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Emerging Therapies and Comprehensive Treatment Approaches for IgA Nephropathy: A Review of Recent Clinical Trials and Future Directions

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Abstract

This paper discusses the latest therapeutic developments and comprehensive approaches to treating IgA nephropathy (IgAN), the most common form of primary glomerulonephritis globally. The review begins by outlining the pathogenesis of IgAN, emphasizing the "multi-hit" hypothesis, where aberrantly glycosylated IgA1 (Gd-IgA1) molecules, autoantibodies, and immune complex deposition in the kidneys drive disease progression. Current treatment strategies focus on supportive care, including blood pressure control and proteinuria reduction using renin-angiotensin system (RAS) blockers. Newer therapeutic approaches are highlighted, such as targeted-release formulations like TRF-budesonide, which delivers corticosteroids to gut-associated lymphoid tissue to minimize systemic side effects. Immunosuppressive treatments, including systemic corticosteroids, mycophenolate mofetil (MMF), and emerging therapies like complement inhibitors (e.g., Eculizumab, Ravulizumab), are explored for their efficacy and safety. B-cell and plasma cell-targeting therapies, complement inhibitors, and personalized medicine approaches represent emerging treatment avenues. Combination therapies, such as corticosteroids with immunosuppressants, are also discussed, aiming to enhance treatment efficacy while minimizing adverse effects. Personalized medicine and the integration of artificial intelligence for optimizing treatment strategies offer promising directions for improving outcomes in patients with IgAN. The review concludes by emphasizing the need for continued research to better understand IgAN's pathogenesis and further develop innovative therapies that prevent progression to end-stage kidney disease.

1. Introduction

1.1 Overview of IgA Nephropathy

1.1.1 Definition and epidemiology

IgA Nephropathy (IgAN), also known as Berger's disease, is recognized as the most common primary glomerulonephritis worldwide, especially in patients undergoing renal biopsy (Gutiérrez et al., 2020). The disease is characterized by the deposition of the immunoglobulin A1 (IgA1) in the glomerular mesangium, which can lead to varying degrees of kidney damage (Pattrapornpisut et al., 2021). The prevalence of IgAN varies geographically, with the highest incidence reported in East Asia, followed by Europe and North America, and is relatively rare in Africa (Zhang & Barratt, 2021). The disease affects individuals of all ages but is most commonly diagnosed in the second and third decades of life, often after an episode of gross hematuria triggered by a respiratory or gastrointestinal infection (Moriyama, 2019).

1.1.2 Pathogenesis and progression

The pathogenesis of IgAN is complex and not fully understood, involving both genetic and environmental factors. The most widely accepted theory is the "multi-hit hypothesis," which suggests a sequence of events leading to the disease: (1) production of aberrantly glycosylated IgA1 molecules, (2) formation of autoantibodies against these IgA1 molecules, (3) formation of immune complexes, and (4) deposition of these complexes in the glomerular mesangium, triggering inflammation and injury (Gutiérrez et al., 2020; Rizk et al., 2019). This mesangial deposition leads to activation of the complement system, particularly the lectin and alternative pathways, which further contributes to kidney damage (Rizk et al., 2019). Genetic studies have identified multiple loci associated with the disease, highlighting the importance of immune regulation and mucosal immunity in its pathogenesis (Pattrapornpisut et al., 2021).

Progression of IgAN can be highly variable. Approximately 20-40% of patients progress to end-stage kidney disease (ESKD) within 20 years of diagnosis (Trimarchi et al., 2022). Factors associated with poor prognosis include persistent proteinuria, hypertension, reduced glomerular filtration rate (GFR) at diagnosis, and certain histopathological features such as the presence of crescents and segmental sclerosis (Kostopoulou et al., 2022). Recent studies have also highlighted the role of systemic

inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), in predicting disease progression (Li et al., 2020).

1.1.3 Clinical presentation and prognosis

Clinically, IgAN can present in various ways, ranging from asymptomatic microscopic hematuria to rapidly progressive glomerulonephritis. The most common initial presentation is episodic macroscopic hematuria, often associated with a respiratory or gastrointestinal infection (Ștefan et al., 2021). Other presentations include persistent microscopic hematuria, proteinuria, nephrotic syndrome, and acute kidney injury (Ștefan et al., 2021). The clinical course of the disease is equally variable, with some patients maintaining stable kidney function for decades, while others progress rapidly to ESKD (Alexander et al., 2020).

The prognosis of IgAN depends on several factors, including the severity of proteinuria, degree of hypertension, and extent of histological damage at the time of diagnosis. The Oxford Classification of IgAN, which includes mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, and tubular atrophy/interstitial fibrosis (MEST score), has been widely adopted to predict the risk of disease progression and guide treatment decisions (Moriyama, 2019). Despite advances in understanding the disease, early identification of individuals at high risk of poor prognosis remains crucial (Mou et al., 2022).

Overall, IgAN is a heterogeneous disease with a broad spectrum of clinical and pathological features. Continuous research is essential to further elucidate its pathogenesis, improve prognostic tools, and develop targeted therapies to prevent progression to ESKD.

2. Current Treatment Strategies

2.1 Supportive Care

2.1.1 Blood pressure control

Effective blood pressure control is fundamental in the management of IgAN due to its direct impact on slowing disease progression and reducing cardiovascular risks. A common target is maintaining blood pressure at or below 130/80 mm Hg, which has been shown to significantly delay the progression to end-stage renal disease (ESRD) (Gleeson et al., 2023). Multiple studies have

demonstrated that achieving optimal blood pressure control can be a crucial component in reducing proteinuria, a key marker of disease activity in IgAN (Maixnerova et al., 2023).

Renin-angiotensin system (RAS) inhibitors, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), are the mainstay for achieving these targets. These medications not only lower blood pressure but also have antiproteinuric effects that are beneficial in managing IgAN (Lennartz et al., 2020). For instance, a study involving normotensive chronic kidney disease (CKD) patients demonstrated that olmesartan and temocapril combination therapy was particularly effective in reducing proteinuria while managing blood pressure (Ye et al., 2020).

2.1.2 Proteinuria reduction

Proteinuria is a critical prognostic marker in IgAN, with higher levels indicating more severe disease and faster progression to ESRD. Reducing proteinuria is a primary goal in IgAN management. Studies have shown that RAS blockade can significantly reduce proteinuria, contributing to better long-term renal outcomes (Roberts, 2023). For example, the STOP-IgAN trial demonstrated that patients maintained on single RAS inhibitor therapy had a stable estimated glomerular filtration rate (eGFR) and reduced proteinuria over a three-year period (Lennartz et al., 2020).

