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REVIEW

Advances in the treatment of IgA nephropathy with biological agents

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Abstract

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease, and the "four-hit" theory represents its currently accepted pathogenic mechanism. Mucosal immunity triggered by infections in the respiratory tract, intestines, or other areas leads to antigen presentation, T cell stimulation, B cell maturation, and the production of IgA-producing plasma cells. The proteins B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) are involved in this process, and alternative complement and lectin pathway activation are also part of the pathogenic mechanism. Kidney Disease Improving Global Outcomes guidelines indicate that a specific effective treatment for IgAN is lacking, with renin–angiotensin–aldosterone system inhibitors being the primary therapy. Recent research shows that biological agents can significantly reduce proteinuria, stabilize the estimated glomerular filtration rate, and reverse some pathological changes, such as endocapillary proliferation and crescent formation. There are four main categories of biological agents used to treat IgA nephropathy, specifically anti-CD20 monoclonal antibodies, anti-BLyS or APRIL monoclonal antibodies, monoclonal antibodies targeting both BLyS and APRIL (telitacicept and atacicept), and monoclonal antibodies inhibiting complement system activation (narsoplimab and eculizumab). However, further research on the dosages, treatment duration, long-term efficacy, and safety of these biological agents is required.

KEYWORDS

anti-CD20 monoclonal antibodies, APRIL, biological agents, BLyS, complement, IgA nephropathy

Key points

- Biological agents for immunoglobulin A nephropathy (IgAN) treatment can significantly reduce proteinuria, stabilize the estimated glomerular filtration rate, and reverse endocapillary proliferation and crescent formation with minimal severe adverse reactions.
- There are four categories of biological agents used to treat IgAN in literature reports, anti-CD20 monoclonal antibodies (including rituximab and ofatumumab), anti-B-lymphocyte stimulator (BLyS) (belimumab) or a proliferation-inducing ligand (APRIL) monoclonal antibodies (BION-1301), monoclonal antibodies targeting both BLyS and APRIL

simultaneously (including telitacicept and atacicept), and monoclonal antibodies inhibiting complement system activation (including narsoplimab and culizumab).

1 | INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is a primary glomerular disease characterized by dominant immunoglobulin A (IgA) deposition in the mesangial area of the glomerulus. In China, it is still one of the most common types of glomerular disease, accounting for 24.09%–35.80% of renal biopsy cases.[1,2] IgAN renal lesions are diverse and can comprise minimal change disease (MCD), focal segmental mesangial proliferative glomerulonephritis, diffuse mesangial proliferative glomerulonephritis with focal segmental glomerulosclerosis, proliferative and sclerosing glomerulonephritis, and even crescentic glomerulonephritis. In 2009, the Oxford MEST score was proposed for prognostic evaluations, and it includes mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T). In 2017, this scoring system was updated to include crescents (C), and the MEST-C score is now recognized as being able to predict the prognosis of IgAN.[3,4]

A cohort study, including 1155 Chinese adults with IgAN, determined the 10-, 15-, and 20-year cumulative survival rates, calculated based on the Kaplan–Meier method, to be 83%, 74%, and 64%, respectively. Moreover, within 20 years, 36% of patients progressed to end-stage renal disease (ESRD), and proteinuria >1.0 g/day (HR, 3.2), an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (HR, 2.6), hypertension (HR, 1.9), hypoalbuminemia (HR, 2.0), and hyperuricemia (HR, 2.1) were determined to be independent risk factors. The time-average proteinuria (TA-P) during follow-up was found to be the most important risk factor for renal failure. Further, the ESRD risk was 9.4 times higher for patients with a TA-P > 1.0 g/day, as than the risk for those with a TA-P < 1.0 g/day, and 46.5 times higher than the risk for those with a TA-P < 0.5 g/day. Herein, the treatment goal is to control urine protein at levels below 0.5 g/day.[5] There is currently no specific treatment for IgAN, and renin–angiotensin–aldosterone–system inhibitors (RASIs) comprise the basic treatment.[6,7] On the basis of in-depth research on the pathogenesis of IgAN, the overproduction of galactose-deficient IgA1 (Gd-IgA1) by B cells, the production of autoimmune antibodies against Gd-IgA1, the formation of a circulating immune complex (CIC), and complement bypass pathway and lectin pathway activation all participate in the development of IgAN.[8] As such, studies on biological agents targeting these IgAN-associated mechanisms have commenced, and they have shown promising therapeutic effects.

2 | PATHOGENESIS

The "four-hit" theory is currently used to describe the pathogenesis of IgAN. The first hit is the excessive production of Gd-IgA1. The abnormal glycosylation of IgA1 plays an important role in the development of IgAN, and IgA1 is a relatively rare O-linked glycoprotein among serum proteins. Patients with IgAN have increased levels of Gd-IgA1, as *O*-polysaccharides of IgA1 lack galactose. As such, the level of Gd-IgA1 is closely related to and an independent risk factor for the progression of IgAN.[9] In patients with IgAN, serum Gd-IA1 levels were found to be significantly correlated with the eGFR, serum IgA levels, and tubular atrophy/interstitial fibrosis. Moreover, chronic kidney disease (CKD) progression is more frequent in patients with IgAN with higher serum Gd-IgA1 levels than in those with lower levels.[10] Mucosal immunity might be the source of Gd-IgA1 produced upon B cell differentiation, and Gd-IgA1 originates from ectopic mucosal B cells. These B cells migrate from the mucosal induction site to the body and then secrete multiple Gd-IgA1 molecules directly into circulation. The chromosomal locus 22q12.2 can affect the susceptibility to IgAN, and this is closely related to the occurrence of inflammatory bowel disease. The second hit is the production of autoantibodies in response to Gd-IgA1 levels. Gd-IgA1 is antigenic, and its abnormal hinge region can stimulate the production of polysaccharide-specific immunoglobulin A (IgG) and IgA autoantibodies. The third hit is the formation of CICs. IgG antibodies against Gd-IgA1 are specific and can bind to Gd-IgA1, leading to the formation of Gd-IgA1–IgG immune complexes. Regarding the process of autoantibody and CIC formation, three loci on chromosome 6p21 are related to IgAN susceptibility.[11] The fourth hit is the deposition of immune complexes in the mesangial area. Transferrin receptor mediates endocytosis in mesangial cells, resulting in mesangial cell damage, complement activation, an increase in cytokines and growth factors, the proliferation of mesangial cells, and accumulation of the mesangial matrix. In IgAN, podocytopathy is the consequence of initial alterations to the mesangial area with the accumulation of IgA-containing immune material. Podocytes are therefore affected by interactions of messages originally driven from the mesangium[12] (Figure 1).

