DOI：10.6314/JIMT.202512_36(6).07 內科學誌 2025：36：397-406

Recent Advances in IgA Nephropathy Treatment

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Abstract

Among patients with IgA nephropathy (IgAN), kidney failure develops in ≥30% of cases within 20 to 30 years, despite optimized standard care. A critical step in the pathogenesis of IgAN is the production of galactose-deficient IgA1(Gd-IgA1), which triggers autoantibody release. Historically, interventions for IgAN have focused on supportive treatments, such as renin–angiotensin system inhibitors. With an improved understanding of disease pathogenesis, treatments can be categorized according to the 'four-hit hypothesis,' targeting different stages of the process. Therapeutic strategies are now divided into non-immunologic (e.g., ACEi/ARBs, Sodium-glucose cotransporter-2 (SGLT2) inhibitors, sparsentan) and immunologic therapies(e.g., corticosteroids, Nefecon, APRIL/BAFF inhibition, complement blockade).Immunologic therapy in IgAN has traditionally been limited to glucocorticoids, which are associated with significant adverse effects. In December 2023, an oral, delayed-release formulation of budesonide (Nefecon) became the first drug to receive full approval from the U.S. Food and Drug Administration (FDA) for the treatment of IgAN. Sparsentan is a dual endothelin and angiotensin II receptor antagonist that has been shown to reduce proteinuria and slow kidney function decline in adults with IgAN who are at risk of disease progression. Atrasentan, a selective endothelin type A receptor antagonist currently being evaluated in a phase 3 clinical trial, has also demonstrated a significant reduction in proteinuria at 36 weeks. This review summarizes key studies on the treatment of IgA nephropathy (IgAN), which is now entering a new therapeutic era.

Key Words: atrasentan, IgA nephropathy, Nefecon, sparsentan, sodium-glucose cotransporter-2 inhibitors

Introduction

IgA nephropathy (IgAN) is the most common cause of primary glomerulonephritis worldwide[1]. Patients may present with a wide range of signs and symptoms, from asymptomatic microscopic hematuria to macroscopic hematuria. The clinical progression of the disease varies, with 30-40% of patients developing end-stage renal disease (ESRD) 20-30 years after their initial clinical presentation[1-3]. Despite the significant burden and prevalence of kidney failure associated with IgAN, the mainstay of disease management has been supportive care using renin angiotensin system (RAS) blockers to attenuate proteinuria and control blood pressure[1]. There were no approved targeted treatments for the condition until recently. With an improved understanding of disease pathogenesis,"the four-

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hit hypothesis" (Figure 1), several pharmacotherapies with novel mechanisms of action are now being evaluated to address this unmet need. With recent advances in the treatment of IgAN, nephrologists are calling for a new paradigm, and KDIGO has just released new 2025 guidelines for IgAN[4]. In this review, we summarize key studies on the treatment of IgAN, including results from several phase 3 trials, to provide updated insights into anticipated changes in management of IgAN over the next 5 to 10 years[5].

IgAN pathogenesis

Recent advancements have improved our understanding of IgAN pathogenesis. A central feature of IgAN is an increase in circulating levels of galactose-deficient IgA1 (Gd-IgA1)[6]. Gd-IgA1 refers to a form of IgA1 that is poorly galactosylated. In a normal IgA1 molecule, there is significant galactosylation at the hinge region. However, in individuals with IgAN, this galactosylation is deficient or absent, which leaves the hinge region exposed. This exposure turns the hinge region into an autoantigen, as the protective galactose is no longer present. The underlying concept is that when galactosylation is removed, the previously hidden antigen is now exposed, triggering an autoimmune response that contributes to the development of IgAN. IgAN has been proposed to develop through a "four-hit hypothesis": (1) overproduction of glycosylated galactose-deficient IgA1 (Gd-IgA1) (2) formation of anti-Gd-IgA1 autoantibodies (3) aggregation of Gd-IgA1 and formation of IgA1 immune complexes (4) and, lastly, deposition of these immune complexes in the glomerular mesangium, leading to kidney inflammation and scarring[6]. The alternative complement pathway is the major complement cascade activator in IgAN, and glomerular C3 deposition has been shown to correlate with disease progression[7].

