large observational studies. For example, patients in a large cohort from China with time-averaged proteinuria of <0.5 g/d were found to have a more favorable prognosis compared with those who had proteinuria of 0.5-1.0 g/d and >1.0 g/d, with a 10-year survival free of kidney failure or 50% decline in eGFR of 100%, 89%, and 42%, respectively. The use of RAS blockade has been demonstrated to effectively decrease the risk of kidney failure in proteinuric kidney disease, including IgAN. While small studies suggest potential for greater proteinuria reduction with combination of ACEI and ARB, a meta-analysis of over 68,000 patients emphasizes the potentially serious risks of AKI and hyperkalemia, particularly in those with decreased eGFR. In the absence of any evidence supporting improved outcome, we do not recommend the use of combination ACEI and ARB in IgAN.

Several clinical trials have focused on the role of novel agents to expand the armamentarium of non-immunosuppressive agents for kidney and cardiovascular protection in proteinuric chronic kidney disease (CKD). For example, the phase 3 PROTECT study (ClinicalTrials.gov identifier NCT03762850) will determine the antiproteinuric and renoprotective effects of sparsentan, a novel dual-acting angiotensin II and endothelin type A receptor antagonist, in IgAN patients with eGFR ≥ 30 mL/min/1.73 m^2 and proteinuria ≥ 1 g/d. The impact of sodium/glucose cotransporter 2 (SGLT2) inhibition on kidney and survival outcomes in nondiabetic proteinuric CKD is also an area of intense study. The DIAMOND study of dapagliflozin included 53 patients with an average GFR of 58 mL/min/1.73 m^2 and proteinuria of 1.1 g/d; nearly half had an underlying diagnosis of IgAN. Six weeks of

Box 1. Comprehensive Supportive Care in IgAN

- ACEI or ARB irrespective of whether patients have high blood pressure
  - ◇ Target: blood pressure 120/75 mm Hg and proteinuria <0.5 g/d
- Statin therapy if persistent hyperlipidemia
- Low-sodium diet (<2 g/d)
  - ◇ 24-hour urinary sodium excretion can be used to verify dietary consumption
- Advice on smoking cessation
- Avoidance of NSAIDs and other nephrotoxic drugs
- Target of healthy weight

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IgAN, immunoglobulin A nephropathy; NSAIDs, nonsteroidal anti-inflammatory drugs.

treatment with dapagliflozin did not result in a reduction of proteinuria. However, a reversible reduction in measured GFR was observed, consistent with favorable hemodynamic effects seen with the treatment of patients with CKD due to diabetes. In the larger DAPA-CKD study, 4,304 patients with and without diabetes were randomized to receive dapagliflozin or placebo, with a mean follow-up period of 2.4 years; 270 participants had IgAN. Patients were eligible for the study if their eGFR was 25-75 mL/min/1.73 m^2 and urinary albumin-creatinine ratio (UACR) was 200-5,000 mg/g. Treatment with dapagliflozin was associated with a significant reduction in the primary composite end point of 50% reduction in eGFR, kidney failure, or death, independent of the presence of diabetes (hazard ratio, 0.61 [95% CI, 0.51-0.72]; $P < 0.001$). Subgroup analysis of patients with IgAN is planned. The safety of concomitant use of SGLT2 inhibition with corticosteroids or other forms of immunotherapy is of concern, given the potential for genitourinary infection complications. In the absence of safety data, institution of this medication may be best reserved for instances where immunotherapy may not be appropriate or has been completed.

There are conflicting data regarding the effectiveness of fish oil on slowing kidney disease progression. The total doses reported in trials ranged from 3 to 12 g/d with varying contents and ratios of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). While not likely harmful, fish oil can be costly at the doses used in IgAN, and the cardiovascular benefits remain unclear. Therefore, to minimize medication burden we suggest prioritization of blood pressure control and institution of RAS blockade. A low-salt diet is recommended for those patients who have not achieved blood pressure goals.

The best answer to the question 2 is (d) because RAS blockade and comprehensive supportive treatment are the first-line therapy for IgAN in the absence of RPGN. Patient weight and hypertension are also important contributors to proteinuria and should be addressed.