Recent advances have introduced new classes of medications such as sodium-glucose cotransporter 2 inhibitors (SGLT2i), which have shown significant efficacy in reducing proteinuria. In a cohort of Chinese patients with IgAN, SGLT2 inhibitors were found to reduce proteinuria by 27.1% at six months, even in patients already receiving full-dose RAS inhibitors (Dong et al., 2023).

2.1.3 Lifestyle modifications

Lifestyle modifications are essential adjuncts to pharmacological treatment in IgAN. Key recommendations include dietary sodium restriction, weight management, and smoking cessation, all of which contribute to better blood pressure control and reduced proteinuria. A healthy lifestyle can mitigate the progression of CKD and improve overall cardiovascular health, which is particularly important given the increased cardiovascular risk associated with IgAN (Floege et al., 2021).

Dietary sodium restriction is emphasized to enhance the effectiveness of RAS inhibitors. Lower

sodium intake reduces blood pressure and proteinuria, thereby slowing disease progression (Roberts, 2023). Smoking cessation is equally critical, as smoking is an independent risk factor for accelerated renal function decline (Chub, 2023).

2.1.4 Renin-angiotensin system blockers

RAS blockers, including ACEIs and ARBs, are foundational in the management of IgAN due to their dual role in lowering blood pressure and reducing proteinuria. Studies consistently show that these agents can significantly delay disease progression and improve renal outcomes (Bagchi et al., 2021).

For instance, a comprehensive review of 17 randomized controlled trials (RCTs) involving 1,006 patients indicated that co-administration of ACEIs and ARBs was the most effective regimen for reducing proteinuria and blood pressure (Huo et al., 2021). Furthermore, the AIIMS Primary IgA Nephropathy Cohort (APPROACH) study reported that meticulous supportive therapy with optimal use of ACEIs/ARBs achieved remission in approximately half of the IgAN patients studied (Bagchi et al., 2021).

Additionally, the combination of olmesartan and temocapril has been shown to have the highest probability of being the most effective treatment for reducing proteinuria in normotensive CKD patients, which includes those with IgAN (Ye et al., 2020).

As showed in Figure 1, supportive care, encompassing blood pressure control, proteinuria reduction, lifestyle modifications, and the use of RAS blockers, remains the cornerstone of IgAN management. These strategies are crucial for slowing disease progression and improving patient outcomes. Future research should continue to explore the combination of these therapies with emerging treatments to optimize care for patients with IgAN.

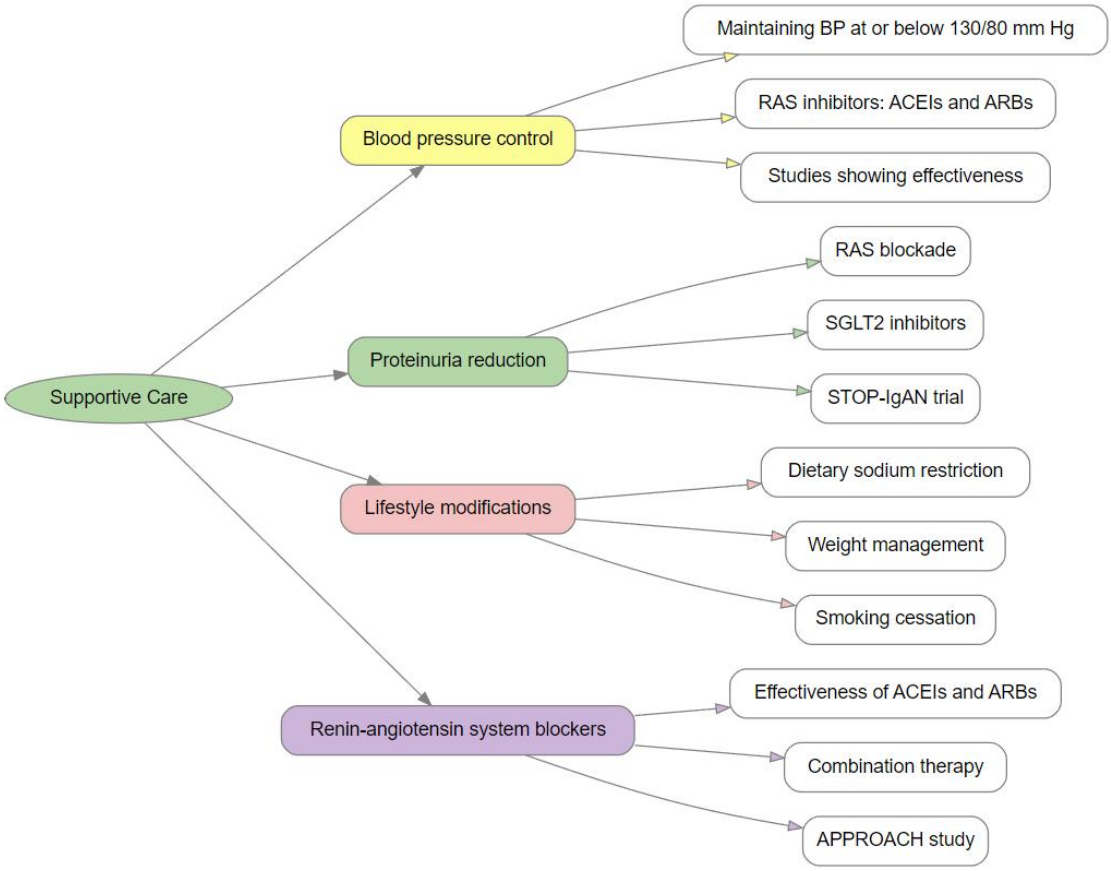

Figure 1 Current Treatment Strategies of IgA Nephropathy

2.2 Immunosuppressive Therapy

2.2.1 Systemic corticosteroids

Systemic corticosteroids have long been a cornerstone in the management of IgAN due to their potent anti-inflammatory and immunosuppressive properties. The efficacy and safety of systemic corticosteroids, however, remain subjects of ongoing debate and investigation.

(1) Efficacy of Corticosteroids in IgAN

Recent studies have provided mixed results regarding the efficacy of systemic corticosteroids in IgAN. The TESTING trial, which evaluated the use of methylprednisolone, demonstrated that corticosteroid treatment significantly reduced the risk of a 40% decline in estimated glomerular filtration rate (eGFR), kidney failure, and kidney death, alongside a sustained decrease in proteinuria compared with placebo. The study noted that while serious adverse events were more frequent with a full-dose regimen, they were less common with a reduced dose regimen (Ghaddar et al., 2023).