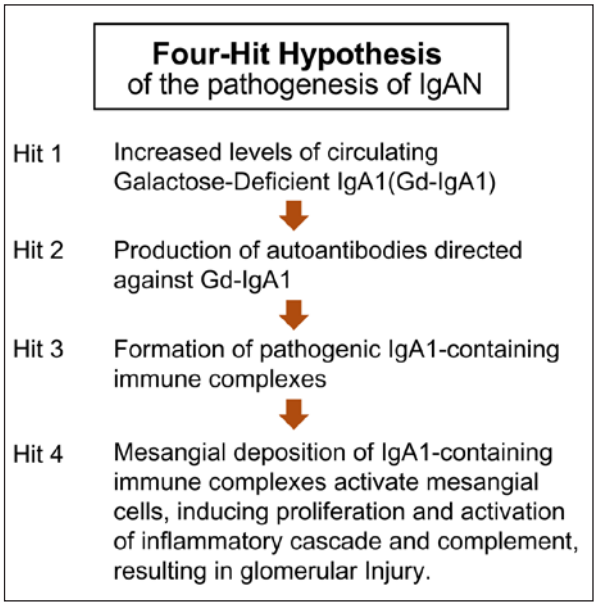

Figure 1.

Treatment strategy

Therapeutic strategies can be divided into non-immunologic (e.g., ACEi/ARBs, SGLT2 inhibitors, sparsentan) and immunologic therapies (e.g., corticosteroids, Nefecon, APRIL/BAFF inhibition, complement blockade)(Table 1)[4,5,8]. Using non-immunologic therapies to manage IgAN as a chronic kidney disease (CKD) aims to decrease proteinuria and slow the decline of renal function. With an improved understanding of disease pathogenesis, treatments can be categorized according to the 'four-hit hypothesis,' targeting different stages of the process. According to the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases, the primary focus of management should be optimized supportive care, which encompasses rigorous BP control (<120/70 mmHg), optimal inhibition of the renin–angiotensin system (RAS), and lifestyle modification, including weight reduction, exercise, smoking cessation, and dietary sodium restriction. KDIGO 2021 guideline recommend a stepwise approach: supportive care as first-line and considering systemic corticosteroids for high-risk cases after ≥3 months of optimized care. Supportive care with RAS inhibitors (RASi) remain

the standard of care for managing adult patients with IgAN. If the patient has proteinuria >0.5 g/d, KDIGO recommend that initial therapy be with either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB)[1].

The 2025 KDIGO guideline introduces a major new concept: treatment simultaneously with (i) therapies aimed at preventing or reducing pathogenic IgA production and immune complex formation, and (ii) interventions that manage the effects of nephron loss due to established IgAN[4]. Although the 2021 guideline recommended reducing proteinuria to <1 g/day, accumulating evidence has shown that proteinuria ≥0.5 g/day is a biomarker of increased risk for kidney disease progression in IgAN. Therefore, the new 2025 KDIGO guideline has revised the proteinuria target to <0.5 g/day, ideally <0.3 g/day, regardless of IgAN treatment status[4].

Renin-Angiotensin System(RAS) inhibitors

Previous randomized controlled trials (RCT) endorse the use of RAS inhibitors (RASi) in IgAN. In a RCT of 109 Asian patients with IgAN, ARB (valsartan) significantly reduced proteinuria and slowed renal deterioration[9]. In an RCT of 44 European patients with IgAN, ACE inhibitors (enalapril) significantly improved renal survival in proteinuric IgAN patients with normal or moderately reduced renal function[10]. On the other hand, according to recent understandings of IgAN pathogenesis, immunologic therapy has become a key strategy to target IgAN-specific mechanisms, such as reducing the production of the pathogenic form of IgA (Gd-IgA1) and its associated complexes. Other new immunologic therapies, including anti-inflammatory approaches, aim to mitigate the downstream effects of immune complex deposition and inflammation in the kidneys. The three main strategies—managing CKD, targeting Gd-IgA1 and immune complexes, and employing anti-inflammatory treatments—represent the primary avenues for advancing IgAN therapy in the coming years[5].

Systemic corticosteroids

However, the safety and efficacy of systemic steroid treatment are still under debate[1,4,5]. The evidence of systemic corticosteroids mainly came from two large RCTs, STOP-IgAN and TESTING trial. The STOP-IgAN trial included 162 IgAN patients who were randomly assigned to either continue supportive care or receiving supportive care plus immunosuppressive therapy[11]. After 3 years, the STOP-IgAN trial found that the addition of immunosuppressive therapy to intensive supportive care in high-risk IgAN patients did not significantly improve outcomes. And, more adverse effects were observed in patients who received immunosuppressive therapy[11]. After 10 years of follow-up, the STOP-IgAN researchers evaluated renal outcomes in terms of the time to first occurrence of a composite endpoint: death, end-stage kidney disease (ESKD), or a decline of more than 40% in estimated glomerular filtration rate(eGFR). The analysis showed no difference between supportive care plus immunosuppression and supportive care alone in IgAN[12].

