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Immunoglobulin A glomerulonephropathy: A review

IGA Nephropathy

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Abstract

In this editorial, we comment on the article by Meng MJ *et al* published in the *World Journal of Clinical Cases*. We comprehensively review immunoglobulin A nephropathy (IgAN), including epidemiology, clinical presentation, diagnosis, and management. Immunoglobulin A nephropathy (IgAN), also known as Berger's disease, is the most frequent type of primary glomerulonephritis (GN) globally. It is mostly found among the Asian population. The presentation can be variable, from microscopic hematuria to a rapidly progressive GN. Around 50% of patients present with single or recurring episodes of gross hematuria. An upper respiratory infection and tonsillitis often precede these episodes. Around 30% of patients present microscopic hematuria with or without proteinuria, usually detected on routine examination. The diagnosis relies on having a renal biopsy for pathology and immunofluorescence microscopy. We focus on risk stratification and management of IgAN. We provide a review of all the landmark studies to date. According to the 2021 kidney disease: Improving Global Outcomes (KDIGO) guidelines, patients with non-variant form IgAN are first treated conservatively for three to six months. This approach consists of adequate blood pressure control, reduction of proteinuria with renin-angiotensin system (RAS) blockade, treatment of dyslipidemia, and lifestyle modifications (weight loss, exercise, smoking cessation, and dietary sodium restrictions). Following three to six months of

conservative therapy, patients are further classified as high or low risk for disease progression. High-risk patients have proteinuria ≥1 g/day or <1 g/day with significant microscopic hematuria and active inflammation on kidney biopsy. Some experts consider proteinuria ≥2 g/day to be very high risk. Patients with high and very high-risk profiles are treated with immunosuppressive therapy. A proteinuria level of < 1g/day and stable/improved renal function indicates a good treatment response for patients on immunosuppressive therapy.

Key Words: Immunoglobulin A Nephropathy; Glomerulonephritis; Nephritic syndrome; Angiotensin-converting enzyme inhibitor; Angiotensin receptor blocker; systemic steroids; Mycophenolate Mofetil

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Core Tip: I

Immunoglobulin A nephropathy is the most common type of glomerulonephritis globally. The management approach differs based on the level of risk for renal disease progression. In low-risk settings, patients are treated with angiotensin system blockade, while patients with a high risk of progressive renal disease are treated with immunosuppressive therapy. Systemic steroids have been shown to have favorable outcomes when compared to the standard of care in high-risk patients. Unfortunately, steroids are associated with numerous side effects. In some studies, mycophenolate mofetil has been shown to have favorable outcomes when compared to steroids with a better safety profile.

INTRODUCTION

Introduction

Epidemiology

Immunoglobulin A nephropathy (IgAN), commonly known as Berger's disease, is the most prevalent type of primary glomerulonephritis (GN) worldwide. The prevalence is higher in people of Asian origin as compared to other ethnicities. [1]. However, recent reports also indicate that it is the most common type of GN among Caucasians [2]. In a study of 13,519 kidney biopsies in China, IgAN accounted for 45% of all primary glomerulonephritis cases [3]. The prevalence also depends on regular screening for hematuria and proteinuria, followed by kidney biopsies. In North America, kidney biopsies are not routinely performed for isolated hematuria or mild proteinuria. Hence, the prevalence may be perceived as lower. Similarly, countries with reduced access to biopsies and routine immunofluorescence microscopy might not have an accurate representation of the disease prevalence IgAN can appear at any point in a person's life, but it is most commonly seen during the second and third decades of life. Both[ME1] men and women are equally affected in East Asia, while reports on the North American population indicate a higher prevalence in males [4].

Pathophysiology

IgAN can be either familial, primary/idiopathic, or secondary to an underlying condition. Familial IgA nephropathy accounts for less than 10% of all cases. IgAN is linked to 6q22-23 and gene locus IGAN1. Idiopathic/sporadic IgAN makes up most cases. Common secondary causes include celiac disease, liver cirrhosis, connective tissue disease, and infections such as human immunodeficiency virus (HIV), hepatitis viruses, malaria, Chlamydia, and Lyme disease [5]. IgAN is not always an isolated condition. In fact, it can be associated with other glomerular disorders, such as minimal change disease and granulomatosis with polyangiitis.

