A Contemporary View On Immunoglobulin A Nephropathy: A Literature Review

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Abstract

Immunoglobulin A nephropathy (IgAN) is a primary glomerulonephritis that affects the kidney mainly, and it is the leading cause of chronic kidney disease worldwide. Its pathogenesis is best illustrated by the multi-hit model, which starts with the overproduction of galactose-deficient IgA1 (Gd-IgA1), continues with the production of anti-glycan autoantibodies, the formation of pathogenic immune complexes, and their mesangial deposition. These processes lead to the activation of inflammatory and complement pathways, which cause glomerular injury and the progression of fibrosis.

From the clinical point of view, IgAN shows hematuria, proteinuria, and disease severity varying from case to case. To confirm the diagnosis, a kidney biopsy is necessary, and the Oxford Classification represents a standardized system for evaluating the histopathologic features and forecasting the results. The most important prognostic features are, on one hand, continuous proteinuria, decreased eGFR, and hypertension.

The treatment originally was only supportive, e.g., with RAAS blockade, but it has been diversified by the addition of new therapies such as SGLT2 inhibitors, sparsentan, and targeted-release budesonide. Next-generation agents, like complement inhibitors and B-cell/BAFF/APRIL–targeted drugs, are on the horizon and can provide a highly personalized medicine approach. However, a lot of work still needs to be done to find dependable biomarkers and fathom patient-specific disease variability despite these achievements.

The present review consolidates leading evidence regarding IgAN epidemiology, pathogenesis, clinical presentation, and treatment and emphasizes that exploring next steps essential for early diagnostic improvement and thus, the prevention of progression to the final stage of the kidney disease.

Introduction

Background of IgA Nephropathy

Immunoglobulin A nephropathy or Berger's disease is the commonest primary glomerulonephritis worldwide (Cheung & Barratt, 2024; Filippone et al., 2024; Ramsawak et al., 2025; Wyatt & Julian, 2013). In 1968, it was identified by Berger and Hinglais when they described the unique feature of the disease: the presence of immune complexes containing dominantly or co-dominantly IgA in the glomeruli revealed by a renal biopsy (Aseem & Zheng, 2024; Cheung & Barratt, 2024; Filippone et al., 2024).

The disease accounts for a very high percentage of cases of kidney failure among both children and adults, and its worldwide incidence is estimated at not less than 2.5 per 100,000

population per year (Cheung & Barratt, 2024; Ellison et al., 2024; Ramsawak et al., 2025). IgAN is an inflammatory glomerular disease marked by the production of galactose-deficient IgA1 (Coppo, 2025). The aberrant IgA1 provokes the production of autoantibodies and IgA immune complexes that subsequently deposit in the mesangium (Coppo, 2025). The deposited immune complexes bind to mesangial cells, thus they proliferate and release cytokines and complement components, which, in turn, induce glomerular and tubular damage and renal insufficiency (Coppo, 2025; Schimpf et al., 2023). Between 20 and 50% of patients with IgAN are estimated to develop kidney failure (Filippone et al., 2024). Usually, the diagnosis of IgAN relies on kidney biopsy, which is generally done after the finding of hematuria or proteinuria by urinalysis (Ramsawak et al., 2025).

Since the initial description of IgAN, a lot has been done in unraveling its pathogenesis, thereby the diagnosis, prognosis, and treatment have been changing very fast in the last ten years (Aseem & Zheng, 2024; Ramsawak et al., 2025). Nevertheless, the etiology is still not fully elucidated (Filippone et al., 2024; Schimpf et al., 2023). Recent studies on this subject refer to the "multi-hit hypothesis" or "4-hit model" for pathogenesis that depicts a sequential event chain driving disease progression and thus suggesting each one as a potential target for the novel therapeutic agents (Knoppová et al., 2021; Ramsawak et al., 2025; Zhou, 2025).

Epidemiology and Prevalence

The prevalence of IgAN changes a lot depending on where one lives and the people one belongs to. Globally, it is considered the most frequent cause of primary glomerulonephritis with the number of patients varying between 20 and 30 per million person-years (Aseem & Zheng, 2024; Tota et al., 2023).

IgAN is especially common in Asians (like 45 per million person-years in Japan) and Whites (for example, 31 cases per million person-years in France) (Aseem & Zheng, 2024; Filippone et al., 2024). However, its incidence in Africa is at a very low level (Aseem & Zheng, 2024; Filippone et al., 2024). The explanation for such differences lies not only in the extent of medical care and research, including the methods of screening, biopsy rates, and referral patterns, but also in the lifestyle of the individuals from these regions (Aseem & Zheng, 2024). A good example for that could be a urinalysis check in Japanese schoolchildren which has been performed all over the country since 1974 and has undoubtedly led to IgAN becoming the most common primary glomerulonephritis in Japan (Aseem & Zheng, 2024).

The age at which IgAN is diagnosed has changed during the recent years. Initially, it was assumed that most cases would be found among youngsters; however, recent findings show that median age at the point of diagnosis is on the rise. The median age in the RaDaR study was 40 years in 2013 and 45 in 2020. Also, the average age in the Spanish patients went up from 37.6 years in 1994–1997 to 44.9 years in 2010–2013 with the proportion of diagnoses in people over 65 years old being 10% (Filippone et al., 2024). Gross hematuria and urinary sediment abnormalities are common features in young patients, while most elderly patients suffer from reduced estimated glomerular filtration rate (eGFR), hypertension, acute kidney injury, and higher proteinuria levels (Filippone et al., 2024).

