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Review Article

IgA Nephropathy: Current Treatment Strategies and Perspectives on Targeted Therapy

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Abstract:

Background: Immunoglobulin A nephropathy is among the most commonly observed glomerular disorders. Its development is associated with immune dysfunction, which initiates a cascade of pathological changes within the glomeruli. The clinical course can range from minimal urinary abnormalities to progressive renal impairment, potentially culminating in end-stage kidney disease. Despite considerable advances in understanding its pathogenesis, optimal therapeutic strategies remain an active focus of scientific investigation.

Aim: To assess current and emerging therapeutic strategies for IgA nephropathy, with an emphasis on efficacy, safety, and the potential of targeted agents addressing key pathogenic pathways.

Methods: We conducted a narrative review of recent literature in PubMed, Scopus, Web of Science, and eLIBRARY databases, focusing on publications from the last decade. Studies published in English and Russian that reported results from clinical trials or meta-analyses on therapeutic interventions for IgA nephropathy were included. Search terms included «IgA nephropathy», «treatment», «targeted therapy», «new therapies», «immunosuppressants», and «clinical trials». Priority was given to randomized controlled trials and studies with high-quality evidence, though relevant observational data were also considered.

Results: Key studies identified included 52 publications, among which 20 were randomized clinical trials and a systematic review. Corticosteroid therapy remains a cornerstone of treatment but is limited by significant adverse effects. Recent therapeutic developments in IgA nephropathy have focused on interventions that selectively target inflammatory and immune pathways involved in disease progression. Certain novel agents aimed at modulating immune signaling or addressing pathogenic plasma cells have shown potential to reduce proteinuria and stabilize renal function. Early-phase clinical investigations indicate promising efficacy and manageable safety profiles, suggesting these approaches may represent important advances in disease management.

Conclusions: Recent progress in targeted and immunomodulatory therapies offers new perspectives for personalized treatment of IgA nephropathy. Comprehensive, large-scale randomized studies with extended follow-up are warranted to thoroughly assess the therapeutic potential, safety profile, and optimal positioning of these interventions within future clinical management strategies.

Keywords: IgA Nephropathy; Targeted Therapy; Budesonide; Immunosuppression; Complement Inhibition; SGLT2 Inhibitors; Treatment; Narrative Review

Introduction

IgA nephropathy (IgAN) represents the most prevalent glomerular disorder globally and constitutes a leading cause of renal failure in adults, particularly in regions such as East and South Asia. The disease is associated with decreased life quality, progression to dialysis or kidney transplantation, and elevated risk of premature mortality [1,2]. Data from the UK Rare Kidney Disease Registry (RaDaR) indicate that adults diagnosed with IgA nephropathy have a substantially increased likelihood of progressing to kidney failure [1,3]. Comparable trends have been documented in reports from the Swedish national registry and in a German prospective cohort of patients with chronic kidney disease [4]. A narrative review has estimated the global incidence of adult IgAN to be at least 2.5 cases per 100,000 individuals annually. The condition most frequently presents in early to mid-adulthood, typically between 20 and 40 years of age and demonstrates a male predominance in Western populations, with ratios of approximately 2:1 in the United States and 3:1 in Europe [5]. By contrast, cohorts from East Asia show a near-equal distribution between males and females, accounting for roughly 30-45% of all diagnosed cases [6,7]. These demographic patterns highlight the notable clinical and societal impact of the disease. Because overt clinical manifestations are frequently absent, many individuals with IgA nephropathy come to medical attention only after the development of laboratory abnormalities suggestive of chronic kidney damage, most commonly hematuria and proteinuria [2, «8-10»]. A definitive diagnosis still relies on a kidney biopsy, which contributes to delayed or missed identification of the disease in settings with limited access to diagnostic services and among patients whose symptoms remain mild or nonspecific [11,12]. Recurrence of glomerular disease after transplantation occurs in approximately 3% to 15% of cases [13,14].

Current understanding of IgA nephropathy has expanded substantially, and a conceptual framework often referred to as the «four-hit hypothesis» is used to describe its pathogenic sequence [15,16]. This model proposes that abnormally glycosylated IgA1 molecules circulate in elevated concentrations and become targets for IgG or IgA autoantibodies, resulting in the formation of immune complexes. These complexes subsequently accumulate within the mesangial compartment, where they trigger inflammatory and injury-related processes. Activation of the complement system particularly the alternative pathway is believed to amplify this response and contributes to the progression of renal damage [«17-19»].

Several clinical and histological features have been associated with an increased risk of progression to end-stage renal disease in patients with IgA nephropathy. Persistent abnormalities in kidney function, elevated blood pressure, ongoing proteinuria, and certain tissue changes can help stratify patients and guide individualized therapeutic strategies, emphasizing the importance of early identification and monitoring of high-risk individuals [16,19].

Study Objective

To assess current and emerging therapeutic strategies for IgA nephropathy, with an emphasis on efficacy, safety, and the potential of targeted agents addressing key pathogenic pathways.

Materials and Methods

For this review, a comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, Web of Science, Google Scholar, and eLIBRARY. The search focused on studies published over the past decade to capture the most recent evidence.

The following keywords and their combinations were used: «IgA nephropathy», «treatment», «new therapies», «immunosuppressants», «targeted therapy», and «clinical trials» (Table 1). Inclusion criteria: Articles containing data from clinical trials (phases II-IV), meta-analyses, or narrative reviews; Publications in English and Russian; Studies addressing new or modified therapeutic approaches. Exclusion criteria: Articles with insufficient methodological descriptions; Outdated approaches lacking current clinical validation; Case reports, and commentaries. Studies were selected based on their contribution to understanding current treatment paradigms. While priority was given to clinical trials, expert opinions and guideline recommendations were also incorporated to provide a comprehensive clinical perspective. The literature was selected based on relevance to current therapeutic strategies and clinical significance.