The third hit and fourth hits are affected by polymorphisms in the gene encoding complement regulatory factor H. This gene is located in 1q32. However, genome-wide association studies (GWASs)

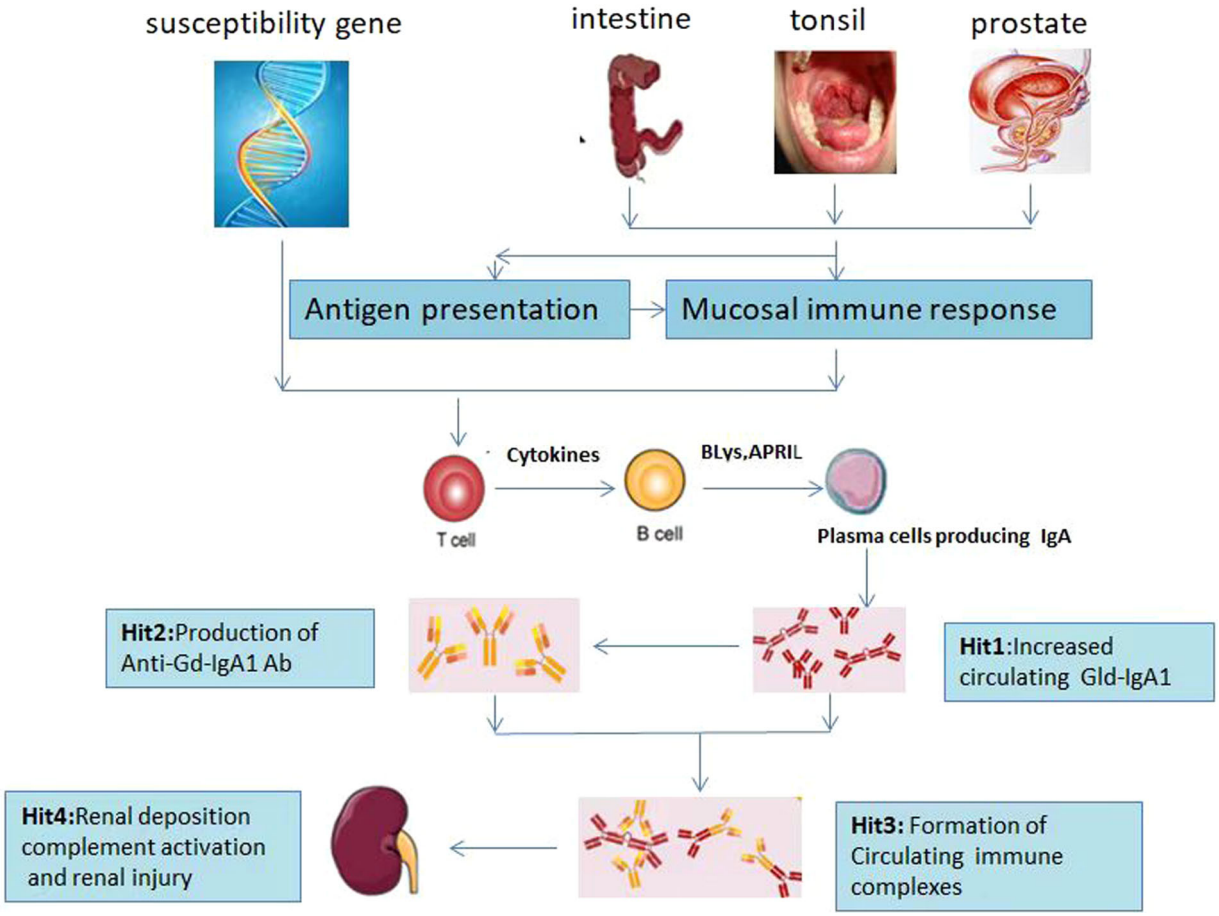

FIGURE 1 Pathogenesis of IgAN: four-hit mechanism. Gld-IgA1, galactose-deficient IgA1. Hit 1: production of Gld-IgA1 by a subpopulation of IgA1-secreting cells. Hit 2: circulating antibodies directed against Gld-IgA1. Hit 3: formation of pathogenic Gld-IgA1-containing immune complexes. Hit 4: mesangial deposition of Gld-IgA1-containing immune complexes, complement activation, and initiation of glomerular injury. APRIL, a proliferation-inducing ligand; BLyS, B-lymphocyte stimulator; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy.