Besides that, race and ethnicity affect the risk and progression of IgA nephropathy (IgAN). Pacific-Asian populations have a higher prevalence than European-Caucasians and are more likely to show severe clinical manifestations, increased active lesions on biopsy, and a higher rate of progression to end-stage kidney disease. The disease is very rare in African Americans. These differences in epidemiology emphasize that genetics and environment do not act independently when it comes to IgAN (Cheung & Barratt, 2024; Jelušić et al., 2022).

Reported Annual incidence of IgA Nephropathy Across Different Regions

Region/Population Group	Reported Annual Incidence Rate	Notes
Australia, Japan, Taiwan	0 to 10.7	Incidence can vary widely within these countries
Mainland China	6.3 to 24.7% (among renal biopsy patients)	Higher rates in East and Pacific Asia generally
United States	0.54 to 2.1	Based on regional studies from 1974-2003; occurrence may vary
Asian American Patients	More than double other races (among biopsy patients)	Reflects higher IgAN diagnosis rates within biopsy cohorts
East and Pacific Asia	Generally higher rates	Overall higher rates are observed in this region

Pathogenesis Overview

The pathogenesis of IgAN is a complicated process and is usually explained by the "multi-hit hypothesis" or "4-hit model" (Aseem & Zheng, 2024; Cheung et al., 2024; Knoppová et al., 2021; Ramsawak et al., 2025; Wyatt & Julian, 2013; Zhou, 2025). This model describes the sequential cascade of stages that are interdependent and ultimately lead to the disease progression:

Hit 1: Aberrant Production of Galactose-Deficient IgA1 The very first stage is the overproduction and increased systemic presence of IgA1 with abnormal O-glycosylation, more specifically the IG is lacking galactose in its hinge region (Cheung et al., 2024; Ramsawak et al., 2025; Wyatt & Julian, 2013). Gd - IgA1 is most likely a product of the gut and nasal mucosa, and its production is influenced by genetic factors, cytokines such as B-cell activating factor and a proliferation-inducing ligand, and changes in the gut microbiome (Ramsawak et al., 2025).

Hit 2: Production of Anti-Glycan Autoantibodies After Gd-IgA1 formation, autoantibodies, mainly IgG but also IgA1, are produced which specifically recognize and bind these galactose-deficient IgA1 molecules (Cheung et al., 2024; Ramsawak et al., 2025; Wyatt & Julian, 2013).

Hit 3: Formation of Pathogenic Immune Complexes Gd-IgA1 and anti-glycan autoantibodies thus formed interact with one another and the result is circulating immune complexes. These complexes are of such size and possess such physicochemical characteristics that make their removal from the circulation quite inefficient (Cheung et al., 2024; Ramsawak et al., 2025; Wyatt & Julian, 2013).

Hit 4: Glomerular Deposition and Injury The immune complexes of the pathogen nature deposit in the glomerular mesangium thereby eliciting an inflammatory response (Cheung et al., 2024; Ramsawak et al., 2025; Wyatt & Julian, 2013; Zhang et al., 2023). This deposition leads to an increased number of mesangial cells and, therefore, expansion of the extracellular matrix, as well as secretion of inflammatory mediators such as interleukin-6 and platelet-derived growth factor by mesangial cells (Ramsawak et al., 2025; Zhang et al., 2023). Complement activation, especially through the alternative and lectin pathways, is also a major factor in glomerular inflammation and injury (Coppo, 2025; Ramsawak et al., 2025; Zhang et al., 2023). Eventually, these processes take place in glomerulosclerosis, interstitial fibrosis, podocyte injury, and gradual loss of renal function (Coppo, 2025; Petrou et al., 2023; Ramsawak et al., 2025; Zhang et al., 2023).

Both genetic predisposition and environmental factors are equally important at every step of the process of mucosal immune system dysregulation and subsequent cascade of events culminating in IgAN (Aseem & Zheng, 2024; Ghozloujeh et al., 2025; Ramsawak et al., 2025).

Scope and Objective of the Review

This review of literature is meant to summarize and give a detailed understanding of the newest knowledge about Immunoglobulin A Nephropathy. After grasping the basics of this common kidney disease concept, the review will explore its epidemiology and various clinical manifestations. Much of the work will be devoted to clarifying the complicated nature of the pathophysiology of IgAN, which involves genetic susceptibilities, abnormal IgA1 glycosylation, immune complex formation, complement activation, and cellular mechanisms of glomerular injury. Besides, this article will evaluate exhaustively the different regimens for medical treatment, ranging from the supportive care and the conventional immunosuppressants to the targeted as well as the new therapeutic approaches. It will also point out the research directions of the future, such as discovering novel biomarkers, therapeutic targets, and personalized medicine strategies, to help fill the gaps in our understanding and make patients' prognosis better.

Pathophysiology of IgA Nephropathy

Genetic Susceptibility

Immunoglobulin A Nephropathy is a disease that features a robust genetic aspect, as familial clustering and significant ethnic and regional differences in its prevalence and progression have been documented(Zhang et al., 2017). Much of the pathogenesis insight has been gained by genetic studies, especially through Genome-Wide Association Studies, which have opened the door wide for the understanding of genetic predisposition to IgAN (Aseem & Zheng, 2024; Filippone et al., 2024).