Another important study by Floege et al. (2021) indicated that systemic corticosteroid therapy should be considered only for a few months, particularly in patients with declining GFR. The potential benefits must be weighed against the significant risk of adverse events, which increase markedly as GFR declines (Floege et al., 2021).

(2) Safety Concerns

The safety profile of systemic corticosteroids is a significant concern. Systemic corticosteroids are associated with a range of adverse effects, including increased risk of infections, hyperglycemia, hypertension, and osteoporosis. A systematic review and meta-analysis by Major et al. (2021) highlighted the frequency of these adverse events in patients treated for autoimmune diseases, including IgAN (Major et al., 2021).

In a retrospective study, patients with IgAN treated with systemic corticosteroids showed a significant reduction in proteinuria and preservation of renal function over a 24-month period. However, the incidence of adverse events such as infections was notable (Ismail et al., 2020).

(3) Targeted-Release Budesonide

To mitigate the adverse effects associated with systemic corticosteroids, targeted-release formulations of budesonide have been developed. These formulations are designed to release the drug in the distal ileum and proximal colon, areas rich in gut-associated lymphoid tissue implicated in IgAN pathogenesis. Studies have shown that targeted-release budesonide significantly reduces proteinuria and preserves renal function with a lower incidence of systemic side effects compared to systemic corticosteroids (Liao et al., 2023).

A phase III trial evaluating the efficacy of targeted-release budesonide reported a significant reduction in short-term proteinuria, leading to its accelerated FDA approval. This formulation represents a promising alternative to systemic corticosteroids for high-risk IgAN patients (Ghaddar et al., 2023).

2.2.2 Mycophenolate mofetil

Mycophenolate mofetil (MMF) is another immunosuppressive agent explored for its potential benefits in IgAN treatment. MMF inhibits lymphocyte proliferation by blocking inosine

monophosphate dehydrogenase, an enzyme critical for the de novo synthesis of guanine nucleotides.

(1) Efficacy of MMF in IgAN

The efficacy of MMF in treating IgAN has been evaluated in several studies with varying results. In Asian populations, MMF has shown promise in reducing proteinuria and preserving renal function. A study by Kunter et al. (2023) highlighted the potential of MMF, particularly in patients of Asian descent, suggesting that ethnic and genetic factors might influence treatment response (Kunter et al., 2023).

In a 10-year real-world study, the combination of corticosteroids with MMF was compared to corticosteroids with cyclophosphamide (CTX) in patients with stage 3 and 4 chronic kidney disease (CKD) and significant proteinuria. The study found that the combination of corticosteroids and MMF did not significantly reduce the risk of a combined event (a ≥50% decrease in eGFR, end-stage renal disease, or death) compared to uncontrolled supportive care. However, the combination of corticosteroids and CTX did show a significant reduction in these risks (Jia et al., 2022).

(2) Safety Profile of MMF

The safety profile of MMF is generally considered favorable compared to other immunosuppressive agents, but it is not without risks. Common side effects include gastrointestinal disturbances, increased risk of infections, and hematologic abnormalities. A study by Delbet et al. (2021) noted that while MMF can be effective, its use must be carefully monitored to mitigate these risks (Delbet et al., 2021).

2.2.3 Risks and benefits of immunosuppression

The decision to use immunosuppressive therapy in IgAN involves a careful balance of risks and benefits. While these therapies can significantly reduce proteinuria and slow the progression of renal disease, they are associated with considerable risks that must be managed.

(1) Benefits of Immunosuppressive Therapy

Proteinuria Reduction: Both corticosteroids and MMF have been shown to significantly reduce proteinuria in patients with IgAN, which is a critical marker of disease progression (Ghaddar et al., 2023), (Jia et al., 2022).

Preservation of Renal Function: Immunosuppressive therapy can help preserve renal function, as evidenced by reductions in the decline of eGFR and delays in the onset of end-stage renal disease (ESRD) (Ismail et al., 2020), (Feng et al., 2022).

(2) Risks of Immunosuppressive Therapy

Infections: The immunosuppressive effects of these therapies increase the risk of infections. This risk is particularly high with systemic corticosteroids, which can lead to serious infections and other complications (Major et al., 2021).

Metabolic and Cardiovascular Effects: Long-term use of corticosteroids is associated with metabolic side effects such as hyperglycemia, weight gain, and hypertension, which can exacerbate the underlying renal disease (Ghaddar et al., 2023).

Gastrointestinal Disturbances: MMF can cause significant gastrointestinal side effects, which can limit its use in some patients (Delbet et al., 2021).

Hematologic Abnormalities: Both corticosteroids and MMF can cause hematologic issues, including leukopenia and anemia, which require regular monitoring (Jia et al., 2022).

As shown in Figure 2, The use of systemic corticosteroids and mycophenolate mofetil in the treatment of IgA nephropathy offers significant benefits in terms of proteinuria reduction and renal function preservation. However, these benefits must be carefully balanced against the potential risks, including serious infections, metabolic disturbances, and gastrointestinal issues. Targeted-release formulations like budesonide present a promising alternative, potentially offering efficacy with fewer systemic side effects. Ongoing research and clinical trials will continue to refine these therapies and develop new strategies to manage IgAN more effectively.

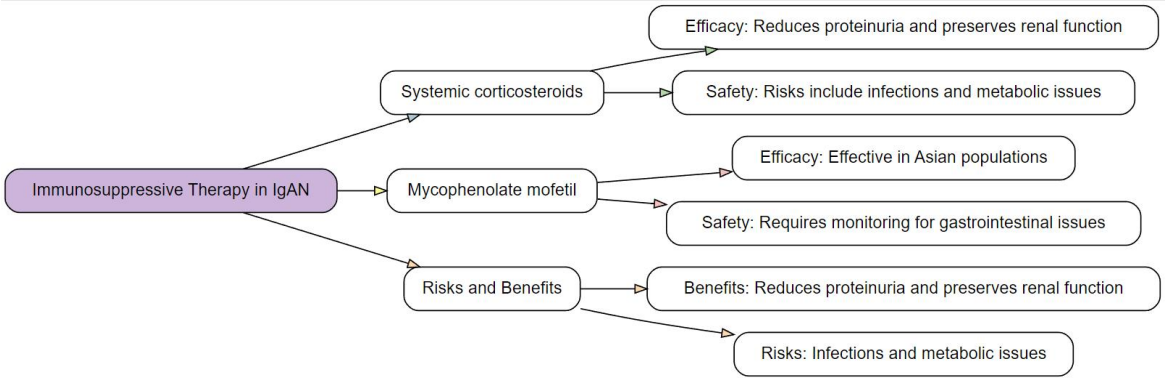

Figure 2 Immunosuppressive Therapy in IgA Nephropathy

3. Emerging Therapies

3.1 Targeted Release Formulations

3.1.1 Introduction to Targeted Release Formulations

Targeted release formulations (TRFs) represent a significant advancement in the treatment of IgAN, primarily aimed at minimizing systemic side effects while maximizing therapeutic efficacy at the disease site. These formulations are designed to deliver medication directly to the gut-associated lymphoid tissue (GALT), which plays a crucial role in the pathogenesis of IgAN. The primary focus has been on budesonide, a corticosteroid, reformulated to target the distal ileum, reducing its systemic absorption and associated side effects (Liao et al., 2023).