confirmed that genetic susceptibility in the Han Chinese population is different from that in the Caucasian population. Moreover, the susceptibility site in 1q32 in the Chinese Han population has not been confirmed. In addition to the major histocompatibility complex (MHC) and 22q12.2 susceptibility loci mentioned previously herein, two new susceptibility genes were found to be located in 17p13 and 8p23. The new Chinese Han susceptibility genes were found in 17p13 (rs3803800 and rs4227) and 8p23 (rs2738048) and encode tumor necrosis factor (TNFSF13) and alpha-defensin.[13] Further, an IgAN GWAS meta-analysis identified three new susceptibility loci, including 1p36.13 (encoding FCRL3), 1q23.1 (encoding DUSP22/IRF4), and 6p25.3 (encoding PADI4). Three HLA polymorphisms and two SNPs in the MHC region are also associated with susceptibility, and 14 susceptibility loci have been discovered, explaining approximately 7.5% of the genetic variation. Further, genetically heterogeneous loci between the Chinese Han population and the European population have been identified.[14]

The alternative complement and lectin pathways play a role in the development of IgAN. Mannose-binding lectin-associated serine protease 2 (MASP-2), a mannan-binding lectin-associated serine protease, is an effector enzyme of the lectin signaling pathway. The mannose ligand–MBL–MASP-2 complex (not including MASP-1) can activate C4 and C2 and induce the formation of C3 invertase (c4b2a), and the complex with Masp-1 can directly cleave and activate C3. Furthermore, it can facilitate the generation of C3b fragments and activate the complement replacement pathway.[15] C3, properdin, C4d, MBL, MASP-1, MASP-2, and C5b-9 are deposited in the mesangium of renal tissue in IgAN, and they are related to disease activity and progression.[8,16] Inhibiting MASP-2 does not affect the classical signaling pathway of the complement system based on the binding of antibodies and antigens, and it does not affect the immune response to foreign infections, avoiding an increased risk of infection for patients. Therefore, targeting the complement pathway has become a new treatment strategy for IgAN.

3 | TREATMENT OF IGAN

3.1 | Nonbiological treatment agents

3.1.1 | Nonimmunosuppressive therapy

Specific effective treatment strategies for IgAN are lacking. To date, the international guidelines for IgAN treatment only include the 2021 Kidney Disease Improving Global Outcomes (KDIGO) guidelines and the 2020 guidelines of the Japanese Society of Nephrology (JSN).[6,17] The 2021 KDIGO guidelines recommend blood pressure management for all IgAN cases. Further, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are recommended with urinary protein levels >0.5 g/day, but combining ACEIs and ARBs is not advised.[6] In addition, sodium–glucose cotransporter 2 inhibitors (SGLT2is) and finerenone have been proven to reduce proteinuria and delay the progression of kidney disease in recent randomized controlled studies.[18–20]

The addition of SGLT2is slows disease progression and reduces cardiac events in both diabetic and nondiabetic patients with CKD. Moreover, dapagliflozin significantly reduces the cardiorenal composite endpoint, renal hard endpoint, risk of cardiovascular death or hospitalization for heart failure, and risk of all-cause mortality by 39%, 44%, 29%, and 31%, respectively.[18] Moreover, a subgroup-pre-specified analysis of the DAPA-CKD study demonstrated that for patients with IgAN (eGFR, 25–75 mL/min/1.73 m^2 and urinary albumin-to-creatinine ratio [ACR] of 200–5000 mg/g), when added to ACEI/ARB therapy, dapagliflozin could significantly and substantially reduce the risk of CKD progression, with a favorable safety profile.[19] Further, finerenone, can reduce the risk of clinically important cardiovascular and kidney outcomes, compared with that with a placebo, across the CKD spectrum in patients with type 2 diabetes.[20] Finerenone was also speculated to reduce proteinuria and cardiac and renal events associated with IgAN. However, acute renal injury and hyperkalemia caused by this drug must be considered.

3.1.2 | Corticosteroids and immunosuppressive agents

Patients with persistent proteinuria greater than 1 g/day after 90 days of optimized therapy are considered at a high risk of IgAN progression.[6] These patients can consider a 6-month course of glucocorticoid treatment, provided that their eGFR is greater than 50 mL/min/1.73 m^2. However, the 2020 JSN guidelines recommend that corticosteroids be used for the treatment of IgA nephropathy when patients have a urinary protein level ≥1.0 g/day and CKD of stages G1 and G2.[17] Patients with IgAN showing MCD pathological features should be managed similarly to those with MCD. Mycophenolate mofetil (MMF) is effective for Chinese patients with IgAN with proliferative lesions, such as endocapillary proliferation or crescent formation and proteinuria >1.0 g/day. Further, it is associated with fewer side effects than standard-dose steroids.[21] However, there is no evidence suggesting its efficacy for IgAN among other ethnicities. Antiplatelet agents, anticoagulants, azathioprine, cyclophosphamide, calcineurin inhibitors (CNIs), rituximab (RTX), fish oil, and other similar treatments are not recommended in the 2021 KDIGO guidelines.[6] However, cyclophosphamide, azathioprine, cyclosporine, tacrolimus, MMF, and mizoribine should be considered when corticosteroids cannot be used because of their side effects or when the use of corticosteroids must be reduced.[17]

In some cases, patients might be resistant to steroids and/or immunosuppressive agents mentally, and the optimal treatment for such patients is unclear. Two retrospective studies were performed based on 34 and 28 cases of IgAN that were resistant to steroids and/or immunosuppressive agents, respectively. These cases were treated with tacrolimus combined with low-dose steroids for at least 12 months. The total effective rate ranged from 73.5% to 83.5%, with a complete remission rate of 40.1%. The average time to a response was 7.0 ± 4.7 weeks, and parameters such as blood creatinine, blood uric acid, and eGFR were normalized. Moreover, few patients experienced upper respiratory tract and urinary tract infections, confirming the safety and efficacy of tacrolimus for the treatment of refractory $IgAN^-$.[22,23]