Numerous large-scale multinational GWAS and meta-analyses have mapped more than 30 different risk loci linked to IgAN, with these loci together explaining about 11% of the total disease risk (Aseem & Zheng, 2024; Filippone et al., 2024; Kiryluk et al., 2023; Qu et al., 2024; Xu et al., 2023). These susceptibility loci often include genes that are essential for immune regulation, mucosal immunity, antigen presentation, adaptive immunity, and complement activation (Aseem & Zheng, 2024; Kiryluk et al., 2023; Magistroni et al., 2015; Zhang et al., 2017). On the other hand, quite a few of these genetic-related risk factors for IgAN are also common to other autoimmune diseases, which is indicative of shared immune dysregulation pathways in the core(Zhang et al., 2017).

Moreover, the genetic factors are the main etiological factors that maintain the aberrant O-galactosylation of IgA1, which is pointed as the crucial "hit" of the multi-hit hypothesis of IgAN etiopathogenesis (Ramsawak et al., 2025; Zhou, 2025). The abnormal galactosylation of IgA may be an inherited characteristic; however, by itself, it is not enough to bring about (Ramsawak et al., 2025)A the full development of (Ramsawak et al., 2025)

The genetic variation plays a large role in the differences of the geographic and ethnic variations of the IgAN. For example, it was observed that Asians have the enrichment of certain susceptibility alleles (Filippone et al., 2024; Qing et al., 2022), and the recent genetic findings are consistent with these geo-ethnic variations in disease vulnerability (Magistroni et al., 2015). Besides that, the African origin has been associated with higher serum IgA levels and more IgA-increasing alleles, which in turn may imply a possible role of these factors in disease mechanisms in this population (Liu et al., 2022). However, even when looking beyond direct genetic variants, epigenetic elements like changed DNA methylation as well as microRNAs that regulate various processes in cells also play a role in the genetic risk that a person may develop IgAN (Filippone et al., 2024). Nevertheless, the etiopathogenesis of this illness is still very complicated and it is characterized by the complex interactions between the genetic predispositions and different environmental factors(Jelušić et al., 2022).

Aberrant Glycosylation of IgA1

Aberrant O-glycosylation of the IgA1 molecule is recognized as the crucial initial event in the pathogenesis of IgAN (Novák et al., 2018; Ohyama et al., 2021; Ramsawak et al., 2025;

Zhou, 2025) This aberration specifically involves the production of IgA1 molecules with a deficiency of galactose in the O-linked glycans within their hinge region, leading to what is known as galactose-deficiency. Gd-IgA1 is believed to originate primarily from mucosal sites, particularly the gut and nasal mucosa, where IgA-producing plasma cells. Several factors contribute to this aberrant glycosylation. Genetic predisposition plays a role and cytokines, such as B-cell activating factor and a proliferation-inducing ligand, are significant regulators of mucosal B-cell survival and proliferation, promoting the formation of plasma cells. Some studies also point to dysregulation of glycosyltransferases, such as C1GalT1, or premature sialylation by ST6GalNAcII, as contributors to the aberrant IgA1.

While elevated levels of circulating Gd-IgA1 are a hallmark of IgAN, it is important to note that their presence alone is not sufficient to cause the disease, as healthy individuals and unaffected relatives can also exhibit increased Gd-IgA1 levels (Filippone et al., 2024). This underscores the multi-hit nature of IgAN, where subsequent events are required for disease development.

Immune Complex Formation and Deposition

The single most common paradigm for IgAN suggests there are multiple sequential events (hitting the same condition) leading to inflammation, out of which the 2nd and the 3rd "hits" originate with the genesis of pathogenic immune complexes and their later glomerular deposition (Cheung et al., 2024; Knoppová et al., 2021; Wyatt & Julian, 2013). Upon the discovery of galactose-deficient IgA1, an immune reaction is generated (Ramsawak et al., 2025).

In brief, the immune complexes, mostly IgG and to a less extent IgA, are the considered autoantibodies that recognize and then bind to the galactose-deficient regions of Gd-IgA1 (Cheung et al., 2024; Knoppová et al., 2021; Ramsawak et al., 2025; Wyatt & Julian, 2013). This interaction gives rise to the immune complexes circulating in blood made up of Gd-IgA1 part and the anti-glycan binding autoantibody fragments (Cheung et al., 2024; Knoppová et al., 2021; Ramsawak et al., 2025; Wyatt & Julian, 2013). These immune complexes are also distinguished by their particular size and physicochemical properties, which are presumed to obstruct their removal from the bloodstream (Wyatt & Julian, 2013).

The step of generating Gd-IgA1-containing immune complexes in circulation is pivotal in the disease mechanism, as inferred from the correlation between clinical and histologic activity and the level of circulating immune complexes. Upon the glomerular mesangium, a site of the kidney where the immune complexes lodge, a crucial event takes place there leading to the subsequent inflammatory cascade and kidney injury. Besides, the deposition of IgA and complement C3 in the glomerular mesangial region is indicative of IgAN and commonly IgG and/or IgM are deposited (Nihei et al., 2023). Regular immunofluorescence on kidney biopsy identifies IgA attached to Gd-IgA1 as the dominant immune complex deposited.

Complement Activation Pathways

Complement activation is a main factor and a decisive agent in the development of glomerular inflammation and injury in IgA Nephropathy. After the mesangial deposition of the IgA-containing immune complexes, the complement system is turned on and it becomes the major aggressor in the disease progression and damage amplification (Cheung & Barratt, 2024). More than 90% of renal biopsies in IgAN show glomerular co-deposition of complement C3 with IgA as a feature, which is linked to the worsening of renal function in the long term, just as lower plasma C3 levels (Cheung & Barratt, 2024).