3.1.2 Mechanism of Action

Budesonide is a potent corticosteroid with strong anti-inflammatory properties. The targeted-release formulation of budesonide (TRF-budesonide) is specifically designed to release the drug in the ileum, targeting the GALT where the pathogenic mucosal immune response in IgAN is believed to originate. This localized release minimizes systemic exposure and thereby reduces the risk of systemic side effects typically associated with corticosteroids (Kunter et al., 2023). Studies have shown that TRF-budesonide effectively reduces proteinuria and stabilizes renal function by suppressing the immune responses in the gut that contribute to kidney damage (Liao et al., 2023).

3.1.3 Clinical Trials and Efficacy

NEFIGAN and NefIgArd Trials

The efficacy of TRF-budesonide was initially demonstrated in the NEFIGAN trial, a phase 2b study that included patients with IgAN who were at high risk of disease progression. The trial showed that TRF-budesonide significantly reduced proteinuria and stabilized renal function compared to placebo (Molyneux et al., 2022). This was followed by the NefIgArd trial, a phase 3 study designed to confirm these findings. Part A of the NefIgArd trial demonstrated a significant reduction in the urine protein-to-creatinine ratio (UPCR) and preservation of the estimated glomerular filtration rate (eGFR) with TRF-budesonide treatment compared to placebo (von Vietinghoff, 2023).

3.1.4 Comparison with Systemic Corticosteroids

Systemic corticosteroids have been a mainstay in the treatment of IgAN due to their potent anti-inflammatory effects. However, their use is limited by significant side effects, including increased risk of infections, hyperglycemia, and osteoporosis. In contrast, TRF-budesonide offers a targeted approach, delivering the drug directly to the site of immune activation in the gut, thereby reducing these systemic risks (Ghaddar et al., 2023). This localized treatment has shown to maintain the beneficial effects of corticosteroids on kidney function and proteinuria while significantly reducing adverse events (Toumaj et al., 2023).

3.1.5 Novel Targeted Release Formulations

In addition to budesonide, other innovative targeted release formulations are being explored. A notable example is the use of orange-derived extracellular vesicles (EVs) encapsulated with dexamethasone, which have shown promising results in reducing proteinuria and renal lesions in IgAN by targeting intestinal lymphocytes (Zhang et al., 2022). This approach leverages the natural targeting properties of EVs to deliver anti-inflammatory drugs directly to the gut, offering a novel and biofriendly therapeutic strategy for IgAN.

3.1.6 Future Directions and Research

Ongoing research is focused on further improving the efficacy and safety profiles of targeted release formulations. The development of more sophisticated drug delivery systems, such as polymer-coated nanoparticles and other biodegradable carriers, is being investigated to enhance the precision and effectiveness of these treatments (Kumeria et al., 2020). Additionally, the integration of artificial intelligence in drug development and personalized medicine is expected to play a crucial role in identifying the most suitable candidates for targeted therapies, optimizing dosage regimens, and predicting treatment responses (Geng, 2020).

Targeted release formulations, particularly TRF-budesonide, represent a promising therapeutic approach for IgAN. By focusing on the gut-kidney axis and minimizing systemic exposure, these formulations offer significant advantages over traditional systemic therapies. Ongoing clinical trials and future research are likely to expand the use of these innovative treatments, providing more effective and safer options for patients with IgAN.

3.2 Complement Inhibitors

3.2.1 Introduction to Complement System in IgA Nephropathy

The complement system is a crucial part of the immune response, consisting of a series of proteins that work to eliminate pathogens. However, in diseases such as IgAN, an overactive or improperly regulated complement system can lead to kidney damage. The complement system can be activated through three pathways: classical, lectin, and alternative. Each pathway converges on the activation of C3 and subsequently C5, which plays a pivotal role in the formation of the membrane attack complex (MAC), leading to cell lysis and inflammation (Duval et al., 2023; Caravaca-Fontán et al., 2023).

3.2.2 Pathogenesis of Complement Activation in IgAN

In IgAN, complement activation primarily occurs through the alternative and lectin pathways. The deposition of galactose-deficient IgA1 (Gd-IgA1) in the glomeruli leads to the formation of immune complexes that activate these pathways, causing inflammation and subsequent kidney damage (Duval et al., 2023). Glomerular C3 deposition has been correlated with disease progression, indicating the critical role of the complement system in IgAN pathogenesis (Caravaca-Fontán et al., 2023; Wooden et al., 2023).

Recent studies have also highlighted the role of factor H–related proteins, particularly factor H-related protein-1 (FHR-1) and factor H-related protein-5 (FHR-5), which can dysregulate complement activation and contribute to disease severity. Additionally, the lectin pathway component C4d has been associated with more severe histologic disease activity and faster progression to kidney failure (Caravaca-Fontán et al., 2023).

3.2.3 Complement Inhibitors in Clinical Use

Several complement inhibitors are currently under investigation or have been approved for the treatment of IgAN. These inhibitors target various components of the complement system to prevent the cascade of activation that leads to kidney damage.

(1) **C5 Inhibitors:** Eculizumab and Ravulizumab are monoclonal antibodies that inhibit C5, preventing the formation of the MAC. These agents have been effective in other complement-mediated diseases and are being evaluated in IgAN (Werion & Rondeau, 2022;

Caravaca-Fontán et al., 2023). Early studies have shown promising results in reducing proteinuria and stabilizing kidney function (Bruchfeld et al., 2022).

(2) **C5a Receptor Inhibitors:** Avacopan is a selective inhibitor of the C5a receptor, which blocks the inflammatory effects of C5a without affecting the formation of MAC. A pilot study has shown that avacopan can significantly reduce proteinuria in patients with IgAN, suggesting its potential as a treatment option (Bruchfeld et al., 2022).