Diagnosis

As mentioned above, the diagnosis relies on having a renal biopsy for pathology and immunofluorescence microscopy. In 2009, the International IgA Nephropathy

Network and the Renal Pathology Society developed a pathologic classification of IgAN, "the Oxford classification" (Table 1), based on clinical data and kidney biopsies from 265 White and East Asian patients followed for five years [6]. IgA deposits can be detected in up to 16% of patients without clinical features of nephritis [7]. These results support the idea that IgAN is often diagnosed late, but IgA deposition doesn't always cause kidney disease.

Clinical presentation

The presentation itself can be variable, from microscopic hematuria to a rapidly progressive GN. Gross hematuria is a symptom that is observed in approximately 50% of patients, either as a single episode or as recurring episodes. An upper respiratory infection and tonsillitis often precede these episodes. Around 30% of patients present microscopic hematuria with or without proteinuria, usually detected on routine examination. Dysmorphic red blood cells would indicate glomerular injury. Nephrotic syndrome, or rapidly progressive glomerulonephritis, occurs in less than 10% of IgAN cases. Similarly, malignant hypertension is a rare presentation. Other pertinent findings in the history and physical exam include extremity pitting edema, frothy urine, and hypertension. Other features of reduced renal function include increased fluid retention (ascites, pulmonary edema), pruritis, and altered mentation secondary to uremia.

Risk stratification

The risk factors for disease progression and a worse prognosis are outlined in Table 2. After making the diagnosis of IgAN, all patients should undergo an initial risk assessment of progressive disease. This can be done *via* a risk prediction tool calculator called the "International IgAN Prediction Tool at biopsy – Adults" found on Calculate by QxMD [8]. A new version of the risk calculator tool was developed to assess the risk of progression one or two years after the initial kidney biopsy [9].

When treating IgAN, the main goal of care is to prevent disease progression. Unlike other glomerulonephritis syndromes, IgAN is commonly treated with non-immunosuppressive therapy.

Treatment

Initial approach

The management of IgAN depends on risk assessment of disease progression to end-stage renal disease. Treatment also depends on whether patients with IgAN have a variant form, such as IgAN with Minimal Change Disease, acute kidney injury, rapidly progressive glomerulonephritis, and pregnancy. According to the 2021 kidney disease: Improving Global Outcomes (KDIGO) guidelines, patients with non-variant form IgAN are first treated conservatively for three to six months. This approach consists of adequate blood pressure control, reduction of proteinuria with renin-angiotensin system (RAS) blockade, treatment of dyslipidemia, and lifestyle modifications (weight loss, exercise, smoking cessation, and dietary sodium restrictions) [10].

Non-immunosuppressive therapy

A landmark study in the management of IgAN was the 2007 IgACE study by Coppo *et al* out of Italy [11]. The IgACE was a multicenter, randomized, placebo-controlled, double-blinded clinical trial that included 66 patients with biopsy-proven IgAN. The patients were randomized to receive either Benazepril 0.2mg/kg/day or placebo. A worsening of creatinine clearance of > 30% was seen in 3.1% in the Benazepril group compared to 14.7% in the placebo group. A multivariate Cox analysis concluded that treatment with Angiotensin Converting Enzyme Inhibitor (ACEI) was an independent predictor of prognosis. In another trial, patients with IgAN whose blood pressure was controlled with antihypertensives other than ACEI were randomized to receive enalapril or placebo. Again, ACEI was associated with better

kidney survival (defined as a <50% increase in serum creatinine from baseline) at a 6-year follow-up [12].

New emerging data showed that patients with persistent proteinuria, despite RAS blockade, could benefit from Sodium-Glucose Transport Ligand 2 (SGLT2) inhibition. Dapagliflozin may be a safe and effective addition to the standard treatment of IgAN, according to a subanalysis of the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease Trial [13]. The study compared dapagliflozin *vs* placebo. The use of dapagliflozin resulted in a reduction of proteinuria and a slowing of the rate of renal function decline. In the dapagliflozin arm, the authors did not report any major hypoglycemia or ketoacidosis. This study, however, had some limitations. Patients enrolled were not medically optimized prior to enrollment. Although all patients were receiving RAS blockade agents, it wasn't clear whether the dosage was increased to a maximally tolerated dose.