The main complement pathways to be activated in IgAN are the alternative and lectin pathways, whereas the classical pathway is mainly excluded from the consideration (Cheung & Barratt, 2024; Filippone et al., 2024; Ramsawak et al., 2025). The strongest evidence of the involvement of the alternative and lectin pathways has been found and that is why we can find more of their fragments in the plasma and urine of IgAN patients (Cheung & Barratt, 2024).

- **Alternative Pathway**: The main mechanism by which the complement system is activated in IgAN is through the alternative pathway (Filippone et al., 2024). The deposition of alternative pathway components together with properdin, factor H, and factor H-related protein 1 and 5 in renal biopsy samples has been increased and correlated with a more severe renal outcome (Cheung & Barratt, 2024). When experimented on, IgA1 was found to be capable of causing C3 cleavage directly through the alternative pathway (Cheung & Barratt, 2024). Analysis of the proteins in the blood that make up the Gd-IgA1 complexes showed the presence of complement components (iC3b, C3c, and C3dg) in these immune complexes, thus it is suggested that Gd-IgA1 complexes create the surface on which alternative complement activation takes place (Cheung & Barratt, 2024). Besides that, the common genetic deletion of the region coding for complement factor H-related protein 3 and 1, which is one factor that can protect against IgAN by increasing the ability of factor H to inhibit the alternative pathway, is a good example (Cheung & Barratt, 2024). Variations in the sequences of genes coding for complement-regulating proteins can also increase the risk of IgAN (Filippone et al., 2024).
- **Lectin Pathway**: The lectin pathway participates in a considerable minority of patients, and it seems that the severity of the disease is related to it (Filippone et al., 2024). Around 40% of patients show glomerular deposition of the lectin pathway components, namely mannose-binding lectin, MBL-associated serine protease 1 and 2 (MASP-1 and MASP-2), and C4d, and are linked to poor long-term renal prognosis (Cheung & Barratt, 2024). MBL binding to polymeric IgA can lead to direct activation of the lectin pathway (Cheung & Barratt, 2024).
- **Classical Pathway**: The classical pathway, unlike the alternative and lectin pathways, is generally not thought to be involved in IgAN, as renal biopsies usually show no C1q deposition (Cheung & Barratt, 2024; Ramsawak et al., 2025).

The differences in complement activation and control among the various patients suggest that personalized treatment strategies specifically aimed at these pathways might be possible (Filippone et al., 2024).

Cellular and Molecular Mechanisms of Glomerular Injury

The development of glomerular damage in Immunoglobulin A Nephropathy is a complicated issue that is mostly explained by a multi-hit hypothesis which involves numerous cellular and molecular occurrences (Cheung et al., 2024; Zhou, 2025). First, the "hit" means the overproduction of galactose-deficient IgA1, a protein that has no galactose in its hinge part because the O-glycosylation is not regulated. It is quite convincing to think that the sources of aberrant IgA1 are the gut and the nasal mucosa, and that their origin is determined by the genome, the presence of cytokines such as B-cell activating factor and a proliferation-inducing ligand, and the changes in the gut microbiome (Ramsawak et al., 2025; Zhou, 2025).

Afterwards, Gd-IgA1 confers auto-antigen properties and the immune complexes are formed as a result of binding of Gd-IgA1 with IgG and IgA antibodies both in the blood (Cheung et al., 2024; Knoppová et al., 2021). These immune complexes which are in circulation eventually lead to the glomerular mesangium, the area where the injury of the kidney is the most important and the beginning of the whole thing (Cheung et al., 2024; Ghozloujeh et al., 2025; Ramsawak et al., 2025).

On arriving at the site, immune complexes turn on the mesangial cells which are the resident cells and the inflammatory reaction cascade is initiated (Ramsawak et al., 2025; Zhang et al., 2023). This is the major response of the interaction between the immune complexes and mesangial cells and leads to the enhanced cellular proliferation of mesangial cells, increased extracellular matrix expansion, and the production of inflammatory mediators such as interleukin-6 and platelet-derived growth factor (Ramsawak et al., 2025; Zhang et al., 2023).

One of the main issues in the inflammatory process described is the complement system engagement. The fixation of C3 in the mesangium is the starting point for both the alternative and the lectin pathways which result in the glomerular inflammation as well as injury (Cheung & Barratt, 2024; Ramsawak et al., 2025). The activation of complement here together with the release of cytokines and the arrival of inflammatory cells causes podocyte injury leading to even more matrix expansion and fibrosis that is at the progressive stage (Zhou, 2025). Moreover, mesangial-derived cytokines (Ramsawak et al., 2025) and mesangial-podocyte crosstalk (Zhang et al., 2023) contribute to the podocyte damage besides direct influence. Finally, this altered glomerular hemodynamics, direct damage to the glomerulus and adjacent tubules, and proteinuria, which is the major factor in the progression of tubular damage, represent the outcome of these happenings (Ghozloujeh et al., 2025).

Clinical Manifestations and Diagnosis

Clinical Presentation

IgA nephropathy is a disease that can show variable symptoms. Hematuria is experienced by numerous patients and may be either microscopic or macroscopic. Macroscopic hematuria is almost always triggered by respiratory or gastrointestinal infections that occurred within the previous few days, a phenomenon that is sometimes called "synpharyngitic" hematuria (Aseem & Zheng, 2024; Novák et al., 2018; Ramsawak et al., 2025; Taliercio & Mehdi, 2023). Proteinuria is frequently present as well, and its level may vary from slight to nephrotic syndrome. There may even be some people who do not show any symptoms, and only through the incidental detection of microscopic hematuria and proteinuria are they found (Novák et al., 2018). In addition to these, hypertension and different stages of renal insufficiency, including acute kidney injury or rapidly progressive glomerulonephritis, may also be the initial symptoms of this disease. The elderly, apart from this, may show proteinuria, microscopic hematuria, or hypertension that can either be present alone or in a combination of two or more (Wyatt & Julian, 2013).