(3) **Factor B Inhibitors:** Iptacopan and Ionis-FB-LRX target factor B, a critical component of the alternative pathway. By inhibiting factor B, these agents prevent the formation of the C3 convertase, thereby reducing downstream complement activation. Clinical trials are ongoing to assess their efficacy in IgAN (Caravaca-Fontán et al., 2023).

(4) **C3 Inhibitors:** Pegcetacoplan, a C3 inhibitor, aims to block all pathways of complement activation by preventing the cleavage of C3. This broad approach may offer a significant therapeutic advantage in diseases with multifactorial complement involvement (Wooden et al., 2023).

3.2.4 Clinical Trials and Emerging Therapies

Numerous clinical trials are currently underway to evaluate the safety and efficacy of these complement inhibitors in IgAN. These trials are crucial for determining the best therapeutic strategies and understanding the long-term outcomes of complement inhibition in this patient population.

(1) **Eculizumab and Ravulizumab:** Studies have shown that these C5 inhibitors can reduce proteinuria and slow the progression of kidney damage in IgAN. However, their long-term efficacy and safety are still under investigation (Werion & Rondeau, 2022).

(2) **Avacopan:** The open-label pilot study on avacopan indicated significant reductions in proteinuria and potential improvements in renal outcomes, suggesting its promise as a therapeutic option (Bruchfeld et al., 2022).

(3) **Iptacopan and Ionis-FB-LRX:** These factor B inhibitors are in the early stages of clinical trials. Preliminary data suggest they could effectively reduce complement activation and protect against kidney damage in IgAN (Caravaca-Fontán et al., 2023).

(4) **Pegcetacoplan:** This C3 inhibitor is being tested in clinical trials to evaluate its efficacy in

reducing the overall activation of the complement system. Initial results are promising, showing a reduction in complement activity and improved renal function (Wooden et al., 2023).

3.2.5 Future Directions and Challenges

The development of complement inhibitors for IgAN represents a significant advancement in the treatment of this disease. However, several challenges remain. Determining the optimal timing and duration of treatment, managing potential side effects, and understanding the long-term impacts of complement inhibition are critical areas for future research (Salvadori, 2023).

Moreover, the heterogeneity of IgAN requires personalized treatment approaches. Biomarkers that can predict response to complement inhibitors and identify patients who would benefit most from these therapies are needed (Juan et al., 2022). Additionally, combining complement inhibitors with other therapeutic strategies, such as immunosuppressants or renin-angiotensin system blockers, may offer synergistic benefits and improve patient outcomes (El Karoui et al., 2023).

3.3 B-Cell and Plasma Cell Targeting

3.3.1 Overview and Importance

B-cell and plasma cell targeting therapies are pivotal in the management of IgAN due to their roles in the production of pathogenic IgA antibodies. IgAN is characterized by the deposition of immune complexes in the glomeruli, primarily composed of galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1 autoantibodies (Maixnerova et al., 2022). B cells and plasma cells, which produce these autoantibodies, are therefore critical targets for therapeutic interventions aimed at reducing antibody production and subsequent kidney damage.

3.3.2 B-Cell Depletion Therapies

B-cell depletion therapies have shown promise in the treatment of IgAN. Rituximab, an anti-CD20 monoclonal antibody, depletes B cells by targeting CD20, a surface marker present on B cells. However, this approach also leads to the depletion of regulatory B cells, which can result in adverse effects and limited efficacy in some patients (Merino-Vico et al., 2023). Recent studies suggest that more selective B-cell depletion strategies may offer improved outcomes. For instance, novel chimerized IgA CD20 antibodies have been developed, showing enhanced neutrophil-mediated killing

of B cells and reduced B cell numbers in vivo (Evers et al., 2020).

3.3.3 Plasma Cell Targeting

Plasma cells, particularly long-lived plasma cells (LLPCs) in the bone marrow, are resilient to many conventional therapies. However, advancements in proteasome inhibitors (PIs) have provided new avenues for targeting these cells. Carfilzomib, a second-generation irreversible PI, has demonstrated efficacy in eliminating bone marrow plasma cells and reducing antibody levels in IgAN patients (Woodle et al., 2020). Furthermore, combining PIs with other therapeutic agents targeting plasma cell survival pathways could enhance treatment efficacy and prevent antibody rebound (Komissarov et al., 2023).

3.3.4 BAFF and APRIL Inhibition

B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are cytokines essential for B-cell maturation, function, and survival. Elevated levels of BAFF and APRIL have been associated with worse clinical outcomes in IgAN (Molyneux et al., 2020). Targeting these cytokines can disrupt the pathological B-cell and plasma cell activity. NEFECON®, a targeted-release formulation of budesonide, has shown to significantly reduce serum levels of BAFF and soluble BCMA (B-cell maturation antigen), thereby modulating key regulators of B-cell maturation in IgAN (Molyneux et al., 2020).

BION-1301, a fully blocking antibody targeting APRIL, has demonstrated promising results in preclinical studies by reducing serum levels of immunoglobulins and APRIL, supporting its continued clinical development for IgAN treatment (Kreijtz et al., 2020).

3.3.5 Targeting Specific B-Cell Subsets

Selective targeting of specific B-cell subsets offers a potential for higher efficacy and reduced adverse effects. Membrane-bound IgA1 (mIgA1) specific antibodies, such as KM4641 and KM4644, have been developed to selectively deplete mIgA1-expressing B cells without affecting soluble IgA1, thereby reducing the risk of adverse effects (Yamasaki et al., 2022).

Another approach involves targeting NF-κB signaling in B lineage cells. Inhibitors of Inhibitor-of-κB-kinase-β (IKKβ) and NF-κB inducing kinase (NIK) have shown efficacy in reducing

B cell proliferation, differentiation into plasmablasts, and antibody production (Merino-Vico et al., 2023).

3.3.6 Combination Therapies and Nanomedicines

Combination therapies that target multiple pathways involved in B-cell and plasma cell survival and function may enhance treatment outcomes. For example, combining BAFF and APRIL inhibitors with other immunomodulatory agents could provide synergistic effects in reducing pathogenic antibody levels and improving clinical outcomes (Castro-Dopico et al., 2020).

Nanomedicines offer a novel approach to B-cell targeting. Polylactic acid nanoparticles encapsulating JAK inhibitors, such as baricitinib, have shown potential in selectively targeting B cells and reducing their activation and proliferation (Álvarez et al., 2023). This approach could enhance the delivery and efficacy of therapeutic agents while minimizing systemic toxicity.