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Immunosuppressive Treatment: Corticosteroids

The decision to use immunosuppression should be guided by evidence-based data, but recommendations should be individualized according to each patient's risk of disease progression and susceptibility to treatment-related toxicity. The variables to be considered when making recommendations on immunosuppression are summarized in Box 2. A general approach to IgAN treatment is reviewed in Figure 4. Because the available immunosuppressive therapies are incompletely effective and associated with significant toxicity, shared decision making with the patient that focuses on the risks and benefits of immunosuppression is essential.

Patients with persistent proteinuria of >1 g/d despite at least 3 months of optimized supportive therapy including RAS blockade are considered to be at higher risk of progression. Corticosteroid is the only currently available immunosuppressive agent with evidence supporting its efficacy. The 2012 KDIGO clinical practice guideline on GN suggests a 6-month course of steroids therapy in patients who have over 1 g/d of proteinuria and eGFR > 50 mL/min/1.73 m^2. However, important clinical trials published since the release of these guidelines emphasize the significant toxicity risk associated with this treatment.

The STOP-IgAN and TESTING trials evolved following the suggestion of efficacy of corticosteroids to reduce proteinuria observed in smaller randomized studies. The

Box 2. The Consideration of "Individualized Treatment" in Patients With IgAN

1. *Clinical practice guidelines, evidence-based data, reviews of literature*
   - Ensure vintage is current
   - Consider quality of studies, level of recommendation
   - Consider generalizability, including countries and ethnicity
2. *Disease phenotype*
   - Progressive versus atypical variants such as RPGN, full nephrotic syndrome
   - Risks of progression: International IgAN Prediction Tool, Oxford histologic classification
3. *Patient phenotype*
   - Susceptibility to toxicity of immunosuppression, such as eGFR < 30 mL/min/1.73 m^2, diabetes, advanced age, BMI > 30 kg/m^2, latent infections, cirrhosis, active peptic ulcer, osteoporosis, or clinically important psychiatric disorder
4. *Toxicity of treatment*
   - Potential adverse reactions and safety profile of each immunotherapy

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RPGN, rapidly progressive glomerulonephritis.

STOP-IgAN study was a multicenter, randomized, controlled trial of supportive care plus immunosuppressive therapy compared with supportive care alone in patients with IgAN. Patients from the centers in Europe (predominantly White race) were eligible to be randomized if they had persistent proteinuria of ≥0.75-3.5 g/d after a 6-month run-in phase of comprehensive supportive care. Within the immunosuppression group, the patients with eGFR ≥ 60 mL/min/1.73 m^2 received steroids monotherapy for 6 months (intravenous methylprednisolone at 1 g daily for 3 days at the beginning of months 1, 3, and 5; oral prednisolone at 0.5 mg per kilogram of body weight every other day), and the patients with eGFR between 30 and 59 mL/min/1.73 m^2 received oral cyclophosphamide at 1.5 mg/kg daily for 3 months followed by oral azathioprine at 1.5 mg/kg daily from months 4 to 36 combined with prednisone. In total, 309 patients completed the run-in phase, and 162 patients underwent randomization (n = 80 in the supportive care group and 82 in the immunosuppression group).

After a 3-year follow-up period, although more patients in the immunosuppression group reached full clinical remission (defined as UPCR < 0.2 g/g and stable eGFR [a decline of <5 mL/min/1.73 m^2 from baseline]) as compared with the supportive care group (17% vs 5%; P = 0.01), there was no significant difference in the proportion of patients experiencing a loss of eGFR ≥ 15 mL/min/1.73 m^2 by the study's end (26% vs 28%; P = 0.75). Furthermore, the patients in the immunosuppression group experienced more adverse effects, including severe infection, impaired glucose tolerance, and weight gain. Long-term data after a median follow-up of 7 years showed that there was no difference in the rate of GFR loss, kidney failure, or death between the immunosuppression and supportive care groups.