The evidence of systemic steroid mainly came from another study, the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study. The TESTING study was a randomized clinical trial comparing oral methylprednisolone with placebo on the risk of important kidney outcomes in people with IgAN receiving appropriate supportive therapy. In the initial full-dose design, patients were randomized 1:1 to oral methylprednisolone (0.6-0.8mg/kg/d; maximum,48mg/d) or matching placebo. Recruitment for this full-dose trial was halted midway due to an increased incidence of serious infections in the corticosteroid group[13].

Then, the study resumed using a reduced-dose regimen (0.4 mg/kg/day, maximum 32 mg/day, tapered by 4 mg/day per month), along with the

addition of antibiotic prophylaxis against Pneumocystis pneumonia for subsequent participants. The recently published TESTING study showed that, among patients with IgAN at high risk of progression, treatment with oral methylprednisolone for 6 to 9 months, significantly reduced the risk of the composite outcome of kidney function decline, kidney failure, or death due to kidney disease compared with placebo. However, the incidence of serious adverse events increased with oral methylprednisolone, mainly with high-dose regimen[14]. The new 2025 KDIGO guideline recommend: "In settings where Nefecon is not available, we suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with a reduced-dose systemic glucocorticoid regimen combined with antimicrobial prophylaxis"[4].

Tonsillectomy

Studies from Japan have reported improved kidney survival following tonsillectomy. In a Japan study included 1065 patients with IgAN, tonsillectomy was associated with a lower risk of renal outcomes (occurrence of a 1.5-fold increase in serum creatinine level from baseline or dialysis initiation) in patients with IgAN[15]. Therefore, tonsillectomy is performed routinely in Japan. However, there is limited evidence supporting the benefit of tonsillectomy in other populations. As a result, the KDIGO 2021 Clinical Practice Guideline suggests that tonsillectomy should not be performed as a treatment for IgAN in Caucasian patients[1].

New treatment direction

Advances in understanding the pathophysiology of IgAN have led to clinical trials of novel targeted therapies with acceptable safety profiles, including SGLT2 inhibitors, endothelin receptor blockers, targeted-release budesonide, B cell proliferation and differentiation inhibitors, as well as blockade of complement components.

The 2021 KDIGO Clinical Practice Guideline recommend: "In view of the current uncertainty over the safety and efficacy of existing immunosuppressive treatment choices, all patients who remain at high risk of progressive CKD despite maximal supportive care should be offered the opportunity to take part in a clinical trial."[1] Two new drugs, Nefecon and sparsentan, have recently been approved for the treatment of IgAN and are now recommended in the 2025 KDIGO guidelines[4]. For systemic glucocorticoid therapy, the 2025 KDIGO guidelines suggest that patients at risk of progressive kidney function loss due to IgAN be treated with a reduced-dose systemic glucocorticoid regimen, combined with antimicrobial prophylaxis, when Nefecon is not available[4].

Furthermore, key mediators of Gd-IgA1 production and its corresponding autoantibody responses are B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL). Both BAFF and APRIL are essential for B-cell survival and humoral immunity. Elevated serum levels of both BAFF and APRIL are observed in patients with IgAN and correlate with disease severity[8]. This enhanced understanding of IgAN pathogenesis has paved the way for the development of novel therapeutic approaches targeting these underlying mechanisms.

Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors)

Evidence for SGLT2 inhibitors comes from subgroup analyses in two major trials: the DAPA-CKD and EMPA-KIDNEY trials. These studies evaluated the use of SGLT2 inhibitors in patients with non-diabetic CKD, the majority of whom had IgAN. In the DAPA-CKD trial, the primary composite endpoint was a sustained decline in eGFR of 50% or more, end-stage kidney disease, or death from a kidney disease-related or cardiovascular cause. Of 270 participants with IgAN, 137 were

randomized to dapagliflozin and 133 to placebo, Dapagliflozin reduced proteinuria and slowed the decline in eGFR. The primary outcome occurred in six (4%) participants on dapagliflozin and 20 (15%) on placebo (hazard ratio, 0.29; 95% confidence interval, 0.12, 0.73). Mean rates of eGFR decline with dapagliflozin and placebo were -3.5 and -4.7 mL/min/1.73m^2/year, respectively. Dapagliflozin reduced the urinary albumin-to-creatinine ratio by 26% relative to placebo[16].