Table 1. Key search terms used for literature identification.re

Database	Keywords and Combinations	Number of Articles Foun
PubMed	«IgA nephropathy» AND («treatment» OR «therapy») AND («new drugs» OR «targeted therapy»)	3850
Scopus	«IgA nephropathy» AND «immunosuppressants» AND («clinical trial» OR «RCT»)	97
Web of Science	«IgA nephropathy» AND («budesonide» OR «SGLT2 inhibitors» OR «complement inhibitors»)	84
Google Scholar	«IgA nephropathy treatment new approaches»	145
CyberLeninka / eLIBRARY	«IgA nephropathy" AND "treatment" AND «new drugs»	32

A total of 52 studies were included in this review, including 20 randomized clinical trials that satisfied the predefined inclusion criteria. The review identified several promising therapeutic approaches that are currently under investigation:

- Targeted therapy: Agents acting on the APRIL/BAFF signaling pathways, such as *atacicept* and *blisibimod*, have demonstrated disease activity reduction and decreased proteinuria.
- Budesonide therapy (Nefecon): Proven to exert localized intestinal effects with minimal systemic adverse reactions.
- SGLT2 inhibitors (e.g., dapagliflozin): Show promising nephroprotective potential, particularly in patients with concomitant diabetes.
- Conventional immunosuppressants (corticosteroids, mycophenolate mofetil): Still in use, but associated with a high incidence of complications.
- Active development of anti-complement therapies is currently underway, targeting components such as C5 and C3. The results indicate that precise, pathogenetically focused interventions in IgA nephropathy are becoming increasingly preferable to non-specific immunosuppression.

The KDIGO 2025 clinical practice guideline emphasizes the importance of recognizing patients with IgA nephropathy who are at increased risk of progressive kidney function decline [11]. Therapeutic interventions are primarily aimed at slowing disease progression, including strategies to reduce nephron loss and preserve glomerular filtration rate, thereby delaying or preventing the onset of end-stage renal disease (ESRD) [1,20]. While there is currently no definitive cure for IgA nephropathy, disease progression can be mitigated through supportive, non-immunosuppressive measures, as well as through adjunctive immunosuppressive therapies for patients at elevated risk, those exhibiting active disease progression, or individuals with particular IgAN variants [15, «21-23»].

Reduction of Proteinuria

Currently, urinary protein excretion remains the only validated early biomarker for guiding clinical decisions in IgAN. The 2021 guidelines [24] recommended aiming for proteinuria below 1 g/day; however, emerging evidence indicates that achieving even lower proteinuria or albuminuria levels is linked with a substantially reduced lifetime risk of kidney failure. Consequently, treatment targets have been refined to less <0.5 g/day during and outside active therapy, with an ideal goal of below 0.3 g/day (or equivalent). Notably, patients with proteinuria between 0.5 and 1 g/day continue to be at risk of progression [11,25], although factors such as blood pressure control (≤120/70 mmHg), biopsy findings, and immunosuppressive treatment were not consistently reported in all studies [«26-28»].

In pediatric patients with IgA nephropathy, the recommended target for proteinuria is below 0.2 g/day/1.73 m² (or <0.2 g/g creatinine) [29], which is lower than the goal for adults. Achieving reductions in proteinuria is generally regarded as a reliable surrogate for improved long-term renal outcomes [29,30]; however, the association between proteinuria decrease and kidney prognosis is not strictly linear [19]. Maintaining or improving estimated glomerular filtration rate (eGFR) remains another key therapeutic objective, with the aim of limiting the annual decline to less than 1 mL/min/1.73 m² over the course of a patient's lifetime [31,32].

Addressing microscopic hematuria is considered an important therapeutic goal in patients with IgA nephropathy, as ongoing hematuria has been

linked to disease progression, whereas remission of hematuria is associated with better long-term kidney outcomes [33,34].

Contemporary management of IgA nephropathy incorporates both supportive therapy and lifestyle interventions. Recommended measures include smoking cessation, maintaining healthy body weight, limiting dietary sodium intake (<2 g/day), and engaging in regular physical activity. Blood pressure should be carefully controlled, aiming for ≤120/70 mmHg [25]. Strategies to reduce glomerular hyperfiltration and minimize proteinuria-associated tubulointerstitial injury involve blockade of the renin–angiotensin system with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) [11,25,27], and in some cases, dual endothelin–angiotensin receptor antagonism, with or without SGLT2 inhibitors [27].

When tailoring therapy for patients at risk of progressive kidney function decline, factors such as age, ethnicity, baseline eGFR, and current use of ACE inhibitors or ARBs should be considered For individuals not classified as very high risk and without evidence of active disease progression, initial management with supportive therapy alone is generally appropriate [11,24,25]. This supportive approach should be maintained long-term, with periodic assessment for signs of disease progression. After approximately 3-6 months or sooner in patients exhibiting rapid deterioration treatment response should be reassessed to determine whether additional interventions are needed to meet therapeutic targets [21].

Optimized supportive therapy is recommended for all patients with IgA nephropathy to slow the progression of chronic kidney disease not directly mediated by immune mechanisms. Key components include pharmacologic interventions to reduce proteinuria and glomerular hyperfiltration, blood pressure management to guideline-recommended targets, treatment of dyslipidemia when present, and lifestyle modifications such as dietary sodium and protein restriction, smoking cessation, weight control, and regular physical activity [11,30].