Diagnostic Criteria and Biopsy Findings

The diagnosis of IgA nephropathy is confirmed through the examination of a renal biopsy that identifies the typical IgA deposits in the glomerular mesangium by immunofluorescence (Pant, 2018; Ramsawak et al., 2025; Selvaskandan et al., 2020; Taliercio & Mehdi, 2023). In most cases, these deposits are either dominantly or codominantly, with C3 being frequently present. The histological changes that occur alongside the proliferative process of the mesangial cells and the mesangial matrix usually come from the light microscopic observation of the tissue. Additional tissue changes may be found such as endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis (Cheung et al., 2024; Pant, 2018). Though electron microscopy helps in locating immune complexes in the mesangium, it is not absolutely needed for establishing the diagnosis.

Histopathological Classification Systems

The Oxford Classification was created and is commonly utilized to standardize the assessment and forecast of IgAN. Initially, the classification evaluated four major pathological features, with crescents (C) being incorporated in a subsequent revision (Aseem & Zheng, 2024; Okonogi et al., 2018; Pant, 2018; Ramsawak et al., 2025):

- **Mesangial hypercellularity**: Increased mesangial cells (≥ 4 in any mesangial area) (Ramsawak et al., 2025)
- **Endocapillary hypercellularity**: Increased cells within the glomerular capillary lumen (Ramsawak et al., 2025)
- **Segmental glomerulosclerosis**: Adhesion or sclerosis not involving the entire glomerulus (Ramsawak et al., 2025)
- **Tubular atrophy/interstitial fibrosis** (Ramsawak et al., 2025)
- **Crescents:** Extracapillary proliferation (cellular, fibrocellular, or fibrous) (Aseem & Zheng, 2024; Wang et al., 2021)

After each feature is scored, the results show that each feature individually has a correlation with kidney outcomes. (Filippone et al., 2024; Ramsawak et al., 2025; Tang et al.,

2021). The Oxford Classification serves as a means to evaluate pathological changes and to steer the therapy forward.

(**Prognostic Factors and Risk Stratification**

Various components influence a patient's progression of IgA nephropathy and hence, the degree of risk stratification (Cheung et al., 2024; Glassock, 2021; Ramsawak et al., 2025). First of all, the main clinical prognostic indicators include continuous proteinuria (especially >1 g/day), serum creatinine concentration, or low eGFR at the time of the sample collection, and also, if blood pressure is not well controlled (Aseem & Zheng, 2024; Cheung et al., 2024; Ramsawak et al., 2025; Riispere et al., 2017; Tang et al., 2021; Zhou, 2025).

The state of the kidney, in particular, the damage to the tubules/interstitium (T score) as well as fibrosis and segmental glomerulosclerosis (S score) according to the Oxford classification, has been confirmed to be the major contributors to adverse renal outcomes (Ramsawak et al., 2025; Riispere et al., 2017; Tang et al., 2021). The formation of crescents (C score) also indicates the fastest disease progression (Aseem & Zheng, 2024; Cheung et al., 2024; Wang et al., 2021). Moreover, old age at the time of diagnosis and male gender have been listed among factors that lead to a worse prognosis (Zhou, 2025). Risk stratification employs these clinical and pathological parameters to identify different groups of patients so that each patient can be treated and followed up according to his/her requirements (Glassock, 2021; Ramsawak et al., 2025; Zandifar et al., 2024).

Current Treatment Strategies

Supportive Care and Renin-Angiotensin System Blockade

Optimized supportive care is the management foundation of IgAN, which applies to every patient irrespective of their risk of progression (Cheung & Barratt, 2024; Karoui et al., 2023). The care should be comprehensive and focus on the patient's lifestyle, e.g., smoking cessation, keeping a normal body weight, restricting sodium intake (< 2 g/day), and managing hyperlipidemia (Aseem & Zheng, 2024; Cheung & Barratt, 2024; Ramsawak et al., 2025).

Most of the non-immunosuppressive actions that should be taken is the inhibition of the renin-angiotensin system by a casp enzyme inhibitor or angiotensin receptor blocker (Floege et al., 2021; Ramsawak et al., 2025; Reid et al., 2011). As proteinuria is more than 0.5 g/day (or >0.75 g/day in some trials), these drugs are strongly recommended to patients who have proteinuria regardless of whether they are hypertensive, as the drugs lead to the reduction of proteinuria, blood pressure lowering, and renal function decline slowing. The target blood pressure that the doctors usually have in mind is 120/70 mmHg or even lower (Aseem & Zheng, 2024; Ramsawak et al., 2025).

Right up to short time ago, sodium-glucose transporter 2 inhibitors (SGLT2i) and sparsentan, a dual endothelin receptor and angiotensin receptor antagonist, were mainly seen as the most groundbreaking innovative elements of supportive care in patients, especially those with chronic kidney injury. One of the SGLT2 inhibitors, dapagliflozin, in particular, had great

success in lowering proteinuria and improving renal outcomes of IgAN patients. This is why sparsentan has been given a very fast FDA approval.