3.3.7 Future Directions

Future research should focus on the development and clinical evaluation of novel agents targeting B cells and plasma cells in IgAN. The identification of new molecular targets and the use of advanced drug delivery systems, such as nanocarriers, will be crucial in optimizing these therapies. Ongoing clinical trials are expected to provide valuable insights into the safety and efficacy of these innovative treatment strategies.

The targeting of B cells and plasma cells in IgAN represents a promising therapeutic approach to reduce the production of pathogenic antibodies and mitigate kidney damage. Advances in selective B-cell depletion, proteasome inhibition, BAFF and APRIL targeting, and the development of novel nanomedicines have opened new avenues for effective treatment. Continued research and clinical trials will be essential in refining these therapies and integrating them into comprehensive treatment strategies for IgAN.

Table 1. Drugs, Targets, And Mechanisms Of Emerging Therapies in IgAN

Drug	Target	Mechanism of Action
TRF-budesonide	Gut-associated lymphoid tissue (GALT)	Delivers medication directly to GALT to minimize systemic side effects.

	Ileum	Releases budesonide in the ileum to suppress immune responses in the gut.
Eculizumab	C5	Inhibits C5 to prevent the formation of the membrane attack complex (MAC).
Ravulizumab	C5	Inhibits C5 to prevent the formation of the membrane attack complex (MAC).
Avacopan	C5a receptor	Selective inhibition of the C5a receptor to block inflammatory effects of C5a.
Iptacopan	Factor B	Inhibits factor B to prevent the formation of C3 convertase and reduce complement activation.
Ionis-FB-LRX	Factor B	Inhibits factor B to prevent the formation of C3 convertase and reduce complement activation.
Pegcetacoplan	C3	Inhibits C3 to block all pathways of complement activation.
Rituximab	CD20 on B cells	Depletes B cells by targeting CD20, including regulatory B cells.
Carfilzomib	Plasma cells	Targets plasma cells, reducing antibody levels.
NEFECON®	BAFF and soluble BCMA	Reduces serum levels of BAFF and soluble BCMA, modulating B-cell maturation.
BION-1301	APRIL	Fully blocks APRIL, reducing serum levels of immunoglobulins.
KM4641	mIgA1-expressing B cells	Selectively depletes mIgA1-expressing B cells without affecting soluble IgA1.
KM4644	mIgA1-expressing B cells	Selectively depletes mIgA1-expressing B cells without affecting soluble IgA1.
Polylactic acid nanoparticles with JAK inhibitors	B cells	Encapsulates JAK inhibitors to selectively target B cells, reducing activation and proliferation.

4. Comprehensive Treatment Approaches

4.1 Combination Therapies

4.1.1 Introduction to Combination Therapies for IgA Nephropathy

Combination therapies involve the use of multiple therapeutic agents that work through different mechanisms to treat IgAN more effectively than single-drug therapies. These approaches aim to maximize therapeutic efficacy while minimizing adverse effects, potentially improving patient outcomes significantly. This section explores various combination therapies, detailing their

mechanisms, efficacy, and the latest research findings.

4.1.2 Corticosteroids Combined with Immunosuppressants

One common combination therapy involves corticosteroids and immunosuppressive agents such as mycophenolate mofetil (MMF) or cyclophosphamide (CTX). Studies have demonstrated the potential benefits of these combinations, particularly in patients with severe proteinuria and declining renal function.

Ma et al. (2020) examined the efficacy of low-dose corticosteroids combined with oral cyclophosphamide in patients with stage 3 or 4 chronic kidney disease and significant proteinuria. This retrospective study showed that the combination therapy significantly reduced the risk of progression to end-stage renal disease (ESRD) compared to supportive care alone. Moreover, patients receiving the combination therapy had a better renal survival rate and fewer adverse events compared to those on corticosteroids alone (Ma et al., 2020).

Similarly, a study by Fontana et al. (2020) compared the efficacy of different immunosuppressive regimens, including corticosteroids combined with either mycophenolate mofetil or azathioprine. The results indicated that the addition of these immunosuppressants did not significantly improve outcomes over corticosteroids alone in terms of proteinuria reduction and renal function preservation (Fontana et al., 2020).

4.1.3 Renin-Angiotensin System Blockers and Immunosuppressive Agents

Renin-angiotensin system (RAS) blockers, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), are often combined with immunosuppressive agents to enhance treatment efficacy. The combination aims to reduce proteinuria and protect renal function more effectively than either treatment alone.

A Bayesian network meta-analysis by Huo et al. (2021) evaluated the relative effects of ACEIs, ARBs, and their combination in patients with IgAN. The study found that the co-administration of ACEIs and ARBs had the highest probability of being the most effective therapy for reducing proteinuria and blood pressure. However, ACEIs alone were found to be more renoprotective (Huo et al., 2021).

4.1.4 Emerging Combination Therapies

Emerging combination therapies are focusing on novel agents that target different pathogenic pathways involved in IgAN. These include the use of agents like budesonide, a targeted release corticosteroid, in combination with other drugs to modulate immune responses more effectively.

Roberts (2023) discussed new formulations of immunosuppressive therapies, including delayed-release budesonide with targeted release in the lower small intestine, where galactose-deficient IgA1 (Gd-IgA1) production occurs. This approach aims to reduce proteinuria and sustain eGFR levels during active treatment periods. Additionally, the dual endothelin A receptor (ETA) and angiotensin II receptor type 1 (AT1) blocker sparsentan showed promising results in reducing proteinuria compared to irbesartan, highlighting its potential as part of combination therapy (Roberts, 2023).

4.1.5 Complement Inhibitors and Other Novel Agents

The role of complement inhibitors in combination therapies is gaining attention due to their potential in targeting the immune complex deposition and inflammation pathways involved in IgAN. Rizk et al. (2019) highlighted the significance of complement proteins, particularly C5 inhibitors like eculizumab, in treating IgAN. These agents, when combined with other treatments, can provide a comprehensive approach to managing the disease by reducing the activation of the complement cascade (Rizk et al., 2019).

Additionally, targeting B-cells and plasma cells involved in the production of pathogenic antibodies is another promising approach. Maixnerova et al. (2022) proposed therapies that focus on depleting CD38-positive plasma cells, which are the source of pathogenic antibodies in IgAN. This strategy, when used in combination with other immunosuppressive agents, holds promise for modifying the course of the disease (Maixnerova et al., 2022).