In patients with IgA nephropathy and proteinuria ≥0.5 g/day, therapy with an ACEi or ARB is recommended [35,36]. For those unable to tolerate these agents, alternatives may include SGLT2 inhibitors, endothelin receptor antagonists, or combined endothelin - angiotensin receptor blockers [37]. ACEi/ARB treatment reduces proteinuria and mitigates secondary glomerular injury by lowering both systemic and intraglomerular pressure, thereby slowing but rarely completely stopping progression of proteinuric chronic kidney disease [38,39]. Treatment should begin at a low dose (e.g., lisinopril 2.5-10 mg or losartan 25-50 mg daily) and be titrated every 2-4 weeks to the highest tolerated dose, aiming for proteinuria below 0.5 g/day. An increase in serum creatinine of up to 30% is considered acceptable. The maximal tolerated dose should be maintained for at least three months before initiating additional therapies [40].

In patients with IgA nephropathy, immunosuppressive therapy is aimed at modulating the immune and inflammatory processes that contribute to glomerular injury and nephron loss. Such therapies can be classified into two main groups: (1) agents that reduce the production of pathogenic IgA and limit immune complex formation, including systemic corticosteroids and targeted-release budesonide (TRF-budesonide) and (2) agents that directly suppress glomerular inflammation, such as systemic corticosteroids, mycophenolate mofetil (MMF), and complement inhibitors [32,41,42].

For patients who cannot tolerate or prefer to avoid systemic corticosteroids, alternative therapies include targeted-release budesonide (TRF-budesonide, Nefecon) or MMF, often in combination with low-dose steroids for induction of remission [43]. TRF-budesonide is designed for release in the distal ileum, targeting Peyer's patches, which are thought to be a source of galactose-deficient IgA1 implicated in IgAN pathogenesis. Its extensive first-pass hepatic metabolism (~90%) limits systemic exposure [44,45]. Despite demonstrated efficacy, its high cost and lack of clear superiority over moderate-dose oral steroids limit its use as a first-line option. The usual dosing regimen is 16 mg/day orally for 9 months, followed by 8 mg/day for 2 weeks [23]. Data on prolonged or repeated treatment courses remain limited [11,25]. Current evidence suggests that TRF-budesonide exerts local intestinal effects, reducing biomarkers of mucosal injury and galactose-deficient IgA1–IgG immune complexes, although further studies are required to establish its comparative role versus systemic or other delayed-release corticosteroid formulations [11,41].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce renal glucose reabsorption in the proximal tubules, leading to glucosuria and providing nephroprotective effects in patients with albuminuria, regardless of diabetic status [19]. For individuals not receiving immunosuppressive therapy, an SGLT2 inhibitor (e.g., dapagliflozin or empagliflozin) may be considered if proteinuria remains ≥0.5 g/day after at least three months of maximal tolerated ACEi or ARB therapy [46,47]. These agents are also appropriate for patients who cannot tolerate ACEi or ARBs. It should be noted that SGLT2 inhibitors do not directly target

inflammatory pathways and cannot replace immunosuppressive therapy when indicated. Typical dosing is 10 mg once daily for either dapagliflozin or empagliflozin. While the majority of renal-protection studies were conducted in diabetic kidney disease, available evidence indicates that benefits also extend to non-diabetic proteinuric patients, including those with IgAN [19]. In a prespecified analysis of 270 IgAN participants in the DAPA-CKD trial, the primary composite endpoint defined as sustained eGFR decline ≥50%, initiation of kidney replacement therapy, or death from renal or cardiovascular causes occurred in 6 patients (4%) receiving dapagliflozin versus 20 (15%) on placebo, independent of baseline proteinuria [47]. Dapagliflozin also decreased the urinary albumin-to-creatinine ratio by 26% compared with placebo, with comparable adverse event rates. The optimal timing for introducing SGLT2 inhibitors alongside ACEi/ARB therapy in IgAN remains to be determined; in DAPA-CKD, participants had received ACEi/ARB therapy for at least four weeks beforehand unless intolerant [47]. Data are insufficient to clarify whether proteinuria was stable or increasing despite maximal ACEi/ARB dosing prior to SGLT2 initiation.

According to KDIGO 2025, SGLT2 inhibitors are recommended for patients with IgA nephropathy who are at risk of progressive decline in kidney function (Grade 2B) [11,48]. In the pivotal studies, participants were not required to have received maximal tolerated ACEi or ARB therapy for three months or longer, and most had longstanding disease with reduced eGFR. This raises uncertainty regarding the extent of benefit in younger patients or those with preserved renal function (eGFR >60 mL/min/1.73 m²) [49]. While SGLT2 inhibitors effectively reduce proteinuria and slow the progression of kidney disease, they do not substitute for immunosuppressive therapy when indicated.

Endothelin receptor antagonists (ERA) and dual endothelin angiotensin receptor antagonists (DEARA) block ET-1 via ETA receptors, reducing podocyte injury, proteinuria, and progression of chronic kidney disease in IgAN patients with persistent proteinuria ≥0.5 g/day despite ≥3 months of optimized ACEi/ARB therapy ± SGLT2 inhibitors [50]. Sparsentan, a DEARA (AT1/ETA), is FDA-approved to reduce proteinuria and slow eGFR decline in adults with IgAN [51]. The starting dose is 200 mg/day, titrated up to 400 mg/day as tolerated; ACEi/ARB therapy should be discontinued when starting sparsentan. Major adverse events include hypotension, peripheral edema, hyperkalemia, dizziness, anemia, and acute kidney injury [52]. Sparsentan (DEARA, AT1/ETA) has been evaluated in a Phase 3 trial including 404 IgAN patients with eGFR ≥30 mL/min and proteinuria >1 g/day [53]. At week 110, sparsentan reduced proteinuria by 42.8% compared with 4.4% for irbesartan, increased the rate of complete proteinuria remission (31% vs 11%), and slowed eGFR decline (-2.7 vs -3.8 mL/min/year) [51].