The EMPA-KIDNEY primarily investigated the effects of empagliflozin, a SGLT2 inhibitor, in patients with CKD, including those with IgAN. Notably, the EMPA-KIDNEY trial included 800 IgAN patients. Subgroup analyses from the EMPA-KIDNEY trials show that empagliflozin substantially slow the progression of CKD irrespective of the primary kidney disease. Among patients with different subtypes of glomerular disease, the relative reductions in chronic rate of eGFR decline were -43% (95% CI -59 to -27) in patients with IgAN nephropathy[17].

Nefecon

The pathologic Gd-IgA1 is believed to originate from mucosal sited B cells, which are abundant in the Peyer's patches-rich distal ileum. Nefecon, an oral, delayed-release formulation of budesonide, is designed to specifically target the mucosa in the Peyer's patches of the distal small intestine, thereby minimizing systemic exposure to corticosteroids. Nefecon works by reducing the production of pathogenic IgA by the mucosal immune system and was recently approved for the treatment of IgAN. The 2-year, phase 3 NefIgArd trial of Nefecon randomized patients to receive either a nine-month course of oral 16 mg Nefecon or a placebo[18]. After nine months, the drug was discontinued, and patients were followed by a 15-month observational follow-up period off study drug. After 9 months of treatment, patients assigned to Nefecon had a 27% reduction in UPCR compared with placebo. Notably, the reduction in proteinuria persisted for about three months after stopping the drug[18]. The average of eGFR over 2 years showed a statistically significant treatment benefit with Nefecon versus placebo (difference 5·05 mL/min/ 1.73 m^2, p<0.0001)[19]. 9 months of Nefecon was seen to be generally well tolerated, with a safety profile consistent with that expected for an oral budesonide. The most commonly reported treatment-emergent adverse events during treatment with Nefecon were peripheral edema (17%) and hypertension (12%). One study from mainland China, which including 62 IgAN patients, the efficacy outcomes were consistent with global study results[20].

Endothelin receptor antagonists

Endothelin-1 (ET-1), largely through activation of endothelin A receptors (ET_AR), has been strongly implicated in renal cell injury, proteinuria, inflammation and fibrosis, all of which contribute to the progression of CKD. Endothelin receptor antagonists have been demonstrated to ameliorate or even reverse renal injury and/or fibrosis in experimental models of CKD[21]. Recent studies have further demonstrated that ET-1 plays a significant role in the pathophysiology of IgAN via activation of ET_AR, leading to a variety of effects including vasoconstriction, podocyte dysfunction, tubular injury, inflammation, and fibrosis[22].

Sparsentan

Sparsentan is a non-immunosuppressive, dual endothelin and angiotensin II receptor antagonist with high selectivity for the ET_AR and angiotensin II subtype 1 receptor (AT1 receptor). The phase 3 PROTECT trial is a double-blind, randomised, active-controll study designed to evaluate the efficacy and safety of sparsentan (400 mg once daily) versus the active control irbesartan (300 mg once daily) in adults with biopsy-proven IgAN and pro-

teinuria of 1.0 g/day or higher despite maximized RASi treatment for at least 12 weeks. At week 36, the proteinuria change change from baseline was statistically significantly greater in the sparsentan group (–49.8%) than the irbesartan group (–15.1%), resulting in a between-group relative reduction of 41% (p<0.0001)[23]. Treatment-emergent adverse events with sparsentan were similar to irbesartan. The 2-year results showed that patients in the sparsentan group had a slower rate of eGFR decline than those in the irbesartan group. eGFR chronic 2-year slope was −2.7 mL/min/1.73 m²/year versus −3.8 mL/min/ 1.73 m²/ year (difference 1.1 mL/min/1.73 m²/ year, 95% CI 0.1 to 2.1; p=0.037)[24]. The significant reduction in proteinuria at 36 weeks with sparsentan was maintained throughout the study period; at 110 weeks, proteinuria was 40% lower in the sparsentan group than in the irbesartan group. The 2-year results showed that treatment with sparsentan versus maximally titrated irbesartan in patients with IgAN resulted in significant reductions in proteinuria and preservation of kidney function[24].