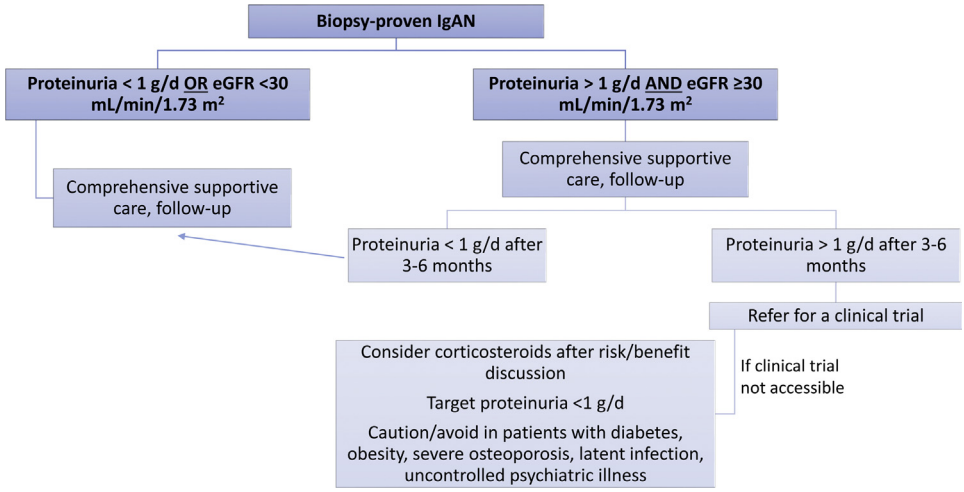

Figure 4. General approach to therapy. Comprehensive supportive care is the mainstay of therapy unless patients present with nephrotic syndrome or RPGN. If proteinuria persists at more than 1 g/d after 3 months of maximal supportive care, immunotherapy is indicated after treatment-related toxicity is discussed with patients or, alternatively, participation in a clinical trial. Continuation of supportive care is the option in patients at high risk for drug-related toxicity. It is important to note that the average level of proteinuria in the TESTING study was over 2 g/d. Further analysis of the TESTING data may change these recommendations; in particular, the benefits of corticosteroids balanced with the toxicity of therapy require clarification for patients with 1-2 g/d of proteinuria. Mycophenolate and tonsillectomy can be used in selected populations. Patients presenting with nephrotic syndrome are treated by steroids regimen as in minimal change disease. RPGN is treated with steroids and cyclophosphamide as in antineutrophil cytoplasmic antibody–associated vasculitis. Abbreviations: eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RPGN, rapidly progressive glomerulonephritis.

The TESTING study is a multicenter, double-blind, randomized controlled trial to evaluate the efficacy and safety of corticosteroids treatment in patients with IgAN. In the original study protocol, patients who had persistent proteinuria of >1 g/d and eGFR of 20-120 mL/min/1.73 m^2 after ≥3 months of the maximum tolerated dose of RAS blockade were recruited and randomized to receive steroids therapy (oral methylprednisolone at 0.6-0.8 mg/kg daily with a maximum dose of 48 mg/d for 2 months with subsequent tapering dose over 4-6 months) or placebo. Enrollment of 750 patients with 5 years of follow-up was planned, but the study was prematurely paused due to the high rates of serious adverse events primarily from infections (11 [8.1%] in the immunosuppression group vs 0 in the placebo group; $P < 0.01$), including 2 deaths.

An early analysis was performed at this juncture, when 262 patients were recruited with a median follow-up of 2.1 years. At this stage only 28 of anticipated 335 events occurred. This analysis suggested the potential early efficacy of corticosteroids with a reduction in the composite outcome of kidney failure, death, or 40% loss of eGFR (15.9% in placebo vs 5.9% in corticosteroid; hazard ratio, 0.37 [95% CI, 0.17-0.85]; *P* 0.02). Due to the low number of events, a definitive conclusion cannot be made until longer follow-up data are available; in the meantime, follow-up evaluation continues for the patients in the original protocol, and a modified protocol was adopted using a lower dose of methylprednisolone (0.4 mg/kg daily) and routine use of prophylaxis for *Pneumocystis jirovecii* (ClinicalTrials.gov identifier NCT01560052).