In a meta-analysis of seven randomized controlled trials (RCTs) involving 374 patients with IgAN, CNIs had a protective effect compared to that by pure steroid therapy or a placebo. Moreover, the associated complete remission rate was higher and proteinuria was significantly decreased (average decrease of −0.46 g/day) with CNIs. However, some parameters, such as the partial remission rate, blood creatinine, and eGFR, were not significantly affected, and side effects including gastrointestinal symptoms, neurological issues, and hirsutism increased. Importantly, these studies did not specifically address different pathological types of IgAN, and further large-sample RCTs are needed to confirm these findings.[24] Moreover, the aforementioned studies suggest that tacrolimus combined with low-dose steroids might be suitable for patients with IgAN with moderate proteinuria and podocytopathy (foot process fusion >70%).

In recent years, certain progress has been made in treatments using nonbiological agents, such as Nefecon (budesonide) and *Tripterygium wilfordii*. Nefecon is a novel, oral, targeted-release formulation of budesonide designed to act at the gut mucosal level. Its therapeutic potential for the treatment of IgAN was first demonstrated in the Phase 2b NEFIGAN trial. Budesonide at 16 mg/day, added to optimized RAS blockade, reduced

proteinuria in patients with IgA nephropathy.[25] The Phase 3 NefigArd trial further confirmed the efficacy and safety of 9 months of Nefecon (16 mg/day) treatment, versus a placebo, in adult patients with primary IgAN at risk of progressing to kidney failure. At 9 months, the urinary protein-to-creatinine ratio (UPCR) was 27% lower in the Nefecon group than that in the placebo group, and this was associated with a benefit in eGFR preservation, corresponding to a 3.87 mL/min/1.73 m^2 difference compared with that with the placebo.[26] A meta-analysis further showed that *T. wilfordii* polyglycoside can effectively improve the remission rate, reduce proteinuria, and protect kidney function in patients with IgAN, and it was also found to have good safety.[27] The mechanism underlying the therapeutic effect of *T. wilfordii* polyglycoside on IgAN includes reducing the production of pathogenic IgA, decreasing renal inflammation and fibrosis, and protecting podocytes.

3.2 | Biological treatment agents

3.2.1 | Mechanism underlying the effects biological treatment agents

Biological agents are high-activity peptides extracted using genetic biotechnology that have immunosuppressive effects. They generally refer to recombinant products of monoclonal antibodies or fusion proteins, which are specific antibodies or natural inhibitors of immune- and inflammation-regulating molecules. These biological agents possess immunomodulatory activity and function by blocking key cytokines or their receptors involved in diseases. Moreover, they can have a therapeutic role by effectively combating inflammation, halting disease progression, and improving patient outcomes.

In terms of addressing the pathogenic mechanisms of IgAN based on the "four-hit hypothesis," inhibiting the production of Gd-IgA1 is one treatment strategy. B cell development in the bone marrow involves several stages, including pro-B, pre-B, immature B, and mature B cells. B cells, influenced by the bone marrow microenvironment, develop into initial B cells. Upon leaving the bone marrow, they settle in the nonthymus-dependent zones of peripheral immune organs, where they become activated, proliferate in response to specific antigens, and further differentiate into plasma cells and memory B cells. B-lymphocyte stimulator (BLyS), also known as B cell-activating factor, belongs to tumor necrosis factor (TNF) family (BAFF) and primarily interacts with three receptors on cell surfaces, namely, B cell activation factor from the TNF family receptor (BAFF-R), transmembrane activator and CAML interactor (TACI), and B cell maturation antigen (BCMA; to a lesser extent). This interaction promotes the transformation of transitional B cells into mature B cells and enhances the survival and proliferation of mature B cells. Another molecule, a proliferation-inducing ligand (APRIL), mainly interacts with TACI and BCMA receptors on B cell surfaces. It is involved in the pathogenesis of autoimmune diseases, facilitating the transformation of mature B cells into plasmablasts and plasma cells. APRIL also stimulates the proliferation and survival of plasma cells and the secretion of antibodies.

In a mouse model of IgAN, TLR9 activation was confirmed to induce the excessive production of APRIL and IL-6. Both APRIL and IL-6 can independently or cooperatively promote abnormal IgA glycosylation.[28] Plasma APRIL levels were measured, using ELISA, in a Chinese study involving 166 IgAN cases and 77 healthy controls in 2016, which assessed the relationship between plasma APRIL levels and IgAN severity. This study found that plasma APRIL levels are elevated in patients with IgAN and closely correlated with the degree of proteinuria and the reduction in the eGFR. Plasma APRIL levels were also positively correlated with Gd-IgA1 levels. Compared with that in the normal control group, patients with IgAN exhibited a significant increase in Gd-IgA1 production when peripheral lymphocytes were exposed to APRIL. Furthermore, the expression of APRIL receptors, including BCMA and TACI, was significantly increased in these patients.[29]

Currently, the biological agents used for the treatment of IgAN encompass four major categories based on literature reports. First, agents that directly inhibit B cell monoclonal antibodies, such as anti-CD20 monoclonal antibodies, include RTX, ofatumumab (OFA), and obinutuzumab. Second, monoclonal antibodies against BLyS or APRIL include belimumab and BION-1301 (a humanized IgG4 monoclonal antibody). Third, monoclonal antibodies targeting both BLyS and APRI simultaneously include telitacicept and atacicept. Finally, monoclonal antibodies targeting the complement pathway include MASP-2 inhibitors (narsoplimab, also known as OMS721) and C5 inhibitors (eculizumab). Eight biological agents used for the treatment of IgAN have been reported in the literature (Figure 2).