Atrasentan

Atrasentan, a selective endothelin type A receptor antagonist, exerts antiproliferative, antifibrotic, and anti-inflammatory effects in experimental models of IgA nephropathy. The ALIGN study is a phase 3, multinational, double-blind, randomized, placebo-controlled trial involving adults with biopsy-proven IgAN, a total urinary protein excretion of at least 1 g per day. Patients were randomly assigned to receive atrasentan (0.75 mg per day) or matched placebo for 132 weeks. An interim analysis was conducted at 36 weeks, with a follow-up for two-year eGFR data. The use of atrasentan was associated with a significant reduction in proteinuria, with a 38% reduction at 9 months. At week 36 visit, the proteinuria change was significantly greater with atrasentan (−38.1%) than with placebo (−3.1%)[25]. Of the most common adverse events, nasopharyngitis(10.1%), fluid retention(11.2%), peripheral edema(8.9%), anemia(6.5%), pyrexia(6.5%), and upper respiratory tract infection(6.5%) were more common in the atrasentan group than in the placebo group[25]. The ALIGN study is an ongoing phase 3 clinical trial, and the effect of atrasentan on kidney function over time requires a longer follow-up for analysis.

Conclusions

To approach patients with IgA nephropathy, standard of care primarily focuses on nonspecific supportive CKD care and non-immunologic therapies, including blood pressure control and the use of ACE inhibitors or ARBs to manage proteinuria, although these have shown only modest efficacy. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are increasingly being utilized in IgAN, as secondary analyses of large phase 3 CKD trials have demonstrated proteinuria reduction and slower kidney disease progression in patients with advanced IgAN. A critical step in IgAN pathogenesis is the production of Gd-IgA1, which triggers the formation of autoantibodies, leading to the formation of immune complexes that deposit in the glomerular mesangium, activating complement, causing inflammation, and resulting in progressive kidney damage.

The 2025 KDIGO guideline introduces a major new concept: treatment simultaneously with (i) therapies aimed at preventing or reducing pathogenic IgA production and immune complex formation, and (ii) interventions that manage the effects of nephron loss due to established IgAN[4]. Immunosuppressive therapies with systemic glucocorticoids in IgAN patients have been associated with substantial adverse events. However, in December 2023, targeted-release budesonide (Nefecon) became the first FDA-approved drug specifically for IgAN. Efforts to cure IgAN now focus on reducing Gd-IgA1 levels. Sparsentan, a dual endothelin and angiotensin receptor antagonist, received

FDA accelerated approval for patients at high risk of disease progression. Nefecon, sparsentan and SGLT2 inhibitors have been listed in the recommendation for IgAN treatment in 2025 KDIGO guideline[4]. Atrasentan, a selective endothelin type A receptor antagonist currently being evaluated in a phase 3 clinical trial, has also demonstrated a significant reduction in proteinuria at 36 weeks. Additionally, to further reduce inflammatory damage, complement inhibitors, which offer a more favorable side effect profile compared to corticosteroids, are being explored[7,26]. Other newly emerging immunologic agents proposed for the treatment of IgAN include (1) mycophenolate mofetil, hydroxychloroquine; (2) B-cell/Plasma cell targeting: anti-APRIL/BAFF antibodies(sibeprenlimab, atacicept zigakibart,); anti-CD38 antibody (felzartamab) (3) complement inhibitors: iptacopan, ravulizumab, avacopan