Atrasentan (ERA, ETA) - oral, FDA-approved to reduce proteinuria. Can be combined with ACEi/ARB. Not for use in pregnant women or liver disease. Dose: 0.75 mg/day. Adverse effects: fluid retention, anemia, hypotension, reduced sperm count [42,43]. Efficacy: Phase 3, 340 IgAN patients with proteinuria ≥1 g/day. At week 36, atrasentan reduced proteinuria by 38% vs 3% for placebo. Final results expected in 2026 [44]. No direct comparative studies between atrasentan and sparsentan exist.

Iptacopan is an oral factor B inhibitor that blocks the alternative complement pathway, a key contributor to IgAN [54,55]. It received accelerated FDA [56] approval to reduce proteinuria in patients at risk of rapid progression (UPCR ≥1.5 g/g), especially those with persistent disease despite glucocorticoids or MMF, or who are ineligible for these therapies [1,57,58]. The standard dose is 200 mg twice daily [60]. Because complement inhibition increases the risk of serious infections from encapsulated bacteria (Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae type B), vaccination and antimicrobial prophylaxis are required, and the drug is distributed through a restricted REMS program [59]. In a Phase 3 trial of 443 adults with biopsy-confirmed IgAN, eGFR ≥30 mL/min/1.73 m², and persistent proteinuria ≥1 g/day despite ≥3 months of maximal ACEi/ARB therapy, iptacopan lowered mean 24-hour proteinuria by 38% versus placebo at 9 months (interim analysis of 250 patients) [61,62]. Resolution of hematuria was also more frequent with iptacopan (39% vs 16%). Adverse events were generally mild to moderate and similar between groups. Full results are expected by the end of 2025 [62].

Other therapies in IgAN have been evaluated with varying levels of evidence. Consistent with the 2021 guideline, KDIGO 2025 does not recommend the routine use of antiplatelet agents, anticoagulants, azathioprine, cyclophosphamide (except in cases of rapidly progressive IgAN), calcineurin inhibitors, rituximab, or fish oil [25]. Mycophenolate mofetil (MMF) has limited supporting evidence and may be considered in Chinese patients based on local trials, particularly to reduce glucocorticoid exposure. Hydroxychloroquine may also be considered in Chinese populations, but data in other ethnic groups are insufficient. Tonsillectomy is endorsed in Japan but is not generally recommended elsewhere [25].

Several novel and experimental therapies are under investigation for IgAN [63]. APRIL (a proliferation-inducing ligand) and BAFF (B-cell activating factor) are key signaling proteins that support B-cell survival, proliferation, and maturation, contributing to IgAN pathogenesis [64]. Serum levels of APRIL and BAFF are elevated in patients and correlate with disease severity [65]. Sibeprenlimab, an intravenous humanized monoclonal antibody against APRIL, reduced proteinuria in a dose-dependent manner, stabilized eGFR, and decreased pathogenic galactose-deficient IgA1 (Gd-IgA1) levels over 12 months in a phase 2 study versus placebo, with comparable serious adverse events [66]. A larger phase 3 trial (NCT05248646) is ongoing. Zigakibart, another anti-APRIL monoclonal antibody, produced similar results in early-phase studies, with phase 3 trials underway (NCT05852938) [66]. Dual APRIL/BAFF inhibitors, such as atacicept and telitacicept, have demonstrated reductions in proteinuria, stabilization of eGFR, and good tolerability in small studies [«67-69»].

Complement pathway inhibitors beyond iptacopan are also being explored [70]. Agents including avacopan, vemicopan, cemdisiran, ravulizumab, and pegcetacoplan are under evaluation [48]. Phase 2 and 3 trials indicate that cemdisiran, an RNA interference therapy targeting hepatic C5 production, and ravulizumab, an anti-C5 monoclonal antibody, significantly reduce proteinuria compared with placebo and have acceptable safety profiles [54,71,72].

Plasma cell-targeted therapy: Proteasome inhibitors and monoclonal antibodies against CD38 target plasma cells and are used in multiple myeloma and other diseases, including glomerular disorders. A small pilot study in 16 adults with IgAN showed that a short course (4-8 doses) of the proteasome inhibitor bortezomib resulted in sustained proteinuria reduction over 24 months without serious adverse events [73]. Ongoing trials are evaluating anti-CD38 monoclonal antibodies felzartamab (NCT05065970) and mesagitamab (NCT05174221) in IgAN patients [73].

- Special Situations. The 2025 KDIGO guidelines for IgAN remain largely unchanged compared with the 2021 version [25].
- Nephrotic Syndrome (NS): In a small subset of IgAN patients, NS may develop [55]. Distinguishing whether NS represents a specific IgAN variant with mesangioproliferative lesions or concurrent minimal change disease (MCD) with mesangial IgA deposits can be challenging [25]. Management depends on the underlying pathology: the IgAN variant is treated according to standard IgAN protocols, whereas coexisting MCD is managed as minimal change disease [25]. Nephrotic-range proteinuria in the absence of NS generally reflects secondary focal segmental glomerulosclerosis or widespread global glomerulosclerosis with tubulointerstitial fibrosis, which can arise from chronic IgAN, obesity, or uncontrolled hypertension [25].
- Rapidly Progressive IgAN (RPGN) is characterized by a rapid decline in eGFR of ≥50% over less than three months, after ruling out other causes of rapidly progressive glomerulonephritis or acute kidney injury [55]. Kidney biopsy is essential for diagnosis, typically demonstrating mesangial and endocapillary hypercellularity, with crescents and focal necrosis affecting a substantial proportion of glomeruli. Notably, the presence of crescents alone without eGFR reduction does not define RPGN, nor does a decline in eGFR without crescents. Treatment is generally based on cyclophosphamide combined with systemic glucocorticoids following KDIGO 2024 ANCA-associated vasculitis guidelines [74]. Some protocols suggest 1-3 intravenous pulses of methylprednisolone (1 g), followed by mycophenolate mofetil and low-dose oral steroids. Evidence for rituximab in RPGN IgAN remains limited [75].