3.2.2 | Research status on biological treatment agents

Anti-CD20 antibodies

Anti-CD20 antibodies exert their effects on B cells via various molecular mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, programmed cell death, and antibody-dependent cellular phagocytosis, among others. The use of RTX for the treatment of IgAN is primarily based on retrospective case summaries with limited case numbers. In four cases of IgAN or IgA vasculitis, confirmed

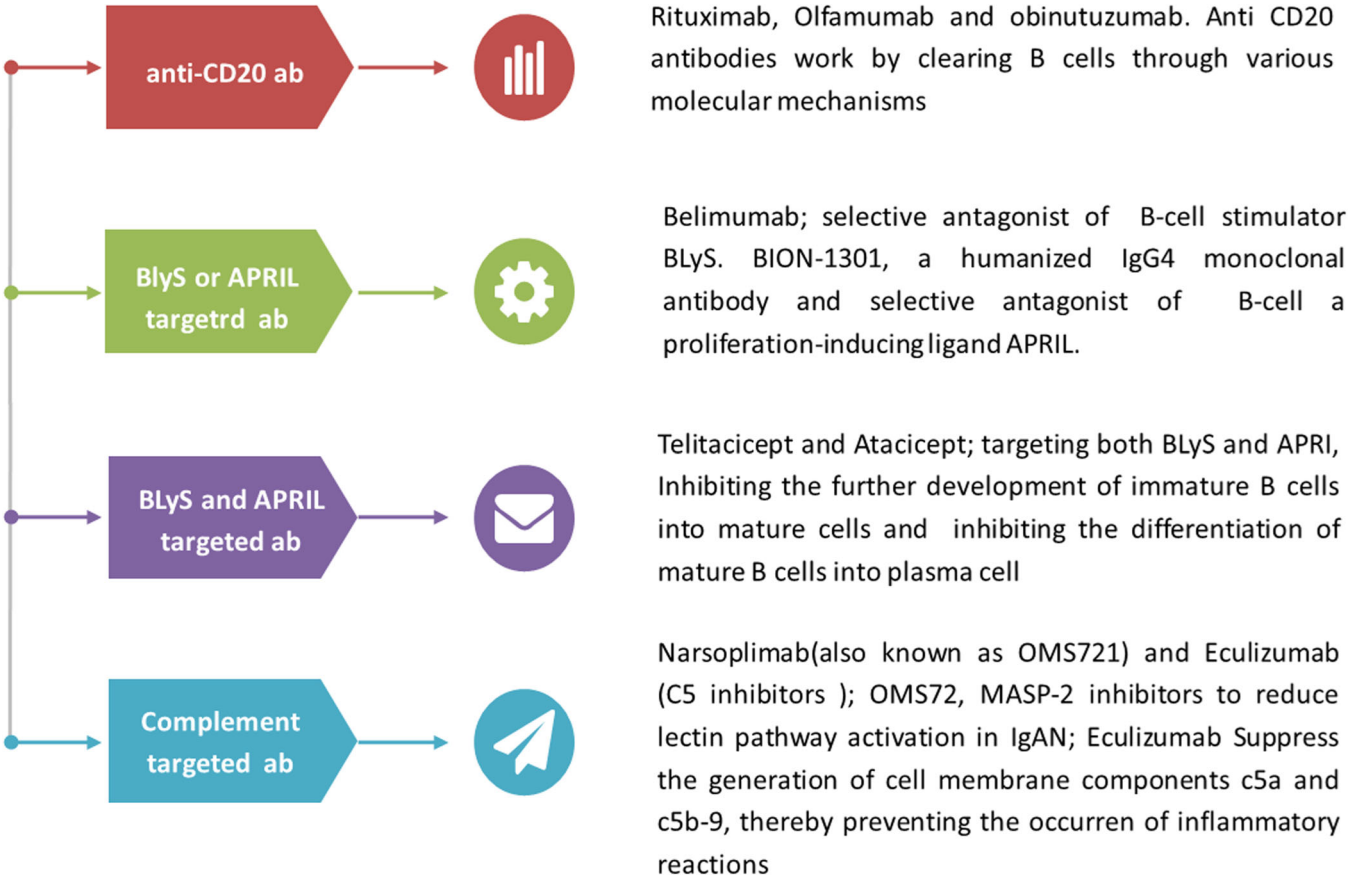

FIGURE 2 Mechanism associated with the biological agents used for the treatment of IgA nephropathy. ab, antibody; APPIL, a proliferation-inducing ligand; BLyS, B-cell-activating factor; IgA, immunoglobulin A; IgG, immunoglobulin G; IgAN, immunoglobulin A nephropathy; MASP-2, mannose-binding lectin-associated serine protease 2.