Corticosteroids and Immunosuppressants

The use of systemic corticosteroids in IgAN has been challenged through divergent debates due to the contradictory nature of the results of the trials, which were cited by Cheung and Barratt (2024), Oruç et al. (2024), and Ramsawak et al. (2025). Although corticosteroids have anti-inflammatory and immunosuppressive properties that can reduce proteinuria and kidney function loss, the fear of long-term toxicity, particularly in patients with advanced chronic kidney disease, is a limiting factor for the widespread use of corticosteroids.

Several trials including STOP-IgAN and TESTING have looked into the safety and efficacy of corticosteroids. Immunomodulatory therapy, including corticosteroid treatment, was linked to the occurrence of severe infections in the STOP-IgAN trial, in which immunosuppression components were withdrawn and the significant part of patients were supported by only standard care (Filippone et al., 2024; Ramsawak et al., 2025). The TESTING research, following an initial halt caused by infection rates, resumed with a few methylprednisolone reduced doses showing a decline in the primary composite endpoint, keeping the side effect profile of the steroid-treated group still high (Aseem & Zheng, 2024; Ramsawak et al., 2025). To improve patient safety and reduce side effects, experimenters have decided to use a shorter duration and a lower dosage of the steroid regimen (Ghozloujeh et al., 2025).

Mycophenolate mofetil (MMF) and cyclophosphamide are the two other immunosuppressants that can be mentioned here. MMF has been effective in providing clinical benefit, especially in the case of Chinese patients, who are at a higher risk of disease progression, in terms of lowering the composite outcomes and eGFR decline, whereby the result of its effect after discontinuation is questionable (Cheung & Barratt, 2024; Ramsawak et al., 2025). As a rule, cyclophosphamide has to be accompanied by steroids and is used to treat a severe case of IgAN in most situations, which especially includes rapidly progressive glomerulonephritis, thus markedly serious eGFR reduction and crescents more than 50% (Filippone et al., 2024; Ghozloujeh et al., 2025).

As a matter of fact, one of the leading immunosuppressors for IgAN is the antibody made by the FDA based on its targeted-release formulation: Budesonide (Liao et al., 2023; Ramsawak et al., 2025; Toumaj et al., 2023). The therapeutic agent undergoes treatment of the small intestine and Peyer’s patches with exclusive delivery, galactose-deficient IgA1, the main source for disease, is located there, consequently, a mediator of the disease is avoided (Ramsawak et al., 2025).

Targeted Therapies

Recent advancements in understanding IgAN pathogenesis have led to the development of therapies that target specific disease mechanisms. These include:

- **Complement Inhibitors**: There is a major focus in complement cascade research that it is the main culprit in the development of IgAN. (Daha & Kooten, 2015; Medjeral-Thomas et al., 2021; Ramsawak et al., 2025). Complement inhibitors are being studied in phase 2 and 3 trials with iptacopan (a factor B oral inhibitor) showing mitigated results of proteinuria and lately receiving fast track FDA approval (Ghozloujeh et al., 2025; Ramsawak et al., 2025). Other complement inhibitors including those that target the lectin pathway are also being reviewed (Barratt et al., 2023; Poppelaars et al., 2021).
- **B-Cell Modulators**: The therapies focus on B-cell activating factor and a proliferation-inducing ligand that are essential for the production and life of B cells and plasma cells which produce pathogenic Gd-IgA1 (Filippone et al., 2024; Ghozloujeh et al., 2025; Zhou, 2025). Substances like atacicept and telitacicept that affect both BAFF and APRIL have been successful in lowering proteinuria and racking up kidney function (Ghozloujeh et al., 2025; Ramsawak et al., 2025). Moreover, monoclonal antibodies that selectively neutralize APRIL (for instance, sibeprenlimab, zigakibart) are at the stage of the research (Cheung & Barratt, 2024; Ramsawak et al., 2025).
- **CD38 Inhibitors:**The highest expression of CD38 is on plasma cells with a long life that are the major producers of Gd-IgA1. The use of CD38 inhibitors such as felzartamab is to eliminate these plasma cells that eventually lead to the reduction of IgA-caused immune activity and the relief of kidney injury (Ghozloujeh et al., 2025; Heeger et al., 2024). Felzartamab is under consideration for early-stage clinical trials (Ghozloujeh et al., 2025; Ramsawak et al., 2025).

Protienuria Reduction from Baseline with Different Therapies in IgA Nephropathy

Therapy	Proteinuria Reduction (%)	Comparator
Dapagliflozin	Significant Reduction	Placebo
Sparsentan	49.8% (from baseline)	Irbesartan
Sibeprenlimab (2 mg/kg)	47.20%	Placebo (20.2%)
Sibeprenlimab (4 mg/kg)	58.80%	Placebo (20.2%)
Sibeprenlimab (8 mg/kg)	62.00%	Placebo (20.2%)
Altrasentan	Significant Reduction	Placebo
Iptacopan	Reduced Proteinura	Placebo

Emerging Therapeutic Approaches

The IgAN treatment landscape is changing fast, and there are many new drug therapies that are only in the initial stages of development and that target different elements of disease pathogenesis (Cheung & Barratt, 2024; Mathur et al., 2024; Yang & Xu, 2025). Such therapies are:

- **FcRn Inhibitors**: These drugs block the neonatal Fc receptor that is responsible for antibody recycling and are being tested for the ability to decrease the IgA level in the blood (Filippone et al., 2024).
- **Spleen Tyrosine Kinase Inhibitors**: Fostamatinib, a Syk inhibitor, can help to reduce mesangial inflammation without causing immunosuppression. Subgroup analysis probably indicates that proteinuric patients at high risk may benefit most (Ghozloujeh et al., 2025).
- **Gut Microbiome-Directed Therapies**: As the gut is the source of IgA1, the use of probiotics or fecal microbiota transplantation to change the gut microbiome is under investigation (Cheung & Barratt, 2024).
- **IgA1 Proteases**: Their purpose is to break down the IgA1 molecules that cause the disease.
- **Other Agents:** Nonsteroidal mineralocorticoid receptor antagonists (e.g., finerenone), glucagon-like peptide 1 receptor agonists, and aldosterone synthase inhibitors are also far along in their clinical trials for chronic kidney disease, which will consist of IgAN patients (Cheung & Barratt, 2024).