Table 1. pharmacologic treatment choices for IgA nephropathy

Pharmacologic category	Trials
■ **Non-immunologic**	
● Treatment goal: Manage of IgAN-induced renal loss	
Renin-angiotensin system inhibitor (RASi)	
angiotensin-converting enzyme inhibitor (ACEi)	
angiotensin II receptor blocker (ARB)	
DEARA (dual endothelin angiotensin receptor antagonist)	
Sparsentan	PROTECT
ERA (endothelin receptor antagonist)	
Atrasentan	ALIGN (phase 3)
sodium-glucose cotransporter-2 inhibitor (SGLT2i)	
Dapagliflozin	DAPA-CKD
Empagliflozin	EMPA-KIDNEY
■ **Immunologic**	
● Treatment goal: reduce pathogenic forms of IgA formation (gd-IgA1) and IgA-IC formation	
♦ **Nefecon** (oral formulation of budesonide)	NefIgArd
● Treatment goal:	
Prevent or reduce IgA-IC–mediated glomerular injury anti-inflammatory and/ or anti-fibrotic	
Systemic glucocorticoids	TESTING
Mycophenolate mofetil (MMF)	
Hydroxychloroquine	
♦ **B-Cell-Targeted Therapies**	
Anti-APRIL ± BAFF monoclonal antibody	
Sibeprenlimab (Anti-APRIL)	Visionary (phase 3)
Atacicept (dual BAFF/APRIL inhibitor)	ORINGIN (phase 3)
Zigakibart (Anti-APRIL)	BEYOND (phase 3)
Anti-CD38 monoclonal antibody	
Felzartamab	IGNAZ (phase 2)
♦ **Complement inhibitors**	
Iptacopan (Factor B inhibitor)	APPLAUSE-IgAN (phase 3)
Ravulizumab (complement C5 inhibitor)	SANCTUARY (phase 2)

IgA-IC, immunoglobulin A–containing immune complex; BAFF, B-cell Activating Factor; APRIL, A PRoliferation-Inducing Ligand.

[7,26-32].(Table 1). In this review, we summarize key studies on the treatment of IgAN, including results from several phase 3 trials. The long-term outcomes of these new therapies are still lacking. Moreover, the addition of SGLT2 inhibitors to RAS inhibitor therapy for IgAN has only been introduced recently. Therefore, it is difficult to compare the results at this time point. The efficacy and safety of these new therapies remain under evaluation. However, based on these promising new therapies, patients with IgAN may consider enrollment in a clinical trial[1].

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. Kidney Int 2021;100(4S):S1-276.
2. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on Progressive Renal Diseases. Am J Kidney Dis 1997;29(4):526-32.
3. Beukhof JR, Kardaun O, Schaafsma W, et al. Toward individual prognosis of IgA nephropathy. Kidney Int 1986;29(2):549-56.
4. Kidney Disease: Improving Global Outcomes (KDIGO) IgAN and IgAV Work Group, Rovin BH, Barratt J, et al. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). Kidney Int 2025;108(4S):S1-71.
5. 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):640-51.
6. Stamellou E, Seikrit C, Tang SCW, et al. IgA nephropathy. Nat Rev Dis Primers 2023;9(1):67.
7. Caravaca-Fontán F, Gutiérrez E, Sevillano ÁM, Praga M. Targeting complement in IgA nephropathy. Clin Kidney J 2023;16(Suppl 2):ii28-39.
8. Cheung CK, Barratt J, Liew A, Zhang H, Tesar V, Lafayette R. The role of BAFF and APRIL in IgAN: pathogenic mechanisms and targeted therapies. Front Nephrol 2024;3:1346769.
9. Li PK, Leung CB, Chow KM, et al.; HKVIN Study Group. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. Am J Kidney Dis 2006;47(5):751-60.
10. Praga M, Gutiérrez E, González E, Morales E, Hernández E. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. J Am Soc Nephrol 2003;14(6):1578-83.
11. Rauen T, Eitner F, Fitzner C, et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. N Engl J Med. 2015;373(23):2225-36.
12. Rauen T, Wied S, Fitzner C, et al. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. Kidney Int 2020;98(4):1044-52.
13. Lv J, Zhang H, Wong MG, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. JAMA 2017;318(5):432-42.
14. Lv J, Wong MG, Hladunewich MA, 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.
15. Hirano K, Matsuzaki K, Yasuda T, et al. Association Between Tonsillectomy and Outcomes in Patients With Immunoglobulin A Nephropathy. JAMA Netw Open 2019;2(5):e194772.
16. Wheeler DC, Toto RD, Stefánsson BV, 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.
17. EMPA-KIDNEY Collaborative Group. Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial. Lancet Diabetes Endocrinol 2024;12(1):51-60.
18. Barratt J, Lafayette R, Kristensen J, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. Kidney Int 2023;103(2):391-402.
19. Lafayette R, Kristensen J, Stone A, 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.
20. Zhang H, Lafayette R, Wang B, et al. Efficacy and Safety of Nefecon in Patients with IgA Nephropathy from Mainland China: 2-Year NefIgArd Trial Results. Kidney360 2024;5(12):1881-92.
21. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. Kidney Int 2014;86(5):896-904.
22. De Miguel C, Speed JS, Kasztan M, Gohar EY, Pollock DM. Endothelin-1 and the kidney: new perspectives and recent findings. Curr Opin Nephrol Hypertens 2016;25(1):35-41.
23. Heerspink HJL, Radhakrishnan J, Alpers CE, et al. Sparsentan in patients with IgAN: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. Lancet 2023;401(10388):1584-94.
24. Rovin BH, Barratt J, Heerspink HJL, 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(10417):2077-90.
25. Heerspink HJL, Jardine M, Kohan DE, et al. Atrasentan in Patients with IgA Nephropathy. N Engl J Med 2025;392(6):544-54.