based on a renal biopsy, where there were manifestations of nephritis or nephrotic syndrome, RTX was administered to patients with crescentic IgAN (the crescent proportion was 30% and 80% in two patients). Treatment involved methylprednisolone pulses followed by daily prednisone and RTX at a dose of 1.0 g every 2 weeks. In the patient with 31% crescents, creatinine decreased from 2.64 to 0.88 mg/dL and the urine ACR decreased from 1415.93 to 77.90 mg/g. Similarly, in the patient with 80% crescents, creatinine decreased from 4.0 to 2.1 mg/dL and ACR decreased from 3867.3 to 22.0 mg/g after 1 year. Moreover, blood creatinine and urinary protein levels decreased significantly. In the other two cases without crescent formation, treatment with RTX or the human anti-CD20 monoclonal antibody OFA was used (OFA at 125 mg/m^2 bovine serum albumin for the first dose, and then, 500 mg weekly ×3), and proteinuria was also decreased significantly.[30] However, in five cases of IgAN with urinary protein levels of 1.0 ± 0.8 g/day, a single dose of RTX at 375 mg/m^2 was administered based on steroid treatment. Although CD19 or CD20 had been cleared, urinary protein levels were not significantly decreased during the 6-month follow-up.[31] In a recent multicenter open-label RCT, 34 patients diagnosed with IgAN confirmed based on a kidney biopsy, with glomerulosclerosis and interstitial fibrosis <50%, urinary protein >1.0 g/day, and a median eGFR of 49 (30–122) mL/min/1.73 m^2, received RTX treatment based on a background of RASIs (days 1 and 15, and 100 mg per dose). In this trial, RTX therapy did not significantly improve renal function or proteinuria, assessed over 1 year, and did not lead to a decrease in serum Gd-IgA1 levels and anti-Gd-IgA1 antibody levels.[32] This study indicated that RTX lacks efficacy for IgAN, at least at this stage and with this severity. Therefore, there is no consensus on the use of RTX for the treatment of IgAN.

IgAN recurrence after kidney transplantation is a common clinical problem, and effective treatments beyond RASI therapy are currently lacking. Recurrent IgAN postkidney transplantation often leads to proteinuria and graft dysfunction due to crescent formation and endocapillary proliferation. There have been reports of the use of RTX alone (with four consecutive months of RTX at a dose of 375 mg/1.73 m^2) to treat three cases of postkidney transplant IgAN. At the median follow-up of

20 months, all three recipients demonstrated a decrease in proteinuria severity and slow disease progression with a well-tolerated condition.[33] A retrospective cohort study was performed on 64 patients with posttransplant recurrent IgAN, urinary protein >1.0 g/day, and creatinine clearance >30 mL/min/1.73 m^2, all with endocapillary proliferation based on the pathology, with or without crescent formation. These patients were divided into a control group (43 cases) and a treatment group (21 cases). The treatment group received RTX in addition to standard therapy (375 mg/m^2/dose was administered monthly for four consecutive months). Meanwhile, methylprednisolone pulse therapy for 3 days was administered to those with cellular crescent formation. Routine prophylactic anti-infection treatment was also administered. On the basis of 60 months of follow-up, in the RTX treatment group, urinary protein levels were significantly lower than those in the control group at 12 months, renal function had improved significantly at 18 months, and the complete remission rate at 30 months (38% vs. 0, $p < 0.001$) and partial remission rate (68% vs. 26%, $p < 0.005$) were higher, with the 60-month graft survival rate also being significantly higher (86% vs. 49%, $p = 0.002$). Repeat renal biopsies also revealed reduced endocapillary hypercellularity despite persistent strong IgA deposition. No RTX-related leukopenia or severe systemic infections were observed. This retrospective cohort study confirmed the efficacy and safety of adjunctive treatment with RTX for recurrent severe IgAN posttransplant, with an improvement in its long-term prognosis.[34]

BlyS- or APRIL-targeting antibodies

Belimumab was the first BLyS-specific inhibitor, and it functions by blocking the binding of soluble BLyS to BLyS receptors on B cells, thereby reducing B cell differentiation into plasma cells. Telitacicept (tabalumab) targets both BLyS and APRIL simultaneously, inhibiting their binding to receptors, thereby suppressing abnormal B cell development and the differentiation of mature B cells into plasma cells, ultimately affecting antibody production by abnormal plasma cells. The Belimumab International Study in Lupus Nephritis (BLISS-LN) study confirmed that combining belimumab with standard therapy enhances the efficacy of lupus nephritis (LN) treatment, reduces relapse rates, and facilitates a glucocorticoid dose reduction. Professor Yu Xueqing and others evaluated the efficacy and safety of belimumab for LN in an East Asian population. The primary endpoint was the primary efficacy renal response (PERR) at week 104, defined as follows: simultaneous achievement of a UPCR ≤ 0.7, an eGFR decline not exceeding 20% from baseline or ≥60 mL/(min/1.73 m^2), and no treatment failure. The study included 142 patients from China and South Korea (74 in the belimumab group and 68 in the placebo group). The results indicated that at both weeks 52 and 104, the belimumab group had higher PERR rates than the placebo group. Compared with the effect of the placebo, belimumab significantly reduced the risk of kidney-related events or death (hazard ratio = 0.37; 95% CI, 0.15–0.91). This study confirmed that the safety and effectiveness of belimumab for the treatment of LN in the East Asian population were consistent with those reported for the overall BLISS-LN population.[35] Further, a Phase II double-blind placebo-controlled study on the safety and effectiveness of intravenous (i.v.) belimumab treatment for IgAN was conducted in Hong Kong of China, with an anticipated duration of 2 years and 21 patients enrolled. However, no reports have been published to date.