4.1.6 Clinical Trials and Future Directions

Several clinical trials are underway to evaluate the efficacy of various combination therapies in IgAN. The ongoing research aims to refine these approaches, ensuring optimal dosing regimens and minimizing adverse effects. For instance, the DAPA-CKD trial examined the effects of dapagliflozin,

a sodium-glucose cotransporter-2 inhibitor, in combination with standard care for patients with IgAN. The study showed a significant reduction in the risk of chronic kidney disease progression with a favorable safety profile (Wheeler et al., 2021).

Another notable study is the Phase II trial of atacicept, a TACI-Ig fusion protein that inhibits B-cell-stimulating factors BLyS and APRIL. Interim analysis results demonstrated a dose-dependent reduction in serum immunoglobulins and proteinuria, suggesting atacicept's potential as part of a combination therapy for IgAN (Barratt et al., 2020).

Combination therapies represent a promising approach for the treatment of IgAN, offering the potential to improve patient outcomes by targeting multiple pathogenic pathways simultaneously. The integration of corticosteroids with immunosuppressive agents, RAS blockers, complement inhibitors, and novel targeted therapies is being actively researched, with encouraging results from recent studies. Continued research and clinical trials will be essential in refining these therapies, ensuring their efficacy and safety for patients with IgAN.

Table 2. Mechanism And Key Findings Of Combination Therapies in IgAN

Therapy Combination	**Mechanism of Action**	**Key Findings**
Corticosteroids + Cyclophosphamide (CTX)	Immunosuppression	Reduces risk of ESRD progression; better renal survival.
Corticosteroids + Mycophenolate mofetil (MMF) or Azathioprine	Immunosuppression	Mixed results; not significantly better than corticosteroids alone.
ACEIs + ARBs	Blood pressure and proteinuria reduction	Co-administration most effective for reducing proteinuria and BP.
Delayed-release Budesonide	Targeted corticosteroid release in the intestine	Targets Gd-IgA1 production; reduces proteinuria and sustains eGFR.
Sparsentan	Dual ETA and AT1 receptor blockade	Reduces proteinuria more effectively than irbesartan.
Complement Inhibitors (e.g., Eculizumab)	Complement cascade inhibition	Reduces complement activation; potential for combination use.
CD38-positive Plasma Cells Depletion	Antibody production reduction	Depletes plasma cells producing pathogenic antibodies.
Dapagliflozin	SGLT2 inhibition	Reduces CKD progression risk; favorable safety profile.
Atacicept	BLyS and APRIL	Reduces serum immunoglobulins

	inhibition	and proteinuria.

4.2 Personalized Medicine

4.2.1 Introduction to Personalized Medicine in IgA Nephropathy

Personalized medicine, also known as precision medicine, tailors medical treatment to the individual characteristics of each patient. In IgAN, this approach is particularly promising due to the disease's heterogeneity in clinical presentation and progression. Personalized medicine involves the use of genetic, biomarker, phenotypic, or psychosocial characteristics to identify the best therapeutic approach for each patient. This section explores the recent advancements and applications of personalized medicine in the treatment of IgAN.

4.2.2 Genetic and Molecular Profiling

Recent advancements in genetic and molecular profiling have paved the way for personalized treatment approaches in IgAN. Studies have identified various genetic markers associated with the disease, which can help predict disease progression and response to therapy. For example, the identification of genetic polymorphisms in genes related to the immune response and kidney function has been crucial in understanding individual variations in IgAN progression and treatment outcomes (Gutiérrez et al., 2020).

The International IgAN Prediction Tool, which uses genetic and clinical data to predict the risk of disease progression, has demonstrated significant improvements in treatment decision-making compared to traditional methods based solely on proteinuria levels (Barbour et al., 2020).

4.2.3 Biomarker-Based Treatment Strategies

Biomarkers are critical in the personalized management of IgAN. Serum levels of galactose-deficient IgA1 (Gd-IgA1), for instance, have been shown to correlate with disease severity and progression, making them valuable for tailoring treatments (Kreijtz et al., 2020).

The use of BION-1301, a humanized monoclonal antibody that targets a proliferation-inducing ligand (APRIL), exemplifies the application of biomarkers in personalized medicine. BION-1301 reduces levels of Gd-IgA1, thereby mitigating the formation of nephritogenic immune complexes

and reducing kidney inflammation (Barratt et al., 2022).

4.2.4 Risk Stratification and Tailored Therapies

Risk stratification based on clinical and histological parameters is essential for individualized treatment plans. The Oxford Classification of IgAN, which includes histological findings such as mesangial hypercellularity and segmental glomerulosclerosis, helps identify patients at higher risk for progression and tailor treatments accordingly (Gutiérrez et al., 2020).

Additionally, integrating non-invasive biomarkers such as urine proteomics and genomics into clinical practice can further enhance risk stratification and treatment personalization. These biomarkers can provide insights into the underlying pathophysiological mechanisms and predict responses to specific therapies (Kunter et al., 2023).

4.2.5 Pharmacogenomics and Drug Response

Pharmacogenomics studies how genes affect a person's response to drugs, which is crucial for optimizing drug efficacy and minimizing adverse effects in IgAN. For instance, variations in the genes encoding for drug-metabolizing enzymes and drug targets can influence the response to immunosuppressive therapies such as corticosteroids and mycophenolate mofetil (Peng et al., 2021).

Incorporating pharmacogenomic testing into clinical practice can help identify patients who are likely to benefit from specific treatments and those who are at risk for adverse drug reactions. This approach not only improves treatment outcomes but also reduces healthcare costs by avoiding ineffective therapies (Selvaskandan et al., 2022).

4.2.6 Personalized Immunosuppressive Therapy

Immunosuppressive therapy remains a cornerstone in the management of IgAN, especially in high-risk patients. Personalized approaches to immunosuppression involve tailoring the type, dose, and duration of immunosuppressive agents based on individual patient characteristics and risk profiles. For instance, patients with specific genetic markers or high levels of certain biomarkers may respond better to targeted therapies such as rituximab or complement inhibitors (El Karoui et al., 2023).

Furthermore, the use of personalized immunosuppressive regimens can minimize the risk of adverse

effects, which are a significant concern with traditional high-dose corticosteroid therapy. Personalized dosing schedules and monitoring can help achieve the desired therapeutic outcomes with fewer side effects (Floege et al., 2021).

4.2.7 Integration of Artificial Intelligence

Artificial intelligence (AI) and machine learning algorithms are becoming increasingly important in personalized medicine. These technologies can analyze vast amounts of clinical, genetic, and biomarker data to identify patterns and predict treatment responses. AI can assist clinicians in making evidence-based decisions tailored to the individual patient, improving the accuracy and efficiency of personalized treatment plans (Geng, 2020).