There are potential explanations for the differences in efficacy of corticosteroids in these 2 studies. First there were important differences in the population demographics. Notably most patients (approximately 96%) in the TESTING study were of Chinese origin as opposed to most STOP-IgAN participants being White. Second, the patients in the TESTING study had higher levels of baseline proteinuria (2.5 vs 1.8 g/d) and noticeably faster annual rate eGFR loss (−6.95 vs −1.6 mL/min/1.73 m^2) in those who only received supportive care. Both studies highlight the potential toxicity of corticosteroids and the need for discovery of more effective and targeted therapies.

The best available evidence therefore points toward the potential benefits of corticosteroids in patients with over 2 g/d of proteinuria. The long-term benefits require further clarification, but early analysis of the TESTING study suggests an impact on kidney function decline at a significant cost of toxicity. The potential morbidity and mortality must be acknowledged and carefully reviewed with patients before proceeding with this therapy. Patients at particularly high risk of toxicity include those with pre-existing obesity, diabetes, and latent infections. Importantly, the mean eGFR in the patients in these trials was around 60 mL/min/1.73 m^2. The presence of cirrhosis, active peptic ulcer, osteoporosis, or history of clinically important psychiatric illness should also be considered high-risk characteristics where the toxicity of corticosteroids likely outweighs the benefit. It is reasonable to assume that the risk of toxicity of corticosteroids is higher in patients with lower eGFR. Furthermore, no randomized study has demonstrated a benefit of corticosteroids in patients with an eGFR below 30 mL/min/1.73 m^2.

For question 3, the best answer is (d). Persistent proteinuria of 1.5 g/d places her at significant risk of progression, particularly given her young age and decreased kidney function. Although her eGFR, at 43 mL/min/1.73 m^2, is decreased, it is not lower than 30, so there is potential for benefit with additional therapy. Her BMI will likely increase with prednisone use, and the risks and benefits should be reviewed carefully with this patient. The average proteinuria in the TESTING study was > 2 g/d, and this has been the largest randomized study to suggest a potential benefit, with the long-term outcomes yet to be reported at this time. Combination of cyclophosphamide and steroids is recommended in IgAN only for patients presenting with RPGN. Given the risk of corticosteroid toxicity and the remaining clinical equipoise, enrollment in a clinical trial would be ideal.

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Immunosuppression: Beyond Corticosteroids

Although the KDIGO GN guideline suggests not using mycophenolate as a treatment for IgAN, there are recent data in Chinese populations to support its use as a steroid-

sparing agent. The combination of mycophenolate mofetil (MMF) at 1.5 g/d with low-dose prednisone for a total course of 6 months was not inferior to full-dose prednisone in inducing proteinuric remission at month 6 and 12 with fewer adverse events such as diabetes. There are insufficient data to suggest efficacy in the use of mycophenolate in other populations, particularly when disease is advanced.

Hydroxychloroquine is proposed to have pleiotropic immunomodulatory effects. Recently, a small randomized trial demonstrated a greater reduction in proteinuria compared with placebo at 6 months in Chinese patients who have persistent proteinuria of 0.75-3.5 g/d despite RAS blockade. Further studies are required given the short duration and small sample size.

Tonsillectomy has been associated with a reduction in proteinuria and improved kidney survival in Japanese populations. In one randomized controlled trial conducted in Japan, tonsillectomy combined with pulse steroids therapy did not have benefits over steroids alone. A retrospective European study also did not show a correlation between tonsillectomy and kidney function outcomes. Although this was a multicenter study, the total number of patients undergoing tonsillectomy was small. Consequently, there are insufficient data to recommend this therapy at this time.

Given the concerns regarding treatment toxicity and equipoise that remain on how to best treat patients with 1-2 g/d of proteinuria, it is recommended that these patients be considered for enrollment in clinical trials. More novel treatment strategies are discussed below.