BION-1301 is a novel humanized monoclonal antibody that binds to and blocks APRIL. By inhibiting the interaction between APRIL and its receptor, BION-1301 results in the depletion of Gd-IgA1 and prevents the formation of pathogenic immune complexes, representing a new approach to addressing the underlying mechanisms driving IgAN. In Phases 1 and 2 studies, the primary focus was assessing the safety and tolerability of BION-1301 (administered subcutaneously or intravenously) in patients with IgAN. Intermediate data were presented at ASN Kidney Week 2022. BION-1301 treatment significantly reduced urinary protein levels in patients with IgAN. The enrolled patients had been diagnosed with IgAN based on a kidney biopsy over 10 years, with baseline urinary protein levels ≥0.5 g/day or a UPCR ≥ 0.5 and an eGFR >45 mL/min/1.73 m^2, and stable or optimized doses of ACEIs and ARBs were used. Cohort 1 received 450 mg via i.v. infusion every 2 weeks for 24 weeks, followed by subcutaneous injections for a total of 52 weeks. Cohort 2 received 600 mg via subcutaneous injection every 2 weeks for 52 weeks. No patients in either Cohort 1 (10 cases) or Cohort 2 (23 cases) discontinued treatment due to adverse events (AEs), indicating the good tolerability of BION-1301. By week 24, the UPCR had decreased by 48.80% and 53.58% in Cohorts 1 and 2, respectively. In Cohort 1, there was a clinically meaningful sustained reduction in the 24 h UPCR within the first 100 weeks (approximately 2 years), reaching 71%. Rapid and sustained reductions in free serum APRIL levels, serum Gd-IgA1, IgA, and immunoglobulin M (IgM) were also observed, with a smaller decrease in IgG, suggesting a lower potential risk of infection and that the production of drug-resistant antibodies had not occurred.

Antibodies simultaneously targeting BlyS and APRIL

Telitacicept (tabalumab) is a TACI–Fc fusion protein with APRIL- and BLyS-dual targeting capacity, exerting multistage inhibitor effects on B cell maturation and differentiation. By blocking BLyS, telitacicept inhibits the further maturation of immature B cells, helping to control the progression of future disease. It also

suppresses the differentiation of mature B cells into plasma cells and influences the secretion of autoantibodies by reactive plasma cells, leading to good disease control.[36]

The results of a Phase II clinical trial of telitacicept for the treatment of IgAN were published in KI Reports in March of this year. The trial was led by Peking University First Hospital, with participation from over 20 hospitals, and in total, 44 adult patients with primary IgAN were enrolled in. Before the trial began, patients had already received 12 weeks of RAS blockade treatment (i.e., ACEIs or ARBs), but their quantitative urinary protein levels still exceeded 0.75 g/day. The participants were divided into three groups based on a nearly 1:1:1 ratio, comprising a telitacicept 160 mg group (16 participants), telitacicept 240 mg group (14 participants), and the placebo group (14 participants). Subcutaneous injections were administered once per week for a total of 24 weeks. Continuous reductions in serum IgA, IgG, and IgM levels were observed in the telitacicept groups. Telitacicept 240 mg therapy reduced mean proteinuria by 49% from baseline (change in proteinuria vs. placebo, 0.88; 95% CI, 1.57–0.20; $p = 0.013$), whereas telitacicept 160 mg reduced it by 25% (0.29; 95% CI, 0.95–0.37; $p = 0.389$). Moreover, the eGFR remained stable over time, and AEs were similar in all groups. The results confirmed that telitacicept treatment led to a clinically meaningful reduction in proteinuria in patients with IgAN.[37]

Atacicept is a fusion protein consisting of the extracellular ligand-binding domain of the TACI receptor and the Fc portion of human IgG. It binds to and inhibits BLyS and APRIL simultaneously, resulting in a reduction in B cell numbers and the disruption of B cell maturation, differentiation, and effector functions. The JANUS trial (NCT02808429) is a Phase IIa randomized, placebo-controlled clinical trial. In total, 16 patients were randomized in a 1:1:1 ratio to receive either placebo ($n = 5$), atacicept 25 mg ($n = 6$), or atacicept 75 mg ($n = 5$), once weekly via subcutaneous injection. Twelve patients (75%) completed 48 weeks of treatment, whereas eight patients (50%) completed 72 weeks of treatment along with the 24-week safety follow-up period. Dose-dependent reductions in serum IgA, IgG, IgM, and Gd-IgA1 levels were maintained from week 24 to week 72 with atacicept. Moreover, a decrease in proteinuria was observed as early as week 24 with this drug. However, renal function progressively declined in the placebo group, but it remained stable when atacicept was administered. Fourteen patients reported treatment-emergent AEs, most of which were mild or moderate in severity. This study suggests that atacicept has a beneficial effect on reducing proteinuria and protecting kidney functions in patients with IgAN.[38]

Monoclonal antibodies targeting the complement pathway

Both the alternative complement and lectin pathways are involved in the occurrence and progression of IgAN. The MASP-2 inhibitor narsoplimab (also known as OMS721) is a human monoclonal antibody targeting the mannose-binding protein MASP-2. Substudy 1 included four cases and was a single-arm open-label study. The median 24 h urine protein level was 4.2 g, and the median eGFR was 44.6 mL/min/1.73 m^2. Four patients received narsoplimab at 4 mg/kg i.v. once weekly for 12 weeks, along with a tapered dose of corticosteroids, and they were followed up for 6 weeks. By week 18, the 24 h urine protein excretion had decreased by 54%–95% compared with the baseline value. The most commonly reported AEs included headache, upper respiratory infection, and fatigue. The majority of AEs were mild or moderate and transient, and no serious AEs related to treatment were reported. In substudy 2, 12 patients with biopsy-proven IgAN, who were not on corticosteroids, were randomized at a 1:1 ratio to receive either narsoplimab 370 mg or vehicle infusions (5% dextrose in water) for 12 weeks (once-weekly administrations), followed by an additional 6 weeks of observation and then an open-label extension period for potential dosing for up to 2 years. The 12 patients had a median 24 h urine protein level of 3.0 g of an eGFR of 37.6 mL/min/1.73 m^2. The vehicle and narsoplimab groups exhibited similar reductions in proteinuria at week 18. Moreover, eight patients (three in the vehicle and five in the narsoplimab group) continued with the dosing extension, and all received narsoplimab. The median reduction in the 24 h urine protein excretion in these eight patients was 61.4% at 31–54 weeks postbaseline. Moreover, the eGFR remained stable in both substudies. These results suggest that narsoplimab treatment might result in clinically meaningful reductions in proteinuria and eGFR stability in high-risk patients with advanced IgAN.[39]