26. Cheung CK, Barratt J. The Rapidly Changing Treatment Landscape of IgA Nephropathy. Semin Nephrol 2024;44(5):151573.
27. Mathur M, Barratt J, Chacko B, et al. A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy. N Engl J Med 2024;390(1):20-31.
28. Barratt J, Barbour SJ, Brenner RM, et al; ORIGIN Phase 2b Investigators. Long-Term Results from an Open-Label Extension Study of Atacicept for the Treatment of IgA Nephropathy. J Am Soc Nephrol 2025;36(4):679-87.
29. Perkovic V, Barratt J, Rovin B, et al. Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy. N Engl J Med 2025;392(6):531-43.
30. Lafayette R, Tumlin J, Fenoglio R,et al. Efficacy and Safety of Ravulizumab in IgA Nephropathy: A Phase 2 Randomized Double-Blind Placebo-Controlled Trial. J Am Soc Nephrol 2025;36(4):645-56.
31. Kooienga L, Lo J, Lee EY,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.
32. Floege J, Lafayette R, Barratt J, et al. Randomized, double-blind, placebo-controlled phase 2a study assessing the efficacy and safety of felzartamab for IgA nephropathy. Kidney Int 2025;108(4):695-706.

IgA 腎病變治療新進展

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摘要

在 IgA 腎病 (IgA nephropathy, IgAN) 患者中，儘管接受了最佳的標準治療，仍有 30% 以上的病例會在 20 到 30 年內發展為腎衰竭。IgAN 發病機制中的一個關鍵步驟是產生 galactose-deficient IgA1 (Gd-IgA1)，這會引發自體抗體的釋放。在過去，IgAN 的治療主要以支持性治療，例如使用腎素—血管緊張素系統抑制劑 (renin-angiotensin system inhibitors)。隨著對疾病發病機轉理解的提升，治療方式可以根據「four-hit hypothesis」進行分類，針對病程的不同階段介入治療。目前的治療策略可分為非免疫療法（如 ACEi/ARB、第 2 型鈉 - 葡萄糖轉運蛋白抑制劑 (Sodium-glucose cotransporter-2 (SGLT2) inhibitors)、sparsentan）和免疫療法（如皮質類固醇、Nefecon、APRIL/BAFF 抑制、補體阻斷）。針對 IgAN，傳統的免疫療法主要侷限於糖皮質激素，但其伴隨著顯著的不良反應。2023 年 12 月，美國食品藥物管理局 (FDA) 已正式批准一款針對 IgAN 治療的口服緩釋劑 budesonide (Nefecon)。此外，另一種新藥 sparsentan 是一種內皮素與血管張力素 II 受體拮抗劑 (dual endothelin and angiotensin receptor antagonist)，研究已顯示用於治療疾病進展高風險的 IgAN 成人患者可減少蛋白尿並減緩腎功能惡化的速度。另一種選擇性內皮素 A 型受體拮抗劑—Atrasentan，正在進行第三期臨床試驗，也顯示在第 36 週時能顯著減少蛋白尿。2025 年 KDIGO 指南引入了一個全新的重要概念：同時雙管齊下的治療策略—(1) 針對預防或減少致病性 IgA (Gd-IgA1) 產生與免疫複合物形成的治療，以及 (2) 用於處理因已存在的 IgAN 所導致腎元喪失後果的治療。2021 年 KDIGO 的指南建議將蛋白尿控制在 <1 g/ 天，新的 2025 年 KDIGO 指南已將蛋白尿控制目標修訂為 <0.5 g/ 天，理想狀況下應低於 <0.3 g/ 天。本文也概述了幾個近年來關於 IgA 腎病 (IgAN) 治療的關鍵臨床研究，顯示該疾病的治療正邁入新的時代。