Most recently, the PROTECT trial investigated the use of Sparsentan, a selective antagonist of angiotensin II receptor and hr endothelin receptor, in the management of IgAN [14]. Patients with persistent proteinuria > 1 g/d despite maximally tolerated doses of RAS blockade agents for at least 12 wk were randomized to receive sparsentan 400 mg once daily or remain on the standard of care with irbesartan 300 mg once daily. Sparsentan had a significantly higher reduction in urine protein-creatinine ratio (UPCR) when compared to irbesartan at week 36. At this time, the Food and Drug Administration (FDA) has conditionally approved the use of sparsentan in IgAN patients at risk of rapid renal function deterioration (UPCR ≥1.5 g/g, approximately equal to ≥2 g/day). Hepatotoxicity and teratogenicity are the main limitations of the use of sparsentan.

Immunosuppressive therapy

Following three to six months of conservative therapy, patients are further classified as high or low risk for disease progression. High-risk patients have proteinuria ≥1 g/day or <1 g/day with significant microscopic hematuria and active

inflammation on kidney biopsy. Some experts consider proteinuria ≥2 g/day to be very high risk. Patients with high and very high-risk profiles are treated with immunosuppressive therapy.

The first line of immunosuppressive treatment is usually systemic glucocorticoids. One of the first landmark trials for the use of glucocorticoids in IgAN was published in the *Lancet* in 1999 [15]. The patients either received supportive care or intravenous methylprednisolone. The latter group had reduced rates of worsening renal function at 5-year follow-up. More recently, two randomized control trials supported the benefit of glucocorticoid use in high-risk IgAN patients. The STOP-IgAN study enrolled patients with persistent proteinuria despite six months of comprehensive supportive therapy, including RAS-blocking agents, and randomly assigned them to receive either immunosuppression or supportive care alone [16]. The immunosuppression arm was further divided into two groups: patients receiving glucocorticoid monotherapy or glucocorticoids/cyclophosphamide followed by azathioprine. At three-year follow-up, patients in the immunosupression group had higher rates of clinical remission [ME2]. This result was mainly driven by the response seen in patients receiving glucocorticoid monotherapy. It is important to note that at the 10-year follow-up, the groups did not have significant differences in the rates of end-stage kidney disease (ESKD). Similarly, the TESTING trial compared the efficacy of high-dose oral glucocorticoids (oral methylprednisolone (0.6-0.8 mg/kg/d; maximum, 48 mg/d) to supportive therapy in patients with proteinuria >1g/d despite at least three months of supportive therapy with RAS-blockade agents [17]. Although the trial was terminated early because of a surplus of serious adverse events in the glucocorticoid group (mainly serious infections), patients receiving immunosuppression had fewer ESKD, mortality due to renal failure, and eGFR decline (hazard ratio, 0.37 [95%CI, 0.17-0.85]). The trial protocol was then adjusted to patients receiving a lower dose of the oral glucocorticoid (0.4 mg/kg/day, maximum dose 32 mg/day) with antibiotic prophylaxis for pneumocystis pneumonia [18]. After an average of 4.2-year follow-up, the risk of ESKD was lower in the immunosuppression group

(hazard ratio 0.59, 95%CI 0.40-0.87). The authors also concluded that the reduced glucocorticoid regimen with antibiotic prophylaxis would lower the risk of progressive renal function decline without the serious adverse events seen with the high-dose regimen. The external validity of the TESTING trial is limited, given that over 75% of patients enrolled were Chinese.

A trial published in the *American Journal of Kidney Disease* also compared MMF to prednisone in IgAN with active proliferative lesions [20]. The primary endpoint was the rate of complete remission, defined as undetectable proteinuria, with a stable serum creatinine level (<25% above the baseline). At both six and nine months, there were no notable variations in the rates of complete remission between the two groups. A landmark study showing the benefits of the use of MMF as a steroid-sparing agent in progressive IgAN was recently published in the *Journal of the American Medical Association (JAMA)* [21]. Patients were randomized to receive MMF with supportive care (SC) (losartan) vs. supportive care alone. The primary outcomes were a composite outcome (doubling of serum creatinine, end-stage kidney disease, death due to kidney or cardiovascular cause) and progression of chronic kidney disease. Patients in the MMF group had lower rates of the primary composite outcome events. Patients receiving MMF also had lower rates of progression of chronic kidney disease.