AKI may be observed in RPGN IgAN but often occurs alongside hematuria flares [25]. Management is primarily supportive, with repeat kidney biopsy recommended if renal function does not improve within approximately two weeks after hematuria resolution. Histological examination typically reveals mesangial proliferation and segmental crescents in at least 25% of glomeruli [76].

Women with IgA nephropathy who have normal or near-normal kidney function generally tolerate pregnancy well [77]. Nevertheless, those with a baseline eGFR below 70 mL/min, uncontrolled hypertension, or significant arteriolar and tubulointerstitial lesions on biopsy are at increased risk of rapid renal function decline [78]. Optimal management during pregnancy has not been clearly defined. Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are contraindicated and should be discontinued prior to conception. Endothelin receptor antagonists (e.g., atrasentan) and dual endothelin–angiotensin receptor blockers (e.g., sparsentan) should also be avoided. When immunosuppressive therapy is needed, systemic glucocorticoids and hydroxychloroquine may be considered, although evidence remains limited [77,78]. Targeted-release formulations of budesonide (TRF) lack pregnancy safety data, whereas inhaled or enteric-

coated budesonide is generally regarded as safe for the fetus due to minimal placental transfer [43]. Mycophenolate mofetil and cyclophosphamide are contraindicated. While iptacopan has no documented pregnancy-specific restrictions, its safety and efficacy in this context remain unknown [79].

Use of ACE inhibitors may be acceptable under obstetric supervision; captopril and enalapril are generally considered safe for breastfeeding infants [74,80]. In contrast, angiotensin receptor blockers (ARBs), SGLT2 inhibitors, dual endothelin–angiotensin receptor antagonists (DEARAs), and endothelin receptor antagonists should be avoided due to insufficient safety data during lactation [74,79]. For mothers requiring immunosuppressive therapy, systemic glucocorticoids and targeted-release formulations of budesonide (TRF-budesonide) are potential options [74,81]. MMF and Iptacopan should be avoided, given the lack of safety data in breastfeeding [79,82]. When maternal immunosuppressive therapy is essential, some authors recommend formula feeding to minimize exposure to the infant [81].

Conclusion

IgA nephropathy, historically viewed as a slowly advancing and relatively mild kidney disorder, is now recognized as a chronically progressive glomerular disease that can eventually culminate in end-stage renal failure if inadequately treated. Therapeutic goals should prioritize the long-term preservation or restoration of renal function. Recent advances have introduced a variety of novel interventions some approved and others undergoing late-phase clinical evaluation that specifically target the underlying pathogenic pathways of the disease. These therapies, including both targeted and immunomodulatory approaches, offer opportunities for more tailored and potentially combinable treatment strategies, with the overarching aim of sustaining kidney function and improving long-term clinical outcomes for patients.

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References

1. Floege J, Bernier-Jean A, Barratt J, Rovin B. Treatment of patients with IgA nephropathy: a call for a new paradigm. Kidney Int. 2025;107(4):640-651. https://doi.org/10.1016/j.kint.2025.01.014
2. Kwon CS, Daniele P, Forsythe A, Ngai C. A Systematic Literature Review of the Epidemiology, Health-Related Quality of Life Impact, and Economic Burden of Immunoglobulin A Nephropathy. JHEOR. 2021;8(2):36-45. https://doi.org/10.36469/001c.26129
3. Pitcher D, Braddon F, Hendry B, Mercer A, Osmaston K, Saleem M, et al. Long-term outcomes in IgA nephropathy. Clin J Am Soc Nephrol. 2023;18(6):727-738. https://doi.org/10.2215/cjn.0000000000000135
4. Grabe DW. Preventing Progression in IgA Nephropathy: A Managed Care Focus on Emerging Therapies. AJMC. 2023;29(3):31-43. https://doi.org/10.37765/ajmc.2023.89344
5. Kwon CS, Daniele P, Forsythe A, Ngai C. A systematic literature review of the epidemiology, health-related quality of life impact, and economic burden of immunoglobulin a nephropathy. JHEOR. 2021;8(2):36-45. https://doi.org/10.36469/jheor.2021.26129