AI-driven predictive models, such as the International IgAN Prediction Tool, are already being used to enhance personalized care by forecasting disease progression and optimizing treatment strategies (Barbour et al., 2020).

4.2.8 Future Directions

The future of personalized medicine in IgAN lies in the continued integration of genetic, biomarker, and clinical data to refine treatment strategies. Ongoing research into novel biomarkers and therapeutic targets will further enhance the ability to tailor treatments to individual patients. Additionally, the development of non-invasive diagnostic tools will make it easier to monitor disease progression and treatment response, facilitating timely adjustments to therapeutic regimens (Wang et al., 2021).

In conclusion, personalized medicine offers a promising approach to the management of IgAN, with the potential to improve patient outcomes significantly. By leveraging advances in genetic and molecular profiling, biomarker discovery, pharmacogenomics, and artificial intelligence, personalized treatment strategies can be developed to meet the unique needs of each patient, ultimately leading to better clinical outcomes and quality of life.

5. Discussion and Perspective

The landscape of IgA Nephropathy (IgAN) treatment is continuously evolving, spurred by advancements in molecular biology, pharmacology, and clinical research. Future research directions

must address several key areas to enhance our understanding and management of IgAN more effectively:

5.1 Elucidation of Pathogenesis

5.1.1 Genetic and Epigenetic Factors

One of the most significant areas for future research in IgAN is the identification of genetic loci and epigenetic modifications contributing to disease susceptibility and progression. Studies have already identified several genetic markers associated with IgAN, but there is a need for comprehensive genome-wide association studies (GWAS) and epigenome-wide association studies (EWAS) to uncover additional genetic and epigenetic factors. Understanding these elements will enable the development of targeted therapies and personalized treatment plans, tailored to the genetic profiles of individual patients.

5.1.2 Molecular Mechanisms

A detailed understanding of the molecular mechanisms underlying IgAN is essential for developing new therapeutic targets. This includes exploring the processes involved in the production of aberrantly glycosylated IgA1, the formation of immune complexes, and their deposition in the glomerular mesangium. Elucidating these pathways can lead to the identification of novel therapeutic targets and biomarkers for early diagnosis and monitoring of disease progression.

5.2 Biomarker Discovery and Validation

5.2.1 Non-Invasive Biomarkers

Developing non-invasive biomarkers, such as urinary proteomics and genomics, is crucial for the early detection, risk stratification, and monitoring of treatment response in IgAN patients. These biomarkers should offer insights into the underlying pathophysiological mechanisms and predict therapeutic outcomes, allowing for more personalized treatment approaches.

5.2.2 Predictive Biomarkers

Identifying biomarkers that can predict responses to specific therapies will facilitate personalized treatment strategies, improving efficacy and reducing adverse effects. Research should focus on

validating these biomarkers across large, diverse patient cohorts to ensure their reliability and applicability in clinical settings.

5.3 Development of Novel Therapies

5.3.1 Targeted Therapies

The continued exploration of targeted therapies, including complement inhibitors, B-cell and plasma cell targeting agents, and specific inhibitors of pathogenic pathways, remains essential. Preclinical and clinical studies should aim to optimize the safety and efficacy profiles of these therapies, ensuring they provide maximum benefit with minimal side effects.

5.3.2 Gene and Cell-Based Therapies

Gene editing technologies, such as CRISPR-Cas9, and cell-based therapies, including mesenchymal stem cell therapy, hold significant promise for treating or potentially curing IgAN. These innovative approaches require rigorous preclinical testing and early-phase clinical trials to assess their safety and efficacy.

5.4 Combination Therapy Strategies

5.4.1 Synergistic Approaches

Research should focus on identifying the most effective combinations of existing and emerging therapies. Combination therapy trials should aim to determine optimal dosing regimens, minimize adverse effects, and enhance therapeutic outcomes by targeting multiple disease pathways simultaneously.

5.4.2 Sequential and Adaptive Therapies

Developing strategies for sequential and adaptive therapies based on patient response and disease progression can enhance IgAN management. Adaptive trial designs and real-time data analysis using artificial intelligence (AI) can facilitate these approaches, allowing for more dynamic and responsive treatment plans.

5.5 Personalized Medicine

5.5.1 Integration of Multi-Omics Data

Integrating genomics, transcriptomics, proteomics, and metabolomics data will provide a comprehensive understanding of IgAN pathogenesis and treatment response. Multi-omics approaches can identify novel therapeutic targets and biomarkers for personalized medicine, leading to more tailored and effective treatments.

5.5.2 Artificial Intelligence and Machine Learning

AI and machine learning algorithms are becoming increasingly important in personalized medicine. These technologies can analyze complex datasets to predict disease progression and treatment response, helping clinicians make evidence-based, personalized treatment decisions.

5.6 Long-Term Outcomes and Quality of Life

5.6.1 Longitudinal Studies

Conducting long-term studies to understand the natural history of IgAN and the long-term effects of various therapies on kidney function, quality of life, and overall survival is vital. These studies should include diverse patient populations to ensure the findings are generalizable.

5.6.2 Patient-Reported Outcomes

Incorporating patient-reported outcomes (PROs) into clinical trials and routine practice will provide valuable insights into the impact of IgAN and its treatments on patients' lives. This information is crucial for developing patient-centered care strategies that improve overall well-being and quality of life.

5.7 Global Collaboration and Data Sharing

5.7.1 International Consortia

Establishing international consortia and collaborative networks to share data, resources, and expertise will accelerate research progress. Collaborative efforts can lead to larger, more diverse study populations and the development of standardized protocols that improve the reliability and applicability of research findings.

5.7.2 Open Data Initiatives

Promoting open data initiatives and creating centralized databases for IgAN research will facilitate

data sharing and collaboration. Researchers can leverage these resources to validate findings, conduct meta-analyses, and generate new hypotheses, ultimately advancing our understanding and treatment of IgAN.

6. Conclusion

IgAN is a complex and heterogeneous disease characterized by the deposition of aberrantly glycosylated IgA1 in the glomerular mesangium, leading to kidney damage. Despite significant advancements in understanding its pathogenesis and improving treatment strategies, IgAN remains a challenging condition to manage due to its varied clinical presentations and unpredictable progression. Current treatment approaches focus on supportive care and immunosuppressive therapies, while emerging targeted therapies and personalized medicine offer promising avenues for more effective and individualized management. Ongoing research and global collaboration are crucial to further elucidate the underlying mechanisms of IgAN, develop novel therapeutic targets, and ultimately improve patient outcomes and quality of life.

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