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# IgA nephropathy

## ■ ABSTRACT

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis in the world. The etiology is unknown but a dysregulated T-cell immune response to viral, bacterial, and food antigens activating mucosal plasma cells to produce polymeric IgA has been proposed. No serological test exists to diagnosis IgAN. A definitive diagnosis requires kidney biopsy which is not always necessary. Kidney failure occurs in 20% to 40% of patients within 10 to 20 years.

## ■ KEY POINTS

The classic presentation of IgAN includes gross hematuria after an upper respiratory infection.

Lifestyle modification and maximal renin-angiotensin system blockade, especially if proteinuria is present, is recommended for all patients.

Prognostication tools are available to assess for progression to kidney failure and to balance the risk and benefits of non-immunosuppressive and immunosuppressive therapies.

New therapies are emerging though long-term data evaluating estimated glomerular filtration rate preservation are needed.

## ■ INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis in the world, with an overall incidence of 2.5 per 100,000 per year.<sup>1</sup> It was first identified in 1968 by French nephrologist Dr. Jacques Berger and therefore was historically referred to as Berger disease.<sup>2</sup> IgAN was initially considered a benign self-limited disease, but epidemiological studies suggest that 20% to 40% of patients will develop kidney failure within 10 to 20 years of diagnosis.<sup>3-8</sup> IgAN has a wide spectrum of clinical manifestations and outcomes, attributable to practice patterns relating to obtaining screening urinalysis and kidney biopsy, environmental and genetic factors, and treatment. There are therapeutic agents under investigation that show promise.

## ■ EPIDEMIOLOGY AND PATHOGENESIS

Individuals of European and East Asian ancestry are at higher risk for IgAN. Onset is typically during the second and third decades with a 2:1 male-to-female predominance in the United States.<sup>9</sup> IgAN is considered to be sporadic, although genome-wide analysis studies have identified non-Mendelian polymorphisms in the major histocompatibility complex (MHC) and non-MHC risk alleles.<sup>10</sup> The etiology of IgAN is unknown, but has been attributed to a dysregulated T-cell immune response to viral, bacterial, and food antigens activating mucosal plasma cells to produce polymeric IgA.<sup>11</sup>

IgA1 is structurally different from IgA2, in that it contains a disulfide hinge region on the heavy chain and contains an oxygen-linked glycosylation of serine and threonine.<sup>12</sup> This hinge region has a high affinity toward type IV collagen, the main component of the glomerulus. Production of galactosylated deficient IgA1 (Gd-IgA1) and formation of an IgG anti-Gd-IgA1 results in antigen-antibody complexes. Complexes deposit in the mesangium and activate the alternative and lectin complement pathways depositing C3.

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## ■ CLINICAL MANIFESTATIONS

Clinical manifestations of IgAN range from asymptomatic microscopic hematuria to rapid progressive glomerulonephritis. Classically patients present with gross hematuria following an upper respiratory tract infection. Others present with microscopic glomerular hematuria, non-nephrotic range proteinuria, and decreased kidney function. Less commonly, patients present with rapid progressive glomerulonephritis manifesting with acute kidney injury and hypertension, with or without nephrotic syndrome.

## ■ LABORATORY AND HISTOLOGIC FEATURES

Unfortunately, there is no serologic test to diagnose IgAN, including serum levels of Gd-IgA1 or IgG anti-Gd-IgA1 antibodies. Screening serologies are negative and complement levels will be normal. A definitive diagnosis requires kidney biopsy, which may not be necessary in all cases. Histologic findings range from mild mesangial expansion to diffuse proliferation with crescents. Immunofluorescence microscopy will have dominant or codominant IgA mesangial staining with lesser degrees of IgG and IgM. C3 is often co-localized, suggesting activation of the alternative complement pathway. Mesangial and occasional subendothelial deposits of IgA will be seen by electron microscopy.