6. Kiryluk K, Freedberg DE, Radhakrishnan J, Segall L, Jacobson JS, Mathur M, Mohan S, Neugut AI. Global Incidence of IgA Nephropathy by Race and Ethnicity: A Systematic Review. Kidney360. 2023;4(8):1112-1122. https://doi.org/10.34067/KID.0000000000000165
7. Lee M, Suzuki H, Nihei Y, Matsuzaki K, Suzuki Y. Ethnicity and IgA nephropathy: worldwide differences in epidemiology, timing of diagnosis, clinical manifestations, management and prognosis. Clin Kidney J. 2023;16(Suppl 2):1-8. https://doi.org/10.1093/ckj/sfad199
8. Rodrigues JC, Haas M, Reich HN. IgA Nephropathy. Clin J Am Soc Nephrol. 2017;12(4):677-686. https://doi.org/10.2215/CJN.07420716
9. Thompson A, Carroll K, Lesley I, Floege J, Perkovic V, Boyer-Suavet S, et al. Proteinuria reduction as a surrogate end point in trials of IgA nephropathy. Clin J Am Soc Nephrol. 2019;14(3):469–481. https://doi.org/10.2215/cjn.08600718
10. Cattran DC, Floege J, Coppo R. Evaluating progression risk in patients with immunoglobulin A nephropathy. Kidney Int Rep. 2023;8(12):2515–28. https://doi.org/10.1016/j.ekir.2023.09.020
11. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). Kidney Int. 2025;108(4S):1–71. https://kdigo.co/KDIGO-IgAN-IgAV-Guideline
12. Duan ZY, Zhang C, Chen XM, Cai GY. Blood and urine biomarkers of disease progression in IgA nephropathy. Biomark Res. 2024;12(1):72. https://doi.org/10.1186/s40364-024-00619-4
13. Wieliczko M, Nazarewski S, Gałązka Z, Jolanta S. Recurrence of glomerulonephritis after kidney transplantation - experience of one center from 2020 to 2023. Transplant Proc. 2024;56(4):789–92. https://doi.org/10.1016/j.transproceed.2024.03.015
14. Lim WH, Shingde M, Wong G. Recurrent and de novo glomerulonephritis after kidney transplantation. Front Immunol. 2019;10:1944. https://doi.org/10.3389/fimmu.2019.01944
15. Ramsawak S, Cohen S, Linares A, Cavanaugh C. IgA nephropathy: update on pathogenesis and treatment. Cleve Clin J Med. 2025;92(6):373-383. https://doi.org/10.3949/ccjm.92a.24105
16. Zhou XJ. Immunoglobulin A Nephropathy: Molecular Pathogenesis and Targeted Therapy. MedComm. 2025;6(9):e70382. https://doi.org/10.1002/mco2.70382
17. Rizk DV, Saha MK, Hall S, Novak L, Brown R, Huang Z, et al. Glomerular immunodeposits of patients with IgA nephropathy are enriched for IgG autoantibodies specific for galactose-deficient IgA1. Clin J Am Soc Nephrol. 2019;30(10):2017–2026. https://doi.org/10.1681/asn.2018111156
18. Chiu YL, Lin WC, Shu KH, Fang YW, Chang FC, Chou YH, Wu CF, Chiang WC, Lin SL, et al. Alternative Complement Pathway Is Activated and Associated with Galactose-Deficient IgA1 Antibody in IgA Nephropathy Patients. Front Immunol. 2021;12:638309. https://doi.org/10.3389/fimmu.2021.638309
19. Gleeson PJ, M O'Shaughnessy M, Barratt J. IgA nephropathy in adults - treatment standard. Nephrol Dial Transplant. 2023;38(11):2464–2473. https://doi.org/10.1093/ndt/gfad146
20. Barratt J, Lafayette RA, Floege J. Therapy of IgA nephropathy: time for a paradigm change. Front Med (Lausanne). 2024;11:1461879. https://doi.org/10.3389/fmed.2024.1461879
21. Zhao H, Li Y, Sun J, Xu G, Wang C, Zhou S, et al. Immunosuppression versus Supportive Care on Kidney Outcomes in IgA Nephropathy in the Real-World Setting. CJASN. 2024;18(9):1186-1194. https://doi.org/10.2215/CJN.0000000000000215

22. El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA Nephropathy: A Rapidly Evolving Field. JASN. 2024;35(1):103-116. https://doi.org/10.1681/ASN.0000000000000242
23. Petrou D, Kalogeropoulos P, Liapis G, Lionaki S. IgA Nephropathy: Current Treatment and New Insights. Antibodies. 2023;12(40):1-14. https://doi.org/10.3390/antib12020040
24. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):1–276. https://doi.org/10.1016/j.kint.2021.05.021
25. Floege J, Barratt J, Cook HT, Noronha IL, Reich HN, Suzuki Y, et al. Executive summary of the KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). (No DOI/URL provided)
26. Yu G, Cheng J, Jiang Y, Li H, Li X, Chen J. Intensive Systolic Blood Pressure Lowering and Kidney Disease Progression in IgA Nephropathy: A Cohort Study. Front Med (Lausanne). 2022;9:813603. https://doi.org/10.3389/fmed.2022.813603
27. Noor SM, Abuazzam F, Mathew R, Zhang Z, Abdipour A, Norouzi S. IgA nephropathy: a review of existing and emerging therapies. Front Nephrol. 2023;3:1175088. https://doi.org/10.3389/fneph.2023.1175088
28. Vivarelli M, Samuel S, Coppo R, Barratt J, Bonilla-Felix M, Haffner D, et al. IPNA clinical practice recommendations for the diagnosis and management of children with IgA nephropathy and IgA vasculitis nephritis. Pediatr Nephrol. 2024;40(2):533–569. https://doi.org/10.1007/s00467-024-06502-6
29. Shima Y, Mukaiyama H, Tanaka Y, Shimabukuro W, Nozu K, Kaito H, et al. Factors related to recurrence of proteinuria in childhood IgA nephropathy. Pediatr Nephrol. 2024;39(2):463–71. https://doi.org/10.1007/s00467-023-06116-4
30. Peruzzi L, Coppo R. Expected and verified benefits from old and new corticosteroid treatments in IgA nephropathy: from trials in adults to new IPNA-KDIGO guidelines. Pediatr Nephrol. 2025;40(7):2121–2131. https://doi.org/10.1007/s00467-025-06725-1
31. Barratt J, Lafayette RA, Rovin BH, Fellström B. Budesonide delayed-release capsules to reduce proteinuria in adults with primary immunoglobulin A nephropathy. Expert Rev Clin Immunol. 2022;19:699-710. https://doi.org/10.1080/1744666X.2023.2206119
32. Xue C, Yu S, Gou W, Xu Y, Yang L, Dai B. Precision Treatment of IgA Nephropathy Based on a New Framework: Angiorenal Protection, Immunity Inhibition, B-Cell/Plasma-Cell Modulation, and Complement Inhibition. Kidney Dis. 2025;11(1):154–159. https://doi.org/10.1159/000544998
33. Sevillano AM, Gutiérrez E, Yuste C, Cavero T, Mérida E, Rodríguez P, et al. Remission of hematuria improves renal survival in IgA nephropathy. J Am Soc Nephrol. 2017;28(10):3089–99. https://doi.org/10.1681/asn.2017010108
34. Weng M, Lin J, Chen Y, Zhang X, Zou Z, Chen Y, et al. Time-Averaged Hematuria as a Prognostic Indicator of Renal Outcome in Patients with IgA Nephropathy. J Clin Med. 2022;11(22):6785. https://doi.org/10.3390/jcm11226785
35. Louise O, Rona S, Alan SD, Jonathan B, Howard T, Moin S. Bridging the 13-Year Evidence Gap: A Time for Age-Inclusive Research. JASN. 2024;35(4):502-504. https://doi.org/10.1681/ASN.0000000000000301
36. Mathur M, Sahay M, Pereira BJG, Rizk DV. State-of-Art Therapeutics in IgA Nephropathy. Indian J Nephrol. 2024;34:417-30. https://doi.org/10.25259/ijn_319_23
37. Kim J, Kamal F, Yeung B, Lafayette R. How should we best manage the consequences of nephron loss in IgAN? Nephrol Dial Transplant. 2025;gfaf225. https://doi.org/10.1093/ndt/gfaf225