The steady stream of new therapies from the already approved drugs like TRF budesonide, sparsentan, and iptacopan to those in late-stage clinical trials, is a major step forward in the treatment of IgAN (Ghozloujeh et al., 2025; Selvaskandan et al., 2024; Yang & Xu, 2025). Increasingly, the emphasis is on particularized treatment regimens that selectively target the pathogenic mechanisms, and the ongoing studies intend to investigate the possible use of combinations, as well as to determine their long-term effectiveness and safety (Ramsawak et al., 2025; Yang & Xu, 2025).

Future Directions and Research Gaps

Biomarkers for Disease Activity and Progression

The invention and substantiation of dependable biomarkers are a must-have for the precise gauging of disease activities, prognosis, and therapy monitoring of IgAN (Duan et al., 2024; Selvaskandan et al., 2020). Proteinuria, estimated glomerular filtration rate (eGFR), hypertension, and the Oxford classification criteria are the most established prognostic indicators for the time being; however, the need for more sensitive and specific non-invasive tools has been acknowledged (Filippone et al., 2024; Ramsawak et al., 2025).

One of the clinical biomarkers that can be used in the future is the level of galactose-deficient IgA1, the anti-Gd-IgA1 antibodies, and the IgA/C3 ratio, but of course, these need further confirmation before being brought into everyday practice (Filippone et al., 2024). Gd-IgA1 determination can be a means of diagnosis and a biomarker, but the ways of its measurement are not easily accessible (Filippone et al., 2024).

Several novel molecular platforms such as genome-wide genotyping, RNA sequencing, and mass spectrometry are being utilized to locate the precise markers connected to the immune system activity (Zanoni et al., 2023). The importance of urinary biomarkers is also growing as researchers seek to understand their relationship with the disease features and their ability to detect the onset of disease progression (Yoon et al., 2024). For example, urinary neutrophil gelatinase-associated lipocalin has been recognized as a pioneer biomarker for renal tubulointerstitial damage in IgAN (Ding et al., 2007). Besides monocyte chemotactic protein-1, matrix metalloproteinase-9, and clusterin as urinary markers are also being examined for their prognostic potential (Keskinis et al., 2025). More studies are pinpointing various aspects of complement activation, gut microbiota interaction with Gd-IgA1 expression, microRNAs, imaging, artificial intelligence, and fibrosis markers (Cattran et al., 2023).

Novel Therapeutic Targets

With an ever-expanding knowledge of IgAN pathogenesis, there has been a resultant explosion in interest to develop therapies targeting specific disease mechanisms (Cheung & Barratt, 2024; Ramsawak et al., 2025). Drug development in the future is heavily leaning towards the following promising paths:

- **Complement Inhibitors:** As a consequence of the critical role played by the complement system, the alternative pathway in particular, in IgAN, the complement inhibitors at different stages of trial 2 and 3 are significantly high. (Floege et al., 2021; Ramsawak et al., 2025). The oral factor B inhibitor Iptacopan has already been given accelerated FDA approval. Besides, the disconcerting prospect of the disease could be alleviated by the use of the likes of cemdisiran and ravulizumab (Filippone et al., 2025), which are the terminal pathway inhibitors.
- **B-Cell and Plasma Cell Modulators**: The blockade of B-cell activating factor and a proliferation-inducing ligand is a key step of the path unfolding, on which the pathogenic production of Gd-IgA1 depends, therefore such therapies are essential (Floege et al., 2021; Ghozloujeh et al., 2025; Ramsawak et al., 2025). In trials, the effectiveness of anti-APRIL monoclonal antibodies (such as sibeprenlimab, zigakibart, atacicept) and anti-plasma cell agents, including the CD38 inhibitors felzartamab and mezagitamab, has been evaluated (Ghozloujeh et al., 2025; Ramsawak et al., 2025).
- **Mucosal Immunomodulators**: Targeted-release budesonide is a therapy approved by the FDA that, by direct action on the gut-associated lymphoid tissue, breaks the cycle of Gd-IgA1 production (Ramsawak et al., 2025; Zhou, 2025).
- **Other Emerging Agents**: These are nonsteroidal mineralocorticoid receptor antagonists such as finerenone, glucagon-like peptide 1 receptor agonists and aldosterone synthase inhibitors that are in the late-stage clinical development for chronic kidney disease and may be of help to IgAN patients (Cheung & Barratt, 2024). Apart from that, the combination therapies like SGLT2 inhibitors with endothelin receptor antagonists that are being looked into for extended benefits are (Yang & Xu, 2025).

Personalized Medicine Approaches

IgA nephropathy is a complex disease characterized by differences in geographic prevalence, genetic susceptibility, clinical manifestations, histological changes, pathogenic pathways, and prognosis (Cheung & Barratt, 2024). These differences indicate that a single therapeutic regimen might not work for all patients and thus, the concept of personalized medicine becomes relevant (Cheung & Barratt, 2024).