## ■ PROGNOSTICATION OF KIDNEY DISEASE PROGRESSION

Clinicians have used various clinical surrogates to prognosticate patients' progression to kidney failure. Risk factors include proteinuria greater than 0.5 to 1 g/day, hypertension, reduced glomerular filtration rate, and persistent microscopic hematuria. Many of these surrogates impact a clinician's decision whether to biopsy a patient with suspected IgAN. The International IgA Nephropathy Network and the Renal Pathology Society developed the Oxford MEST-C pathologic scoring system, which should accompany all kidney biopsy reports to help predict kidney outcomes in patients with IgAN.<sup>13</sup> The score is based on the presence or absence of the following 5 histologic features:

- Mesangial IgA deposits
- Endocapillary hypercellularity
- Segmental glomerulosclerosis
- Tubular atrophy/interstitial fibrosis
- Crescents.

Kidney biopsies that reveal chronic lesions (higher S

and T scores) are probably less likely to be amendable to immunosuppressive therapy. The International IgA Nephropathy Prediction Tool (<https://ukkidney.org/resource/international-iga-nephropathy-prediction-tool>), an online calculator derived from a cohort of 2,781 patients with IgAN confirmed by kidney biopsy, may be used to impute clinical data and MEST-C scores to predict the risk of a 50% decline in estimated glomerular filtration rate (eGFR).<sup>14</sup>

## ■ DIFFERENTIAL DIAGNOSIS

Mesangial IgA deposition has been identified in up to 16% of renal allograft donors.<sup>15</sup> IgA is primarily catabolized by hepatocytes, and chronic liver disease may lead to increased circulating IgA1 and increased nonpathogenic mesangial deposition. *Staphylococcus aureus* infection-associated glomerulonephritis is a well-described entity that may have similar clinical characteristics, including multisystem small-vessel vasculitis manifestations and kidney biopsy pathology.<sup>16</sup> Assessing for occult infection is critical when considering immunosuppressive therapy for patients with presumed primary IgAN. IgA vasculitis (formerly referred to as Henoch-Schönlein purpura) is a systemic small-vessel vasculitis associated with leukocytoclastic vasculitis of the skin, abdominal pain, and arthralgias. Although kidney biopsy would reveal the same histologic finding of IgAN, many experts believe that the epidemiology, prognosis, and treatment are different.

## ■ NONIMMUNOSUPPRESSION MANAGEMENT

Conservative strategies that may reduce disease progression include sodium intake of less than 2 g/day, weight management, smoking cessation, regular activity, and avoidance of nonsteroidal anti-inflammatory medications. Clinicians should target blood pressure less than 130/80 mm Hg and proteinuria to less than 1 g/day or lower if possible, using maximal renin-angiotensin system (RAS) blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Fish oil greater than 3 g/day has been touted as beneficial with little known downside, but results are conflicting, so it should not be used in place of proven therapies.<sup>17</sup>

Sodium-glucose cotransporter 2 inhibitors have recently been approved by the US Food and Drug Administration (FDA) for patients with or without diabetes and with an eGFR greater than or equal to 25 mL/min/1.73 m<sup>2</sup> of body surface area after showing reductions in chronic kidney disease (CKD) progres-

sion in the DAPA-CDK (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) study.<sup>18</sup> The study randomized 270 patients with IgA nephropathy. Subgroup analysis demonstrated that dapagliflozin decreased the risk of CKD progression by 1.2 mL/min/1.73 m<sup>2</sup> per year and reduced the urine albumin-creatinine ratio by 26%. These benefits were confirmed in a meta-analysis of 817 patients with IgAN enrolled from the EMPA-Kidney (Study of Heart and Kidney Protection With Empagliflozin) trial, which demonstrated a 44% relative risk reduction in kidney disease progression.<sup>19</sup>

On February 17, 2023, the FDA granted accelerated approval for sparsentan, a single-molecule dual endothelin-1 angiotensin receptor II antagonist, for reduction in proteinuria in patients with IgAN at high risk of progression based on the phase 3 Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy (PROTECT).<sup>20</sup> Entry criteria required patients to have a urine protein-to-creatinine ratio greater than 1.5 g/g. Sparsentan reduced proteinuria by 45% compared with 15% in the irbesartan group. Prescribers are required to meet FDA Risk Evaluation and Mitigation Strategy requirements, and the drug's approval may be contingent on the demonstration of slowing CKD progression.