38. Momoniat T. ACE inhibitors and ARBs: Managing potassium and renal function. Cleve Clin J Med. 2019;86(9):601-607. https://doi.org/10.3949/ccjm.86a.18024
39. Zeier M. ACE Inhibitors and ARB in Chronic Kidney Disease: What Has to Be Considered. Dtsch Med Wochenschr. 2018;143(12):880-885. https://doi.org/10.1055/a-0549-9662
40. Stamellou E, Seikrit C, Tang SCW, Boor P, Tesař V, Floege J, et al. IgA nephropathy. Nat Rev Dis Primers. 2023;9(1):67. https://doi.org/10.1038/s41572-023-00476-9
41. Lv J, Wong MG, Hladunewich MA, Jha V, Hooi LS, Monaghan H, et al. Effect of oral methylprednisolone on decline in kidney function or kidney failure in patients with IgA nephropathy: the TESTING randomized clinical trial. JAMA. 2022;327(19):1888–98. https://doi.org/10.1001/jama.2022.5368
42. Glassock RJ. An expert opinion on current and future treatment approaches in IgA nephropathy. Adv Ther. 2025;42(6):2545–58. https://pubmed.ncbi.nlm.nih.gov/40220242
43. Lafayette R, Kristensen J, Stone A, Floege J, Tesař V, Trimarchi H, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. Lancet. 2023;402(10405):859–70. https://doi.org/10.1016/s0140-6736(23)01554-4
44. Rovin BH, Barratt J, Heerspink HJL, Alpers CE, Bieler S, Chae DW, et al. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. Lancet. 2023;402:2077-2090. (No DOI provided)
45. Wimbury D, Muto M, Bhachu JS, Scionti K, Brown J, Molyneux K, et al. Targeted-release budesonide modifies key pathogenic biomarkers in immunoglobulin A nephropathy: insights from the NEFIGAN trial. Kidney Int. 2024;105(2):381–8. https://doi.org/10.1016/j.kint.2023.11.003
46. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46. https://doi.org/10.1056/nejmoa2024816
47. Wheeler DC, Toto RD, Stefánsson BV, Jongs N, Chertow GM, Greene T, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. Kidney Int. 2021;100(1):215–24. https://doi.org/10.1016/j.kint.2021.03.033
48. Zurowska A. Game Changers in IgA Nephropathy. EMJ. 2025;13(1):23-27. https://doi.org/10.33590/emjnephrol/YKIN5558
49. Lerma EV, Batuman V. Diabetes and Kidney Disease. Second Edition. 2022. p.21-37. (No DOI provided)
50. Konda R, Rajasekaran A, Rizk DV. What do clinical trials teach us about the pathophysiology of human IgA nephropathy? NDT. 2025. https://doi.org/10.1093/ndt/gfaf144
51. Heerspink HJL, Radhakrishnan J, Alpers CE, Barratt J, et al. Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. Lancet. 2023;401(10388):1584–94. https://doi.org/10.1016/s0140-6736(23)00569-x
52. Selvaskandan H, Jhaveri KD, Rizk DV. Primary IgA Nephropathy: New Insights and Emerging Therapies. Adv Kidney Dis Health. 2024;31(3):180-193. https://doi.org/10.1053/j.akdh.2024.04.002
53. Vecchio LD, Allinovi M, Comolli S, Peiti S, Rimoldi C, Locatelli F. Drugs in Development to Treat IgA Nephropathy. Drugs. 2024;84:503-525. (No DOI provided)
54. El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA Nephropathy: A Rapidly Evolving Field. JASN. 2024;35(1):103–116. https://doi.org/10.1681/ASN.0000000000000242
55. Wendt R, Sobhani A, Diefenhardt P, Trappe M, Völker LA. An Updated Comprehensive

Review on Diseases Associated with Nephrotic Syndromes. Biomedicines. 2024;12(10):2259. https://doi.org/10.3390/biomedicines12102259