The objective is to determine the proper medicine for an individual patient at a particular stage of their disease (Cheung & Barratt, 2024). Understanding the genetic factors of IgAN with the recognition of risk loci and epigenetic factors gives the basis for the development of the targeted therapies (Filippone et al., 2024). Besides, the 4-hit model of pathogenesis can be looked at as a map for the directed treatment dependent on the person's disease drivers (Ramsawak et al., 2025).

Present recommendations encourage individualized therapy based on immunologic activity and prognosis (Zanoni et al., 2023). The continuous improvement of ultra-modern molecular technologies and the discovery of definite biomarkers of immune activity will greatly facilitate personalized treatment decisions (Aiello et al., 2023; Zanoni et al., 2023). To be able to better forecast the chance of the disease getting worse is very important for patient advising and for the choosing of therapies that put patients at high risk (Selvaskandan et al., 2024).

Unanswered Questions and Future Studies

Despite the quick advances, a dozen or so critical questions still linger and demand further investigation:

- **Treatment Combinations and Duration**: The question of how to combine the rising number of new treatments and what duration the therapy should be to maintain the optimal long-term results still remains (Ramsawak et al., 2025)?
- **Impact on End-Stage Kidney Disease:** Are the new treatments effectively lowering the rate of progression to ESKD, which is the main cause of about one-third of patients over their lifetime, or is it just a matter of time (Cheung & Barratt, 2024; Ramsawak et al., 2025)?
- **Specific Patient Populations:** The problem of finding the best method of treatment for children with IgAN, patients with late-stage chronic kidney disease, and people who have undergone renal transplantation and have developed recurrent IgAN still remains unsolved (Cheung & Barratt, 2024).
- **Refinement of Classification Systems**: Defining features such as thrombotic microangiopathy, C4d staining, and podocyte abnormalities in the next revisions of the Oxford Classification will be addressed (Filippone et al., 2024).
- **Pathogenesis of Nephritogenic IgA**: More in-depth knowledge about the unique features of nephritogenic IgA and how it causes inflammation is still lacking (Nihei et al., 2023).
- **Diagnostic Challenges**: The distinction between infection-related IgAN and IgA-dominant postinfectious glomerulonephritis is the subject of a debate that needs to be settled (Dabaghi et al., 2021).

- **Cost and Access:** Discussions about the costs and accessibility of the therapy are significant for both patients and clinicians (Ramsawak et al., 2025).
- **Long-term Efficacy and Safety**: It is imperative that the long-term effectiveness and safety of the newly introduced treatments be regularly verified as a prerequisite for their gradual integration into IgAN care (Ghozloujeh et al., 2025; Mikhail, 2024).

Conclusion

IgA nephropathy is a layered autoimmune disorder that involves the deposition of galactose-deficient IgA1 immune complexes in the glomerular mesangium, which causes inflammation and eventually, kidney damage. The disease is fundamentally a "multi-hit" one, as it features abnormal IgA1 glycosylation, the formation of pathogenic immune complexes, mesangial cell activation, and complement activation that lead to glomerular injury and fibrosis in the end (Cheung et al., 2024; Ramsawak et al., 2025; Zhou, 2025).

In terms of clinical manifestations, IgAN can manifest in a variety of symptoms, the most frequent of which are hematuria and proteinuria, and the latter is typically induced by mucosal infections (Aseem & Zheng, 2024; Ramsawak et al., 2025; Taliercio & Mehdi, 2023). A biopsy showing mesangial IgA deposits (Ramsawak et al., 2025; Taliercio & Mehdi, 2023) is the gold standard for diagnosis, and the Oxford Classification serves as an essential histopathological guide in determining the extent of the disease and helping predict the outcome (Pant, 2018; Ramsawak et al., 2025). Prognostic factors such as continuous proteinuria, low eGFR, high blood pressure that is not under control, and certain Oxford scores are significant indicators of the level of risk (Cheung et al., 2024; Zhou, 2025).

The treatment options for IgAN are changing quite fast. The basic therapy for the disease comprises the best supportive care and renin-angiotensin system blockade and, in addition to this, we have quite a few new drugs, like SGLT2 inhibitors and sparsentan for example, that help to both reduce proteinuria and slow down kidney dysfunction (Cheung & Barratt, 2024; Karoui et al., 2023; Ramsawak et al., 2025). Systemic corticosteroids, although can be helpful, are used very cautiously due to the possible side effects, with the targeted-release budesonide being an example of the gut-targeted immunosuppressive agent (Ghozloujeh et al., 2025; Ramsawak et al., 2025). A lot of breakthroughs have been made along the way in terms of targeted drugs that help with the activation of certain inflammatory pathways, like complement blockers (e.g., iptacopan), B-cell and plasma cell modulators (e.g., those binding to BAFF and APRIL), and CD38 inhibitors (Filippone et al., 2024; Ghozloujeh et al., 2025; Ramsawak et al., 2025).

However, even with all this progress, the outstanding issues are the demand for more trustworthy biomarkers that will point to the disease activity as well as the progression, the expected effectiveness of the combination therapies and treatment durations, and the matter of addressing the heterogeneity of the disease by using personalized approaches in medicine (Cheung & Barratt, 2024; Duan et al., 2024). To be able to stop the progression to end-stage renal disease and to improve the expected outcomes for all patients, research on new treatment targets and a thorough understanding of IgAN pathogenesis must go on.

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