The NefIgArd trial evaluated the efficacy and safety of the targeted-release formulation of budesonide (TRF-budesonide) for the treatment of IgAN compared to placebo. All patients were on optimized dosing of RAS-blockade agents [22]. Patients receiving TRF-budesonide, compared to placebo, had a greater reduction in UPCR at 9 and 12 months. At 24 months, the eGFR in the TRF-budesonide group had a lesser reduction from baseline compared to placebo (6.1 mL/min/1.73m^2 vs. 12 mL/min/1.73m^2).

Other regimens include Calcineurin inhibitors, Rituximab, Cyclophosphamide, and Azathioprine. Studies on these agents did not strongly show any benefit when compared to either standard of care or systemic steroid therapy.

Monitoring of therapy

While on therapy, patients with IgAn receive monitoring of the serum creatinine, UPCR, and urine analysis every three months. For patients who are receiving supportive therapy, an increase in proteinuria or worsening in renal function often necessitates a renal biopsy to evaluate for the need for more aggressive therapy. Patients receiving immunotherapy are evaluated for treatment response after four to six months of therapy. A < 1g/day proteinuria level and stable/improved renal function indicate a good treatment response. At that point, glucocorticoid therapy can be discontinued. According to expert opinion, MMF can be added as a maintenance therapy for patients with persistent proteinuria >0.5g/day and hematuria. Persistent proteinuria ≥1 g/day without a ≥50 percent reduction in proteinuria from its peak value or worsening kidney function is treated with steroid taper and a six-month trial of MMF. Some experts recommend pulse methylprednisolone or switching to TRF-budesonide.

Editorial comments[ME3]

This editorial also serves to comment on the article published by Meng MJ *et al* in the *World Journal of Clinical Cases* [19].[ME4] The authors aimed to assess the efficacy and safety of mycophenolate mofetil (MMF) compared to glucocorticoid monotherapy in patients with IgAN and moderate-to-severe renal disease. One hundred patients were randomized to each arm. The trial shows that treatment with MMF at 9 and 12 months had greater reductions in 24-hour protein concentration and serum creatinine levels without a significant difference in the occurrence of adverse events (Table 3). No significant difference in outcomes was noted between the two groups at three and six months after treatment. It is important to note that this study has several limitations that need to be acknowledged. First, in the methods, the authors were not clear on the prior use of RAS-blockade agents. More specifically, they did not mention whether the patients received optimized comprehensive therapy or for how long. Second, a patient flow diagram was not provided, and the authors didn't make it clear how many

patients were lost to follow-up from the initial enrollment phase. Third, the authors failed to mention how the sample size was calculated under the statistics section. It is important to know the number of participants needed to adequately power the results. Fourth, the authors are targeting IgAN patients with moderate to severe renal disease. Although this is noted in the degree of proteinuria and the biopsy pathology, we note that the average GFR in both groups was around 55+/-3 mL/min. The authors are expected to present data on the proportion of patients with a greater reduction in GFR. Five, when discussing the safety endpoints, the authors do not elaborate on what is considered a "serious infection." While they note that serious infections were higher in the glucocorticoid group, the only infection they actually report is pneumonia, which, in fact, was more prevalent in the MMF group compared to the glucocorticoid group. Finally, since all the patients are Chinese, this limits the external validity of the trial. The study also had several strengths. First, all the patients included have biopsy proven disease. They even only selected biopsies that met specific quality standards (the quantity of glomeruli obtained was ≥ 10). [ME5] Second, there was no cross-over between the two groups. After allocation, patients only received the initial assigned therapy. This allows the study to be one of the few trials that look at MMF as a steroid-sparing agent in the management of IgAN. Fourth, the enrolled patients in the two groups had similar baseline characteristics, especially the conditions associated with worse outcomes, such as smoking status.

CONCLUSION

There is a need for future studies with larger sample sizes to determine the role of MMF in the management of patients with IgAN and moderate to severe renal dysfunction.

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