Eculizumab, a C5 inhibitor, was also used, in a case report, for the treatment of IgAN accompanied by atypical hemolytic uremic syndrome (aHUS). A 42-year-old man with acute kidney injury, clinically and histologically diagnosed with the coexistence of aHUS and crescentic IgAN, was treated with steroids, plasmapheresis, and hemodialysis. Eculizumab treatment was initiated on hospital day 21, eculizumab was continued at 900 mg every week for a total of 4 weeks, and then, the patient was transitioned to 1200 mg every 2 weeks. The clinical remission of aHUS was achieved on day 70. The serum creatinine level decreased from 18.78 to 7.22 mg/dL, and hemodialysis was continued.[40] Moreover, a 16-year-old male with the vasculitic form of IgAN who did not respond to aggressive conventional therapy, including high-dose steroids, cyclophosphamide, and plasma exchange, was treated with four weekly doses of

900 mg eculizumab followed by a single dose of 1200 mg. He responded rapidly to this treatment and has had stable creatinine levels of approximately 150 μmol/L (1.67 mg/dL) for >6 months. Segmental glomerulosclerosis and renal tubular atrophy and interstitial fibrosis were found based on a second renal biopsy 11 months later.[41]

4 | APPROPRIATE PATIENT POPULATION FOR THE USE OF BIOLOGIC AGENTS FOR IGAN TREATMENT

Treatments with biologic agents are not universally applicable to all patients with IgAN, and to date, there is no consensus or guidelines for this, although some research results have been mentioned previously herein. The cost of biologic therapies is also quite high, and many patients cannot afford the expenses associated with such medications. Given the existing limited evidence, identifying the appropriate patient population for the application of these drugs becomes crucial. Regarding IgAN treatment with biological agents, the suitable patient population is outlined in Table 1. Such drugs are mainly used for progressive IgAN, IgAN with podocytopathy, crescentic IgAN, and the recurrence of IgAN postkidney transplantation. However, RTX and OFA have a broader range of suitable patients, including those with MCD-like IgAN with steroid dependence or relapse, progressive IgAN, crescentic IgAN, IgAN with membranous nephropathy, and IgAN recurrence after kidney transplantation.[30–34] Telitacicept, atacicept, BION-1301, and narsoplimab are mainly indicated for progressive IgAN, with persistent urine protein >0.5 g/day and an eGFR >30 mL/min/1.73 m^2 based on a background of standard ACEI or ARB treatment.[37–40] Meanwhile, eculizumab is primarily used for IgAN with aHUS and crescentic IgAN.[40,41]

5 | CONCLUSION

IgAN is the most common primary glomerular disease, primarily driven by a mechanism associated with the "four-hit hypothesis." B cells and complement activation (including lectin and alternative pathways) play crucial roles in the pathogenesis of IgAN, with BLyS and APRIL being significant cytokines contributing to its development. The KDIGO guidelines note the lack of specific effective therapeutic drugs for IgAN and do not recommend anti-CD20 treatment for this disease. RASIs form the foundation of treatment, whereas combined prednisolone and CNI therapy is one of the strategies used for refractory IgAN. Sodium–glucose cotransporter inhibitors, finerenone, budesonide, and *T. wilfordii* might also be considered for the treatment of IgAN. Eight biologic agents have entered the clinical exploration stage for the treatment of IgAN. They exhibit notable characteristics, such as rapid efficacy, targeted action, and high specificity. These agents have shown the potential to significantly reduce proteinuria, stabilize the eGFR, and reverse pathological changes, such as endocapillary proliferation and crescent formation, and they have promise for a new era of IgAN treatment. Treatment with biological agents is suitable for patients with refractory IgAN, including those with progressive IgAN, IgAN with podocytopathy, crescentic IgAN, and the recurrence of IgAN after renal transplantation. However, further research is required to explore the optimal dosages, treatment durations, long-term effects, and safety profiles of these biological agents.

TABLE 1 Suitable population for the use of various types of biological agents for IgAN treatment.

Types of biological agents	Suitable population
Rituximab or ofatumumab	MCD-like IgAN with hormone dependence or recurrence, progressive IgAN, crescent-type IgAN, MsPGN-IgAN with podocytopathy, recurrent IgAN after kidney transplantation
Belimumab	Progressive IgAN
Telitacicept or atacicept	Progressive IgAN, urinary protein >0.75 g/day on the basis of a sufficient dose of ACEIs or ARBs, and eGFR >30 mL/min/1.73 m^2
BION-1301	Progressive IgAN, urinary protein >0.5 g/day on the basis of a sufficient dose of ACEIs or ARBs, and eGFR >45 mL/min/1.73 m^2
Narsoplimab	Progressive IgAN, urinary protein >1.0 g/day on the basis of a sufficient dose of ACEIs or ARBs, and eGFR >30 mL/min/1.73 m^2
Eculizumab	IgAN with aHUS, crescent-type IgAN

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; aHUS, atypical hemolytic uremic syndrome; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; MCD, minimal change disease; MsPGN, mesangial proliferative glomerulonephritis.

AUTHOR CONTRIBUTIONS

Yongze Zhuang conceived the idea and wrote the manuscript. Hailing Lu participated in the partial writing of the paper and the English revision of the paper. Junxia Li participated in literature collection work and the partial writing of the paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon request.

ETHICS STATEMENT

None.

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