56. FDA. Letter approving Fabhalta (iptacopan) for primary IgA nephropathy (NDA 218276/S-001). Silver Spring, MD: FDA; 2024 [cited 2025 Nov 26]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/218276Orig1s001ltr.pdf
57. Coppo R, Troyanov S, Camilla R, et al. Pathogenesis and therapy of IgA nephropathy: Focus on complement activation. J Nephrol. 2022;35:123–135. (No DOI provided)
58. Floege J, Barratt J, Tang SCW. IgA nephropathy: recent developments and therapeutic strategies. Lancet. 2019;393:2287–2298. (No DOI provided)
59. Bo S, Sun A, Yang W, Wang X, Liu L. Targeted therapeutic options based on the pathogenesis of IgA nephropathy. NDT. 2025;gfaf167. https://doi.org/10.1093/ndt/gfaf167
60. Bryce B, Sean B. New therapies for immunoglobulin A nephropathy: what's the standard of care in 2023? Nephrol Hypertens. 2024;33(3):311-317. (No DOI provided)
61. Willcocks L. ALIGNing the treatment of IgA nephropathy: Reducing proteinuria with endothelin A receptor inhibition. Med. 2025;6(10):100564. https://doi.org/10.1016/j.medj.2024.11.017
62. Perkovic V, Barratt J, Rovin B, Kashihara N, Maes B, Zhang H, et al. Alternative complement pathway inhibition with iptacopan in IgA nephropathy. N Engl J Med. 2025;392(6):531–43. https://doi.org/10.1056/nejmoa2410316
63. Praga M, Caravaca-Fontán F, Da Silva I, Fernández-Juárez G, Gutiérrez E, Sevillano AM, Trimarchi H. Tailored management strategies for IgA nephropathy based on clinical presentations. NDT. 2025;40(5):874-883. https://doi.org/10.1093/ndt/gfae289
64. Cheung CK, Barratt J, Liew A, Zhang H, Tesar V, Lafayette R. The role of BAFF and APRIL in IgA nephropathy: pathogenic mechanisms and targeted therapies. Front Nephrol. 2024;3:1346769. https://doi.org/10.3389/fneph.2023.1346769
65. Han HS, Lubetzky ML, Anandasivam NS, Cox RA, Lee BK. Recurrent Immunoglobulin A Nephropathy after Kidney Transplant - An Updated Review. Transplantology. 2023;4(3):161-177. https://doi.org/10.3390/transplantology4030016
66. Kooienga L, Lo J, Lee EY, Kim SG, Thomas H, Workeneh B, et al. Zigakibart demonstrates clinical safety and efficacy in a phase 1/2 trial of healthy volunteers and patients with IgA nephropathy. Kidney Int. 2025;108(3):445–54. https://doi.org/10.1016/j.kint.2025.05.006
67. Lv J, Liu L, Hao C, Li G, Fu P, Xing G, et al. Randomized phase 2 trial of telitacicept in patients with IgA nephropathy with persistent proteinuria. Kidney Int Rep. 2023;8(3):499–506. https://doi.org/10.1016/j.ekir.2022.12.014
68. Barratt J, Tumlin J, Suzuki Y, Kao A, Aydemir A, Pudota K, et al. Randomized phase II JANUS study of atacicept in patients with IgA nephropathy and persistent proteinuria. Kidney Int Rep. 2022;7(8):1831–41. https://doi.org/10.1016/j.ekir.2022.05.017
69. Lafayette R, Barbour S, Israni R, Wei X, Eren N, Floege J, et al. A phase 2b, randomized, double-blind, placebo-controlled, clinical trial of atacicept for treatment of IgA nephropathy. Kidney Int. 2024;105(6):1306–15. https://doi.org/10.1016/j.kint.2024.03.012
70. Floege J, Latus J, O'Shaughnessy M. Revolutionising IgA Nephropathy Care in the Era of Precision Medicine: Diagnostic Approaches, Evolving Guidelines, and Emerging Therapies. EMJ Nephrol. 2025;13(S1):2-10. https://doi.org/10.33590/emjnephrol/KZVG1889
71. Barratt J, Liew A, Yeo SC, Fernström A, Barbour SJ, et al. Phase 2 trial of cemdisiran in adult patients with IgA nephropathy: a randomized controlled trial. Clin J Am Soc Nephrol. 2024;19(4):452–

62. https://doi.org/10.2215/cjn.0000000000000384
72. Barratt J, Liew A, Yeo SC, Fernström A, Barbour SJ, Sperati CJ, et al. Efficacy and safety of ravulizumab in IgA nephropathy: a phase 2 randomized double-blind placebo-controlled trial. Clin J Am Soc Nephrol. 2025;36(4):645–56. https://doi.org/10.2215/cjn.0000000000000384
73. Lin L, Ren H, Li X, Xie J, Chen N. Prospective pilot study of plasma cell-targeted therapy with bortezomib in refractory IgA nephropathy. Kidney Int Rep. 2025;10(9):3023–31. https://doi.org/10.1016/j.ekir.2025.06.006
74. KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2024;105(Suppl 1):S1–S200. (No DOI provided)
75. Sethi S, De Vriese AS, Fervenza FC. Acute glomerulonephritis. Lancet. 2022;399(10335):1646-1663. (No DOI provided)
76. Caster DJ, Abner CW, Walker PD, Wang K, Heo J, Rava AR, Bunke M. Clinicopathological Characteristics of Adult IgA Nephropathy in the United States. Kidney Int Rep. 2023;8(9):1792-1800. https://doi.org/10.1016/j.ekir.2023.06.016
77. Chen H, Li X, Wu Y, Fan L, Tian G. Pregnancy-induced complications in IgA nephropathy: a case report. Medicine (Baltimore). 2018;97(15):e0470. https://doi.org/10.1097/md.0000000000010470
78. Shima H, Doi T, Okamoto T, Inoue T, Tashiro M, Wariishi S, et al. Successful treatment of nephrotic syndrome due to pregnancy-related crescentic IgA nephropathy: a case report. BMC Nephrol. 2023;24(1):92. https://doi.org/10.1186/s12882-023-03152-y
79. Fabhalta (Iptacopan) [prescribing information]. U.S. Food and Drug Administration; 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/218276Orig1s000Lbl.pdf
80. Ito S, et al. Drug therapy and lactation: clinical pharmacology of drugs in breast milk. Clin Pharmacokinet. 2020;59:121–143. (No DOI provided)
81. Rovin BH, et al. Management of IgA nephropathy: recent advances. Kidney Int. 2022;101:799–812. (No DOI provided)
82. Drugs.com. Iptacopan and breastfeeding. Available from: https://www.drugs.com/pregnancy/iptacopan.html