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Experimental Therapies

Targeted-Release Budesonide

A targeted-release formula of budesonide (Nefecon) was developed for use in IgAN. The rationale for design of this compound was to release drug at the distal ileum where the largest site of Gd-IgA1 secreting cells is located: namely, the mucosal-associated lymphoid tissue. This is hypothesized to result in a reduction in production of Gd-IgA1 by cells originating from these sites or by mucosal-derived cells that migrate from the intestinal lymphoid tissue to other sites such as the bone marrow. Any absorbed drug is hypothesized to primarily undergo first-pass metabolism, thereby limiting systemic steroid exposure.

The phase 2b NEFIGAN study was a double-blind, randomized controlled trial of the targeted-release formula of budesonide in patients with IgAN. Participants in this study had an eGFR ≥ 45 mL/min/1.73 m^2 and persistent proteinuria of ≥0.75 g/d despite a 6-month course of RAS inhibitors. Patients were assigned to 16 mg daily or 8 mg daily of drug, or placebo (n = 48, 51, and 50, respectively). Most patients were White. The primary outcome was the mean change of UPCR from baseline at 9 months. The patients receiving the drug had a 24.4% decrease in UPCR compared with the 2.7% increase in the placebo group ($P = 0.0066$). The eGFR was stable in the treatment group as opposed to a −9.8% change from baseline in the placebo group. There were more frequent corticosteroid-related adverse events in patients who received the targeted-release formula of budesonide, indicating that some of the drug is absorbed and able to escape hepatic metabolism. However, no serious infection was reported.

A phase 3 randomized controlled trial of 16 mg of the targeted-release formula of budesonide versus placebo is actively recruiting patients with eGFR ≥ 35 and ≤ 90 mL/min/1.73 m^2 and proteinuria ≥ 1 g/d (NEFIGARD study; ClinicalTrials.gov identifier NCT03643965). The preliminary analysis including 199 participants shows the benefits in both proteinuria reduction and slowing eGFR decline after 9 months of treatment.

Complement Inhibitors

Given the recent advances in our understanding of complement in the pathogenesis of IgAN, there has been an interest in drugs targeting complement, particularly in those that show evidence of complement activation on kidney biopsy. Currently, there are several ongoing clinical trials of complement inhibitors being tested with various eGFR inclusion criteria: eGFR > 30 mL/min/1.73 m^2 for OMS721 (Narsoplimab, a monoclonal antibody against

MASP-2), LNP023 (a complement factor B inhibitor), Cemdisiran (small-interfering RNAs directed against C5), and APL-2 (a C3 inhibitor); eGFR > 40 mL/min/1.73 m^2 for IONIS-FB-LRx (an antisense inhibitor of complement factor B); and eGFR > 60 mL/min/1.73 m^2 for CCX168 (Avacopan; a C5a receptor antagonist).

Treatment of IgAN Variants: Nephrotic Syndrome and Rapidly Progressive Disease

The 2012 KDIGO GN guideline advised approaching the treatment of IgAN with overt nephrotic syndrome similarly to the treatment of minimal change nephropathy. Specifically, corticosteroids were recommended, and a steroid-sparing regimen is often required to maintain remission. Although this recommendation was based upon lower quality observational data, given the rarity of this entity data from large randomized studies are not likely to be available for further guidance.

In patients with RPGN, intravenous methylprednisolone followed by a combination of either oral or intravenous cyclophosphamide and corticosteroids, as in ANCA-associated vasculitis, is recommended; however, there are no randomized studies to support these recommendations. Rather, this is based upon observational data, and one of the largest studies also included patients with evidence of IgA vasculitis. Very small case series of patients successfully treated by plasmapheresis (with immunosuppression) suggest the potential use of apheresis in patients with RPGN with IgAV; however, this is not the standard of care, and there are no clinical trial data to support the use of rituximab in RPGN due to IgAN. Anecdotal successful use of rituximab has primarily been reported in IgAN presenting with IgA vasculitis; a lack of improvement in proteinuria or kidney function in patients with IgAN without RPGN suggests a lack of a role for rituximab in this context.

Since publication of the KDIGO guideline, there have been no additional randomized trials published that describe treatment of patients with RPGN due to IgAN. This is an area where multicenter randomized clinical trials are urgently needed.

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Article Information

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