## ■ IMMUNOSUPPRESSION

A trial of oral glucocorticoid may be indicated if greater than 1 g of proteinuria persists for 3 or more months after maximal non-immunosuppressive therapy has been tried or the patient is already at high risk of kidney disease. Glucocorticoid therapy and other immunosuppressive medications have been studied yielding conflicting results. The STOP-IgAN (Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy) trial enrolled 337 patients with IgAN to supportive care (n = 80) or cyclophosphamide 1.5 mg/kg/day for 3 months, followed by azathioprine 1.5 mg/kg/day for 36 months, plus oral prednisolone 40 mg/day with taper (n = 82).<sup>21</sup> Patients with CKD stage 1 to 3 and proteinuria less than 3.5 g/day treated with immunosuppression had no difference in eGFR decline and were at higher risk for severe infections.

The TESTING (Therapeutic Effects of Steroids in IgA Nephropathy Global) trial randomized 503 patients to oral methylprednisolone initially 0.6 to 0.8 mg/kg/day (maximum 48 mg/day), weaning by 8 mg/day/month vs placebo and showed a reduction of kidney composite outcomes including kidney failure

or death due to kidney disease.<sup>22</sup> Unfortunately, the incidence of serious adverse events was increased in the high-dose methylprednisolone group.

Gut-associated lymphoid tissue and Peyer patches located in the ileum are a source of Gd-IgA1 antibody production. A targeted-release formulation of oral budesonide, postulated to release drug in the ileum, has been granted FDA approval under the accelerated approval program for patients with IgAN who are at high risk for progression (urine protein-to-creatinine ratio greater than or equal to 0.8 g/g or proteinuria greater than or equal to 1 g per 24 hrs). The NeflgArd Part A trial randomized 199 patients with IgAN on maximal RAS blockade and targeted-release formulation budesonide 16 mg/day or placebo for 9 months and demonstrated a 27% reduction in proteinuria and eGFR preservation difference of 3.87 mL/min/1.73 m<sup>2</sup> compared with placebo.<sup>23</sup> As expected, there were more side effects in the treatment arm, and despite a targeted-release steroid, patients experienced systemic glucocorticoid-related adverse effects. As a precondition of the accelerated approval program, part B of the trial will need to confirm preservation of kidney function assessing a GFR-based end point over 2 years, with final results expected in 2023 (NCT03643965).

A randomized trial of mycophenolate mofetil in 170 patients with IgAN at high risk of kidney function decline reported primary composite outcome events occurred in 6 patients (7.1%) in the mycophenolate mofetil group compared with 18 patients (21.2%) in the standard-of-care group.<sup>24</sup> Patients who discontinued mycophenolate mofetil in post-trial follow-up had eGFR loss of 6.1 mL/min/1.73 m<sup>2</sup> compared with an eGFR loss of 2.9 mL/min/1.73 m<sup>2</sup> in the standard-of-care group. There was no difference in serious adverse events. In small trials, calcineurin inhibitors, rituximab, cyclophosphamide, and hydroxychloroquine provided no clear benefit.

The alternate and lectin pathways are hypothesized to be involved in the pathogenesis of IgAN as evidence of C3 deposition. Avacopan, an oral C5a receptor inhibitor, has demonstrated encouraging results in reducing proteinuria in a small phase 2 pilot study of 15 patients with high-risk IgAN on maximal RAS inhibition.<sup>25</sup> In a phase 2 study of iptacopan, a factor B inhibitor, 112 patients with IgAN were randomized to placebo or various doses of iptacopan. Investigators reported a 23% reduction in proteinuria in patients taking high-dose iptacopan compared with placebo at 90 days.<sup>26</sup> We anxiously await the phase 3 trials results (NCT04578834).

**CONCLUSION**

IgAN has a wide spectrum of clinical presentations and 20% to 40% of patients will develop kidney failure within 10 to 20 years of diagnosis. All patients should be treated with lifestyle modification and maximal RAS blockade, especially if proteinuria is present. Prognostication tools are available to balance the risk and benefits of non-immunosuppressive and immunosuppressive therapies. New therapies have been granted FDA accelerated approval, but long-term data regarding preservation of eGFR are still needed. Finally, IgAN is receiving the attention it deserves, and the nephrology community should remain optimistic about novel treatment options for our patients.

**DISCLOSURES**

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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