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B-Cell- and Plasma-Cell-Targeted Therapies in Pediatric IgA Nephropathy: Research Advances in Efficacy and Safety

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Abstract

IgA nephropathy (IgAN) is the most common primary glomerular disease in children, characterized by the deposition of galactose-deficient IgA1 (Gd-IgA1) and its immune complexes in the glomeruli, which trigger mesangial proliferation and complement activation. Traditional therapeutic strategies have centered on glucocorticoids and immunosuppressive agents. Their clinical utility in pediatric IgAN remains constrained by treatment resistance, relapse, and growth impairment, highlighting the urgent need for novel targeted agents. In recent years, B cells and B cell-mediated immune dysregulation have been increasingly recognized as a key pathogenic driver of IgAN, providing a rationale for B cell-targeted therapies. In addition, antibody-secreting plasma cells—the main source of Gd-IgA1—represent another potential therapeutic target, supporting the emergence of plasma-cell-targeted strategies such as anti-CD38 agents. This review narratively summarizes the mechanisms of action, clinical evidence, and safety data of B-cell- and plasma-cell-targeted therapies in pediatric IgA nephropathy, aiming to provide a reference for clinical decision-making in this population.

Keywords

Children, IgA Nephropathy, B Cells, Targeted Therapy

1. Introduction

Immunoglobulin A nephropathy (IgAN) is one of the leading primary glomerular diseases causing hematuria and/or proteinuria in children. The incidence of the disease exhibits significant geographic variation, with the highest rates observed in Asia. A multicenter study of 4006 pediatric patients with IgAN across 22 hos-

pitals in China showed that the incidence among males gradually increased with age, and that the incidence in less economically developed regions was significantly lower than that in developed regions [1]. With respect to renal biopsy pathological spectrum, another study covering 21,311 pediatric patients from 232 hospitals across China reported that IgAN accounted for 22.7% of pediatric glomerular diseases and up to 60.75% of cases in children presenting with hematuria [2]. In Europe, the incidence of IgAN in children is 2.0 per million per year. However, in Japan, the incidence of IgAN among children undergoing school urinary screening has been reported to be 99 per million per year [3]. IgAN is also a major cause of chronic kidney disease and end-stage renal disease (ESRD) in children. It is estimated that approximately 20% of children with IgAN will progress to ESRD within 20 years after diagnosis [1].

To date, conventional management of pediatric IgAN has relied mainly on optimized supportive care, corticosteroids, and immunosuppressive therapy. The 2025 IPNA guidelines recommend the following for the treatment of IgAN in children: 1) Lifestyle management, including a low-sodium diet, weight control, and regular aerobic exercise. 2) Optimization of supportive care with ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB). 3) In children at risk of clinical progression, a 4 - 6-month course of glucocorticoid treatment should be considered. 4) In pediatric IgAN patients exhibiting rapidly progressive disease with acutely decreased eGFR, or in those who do not respond to optimized supportive care, the use of immunosuppressive agents in combination with corticosteroids may be considered [4]. Nevertheless, persistent proteinuria remains in some children despite conventional treatment, and prolonged corticosteroid therapy is associated with serious adverse effects—including growth impairment, metabolic abnormalities, immunosuppression, and infection—all of which impose a considerable physical and psychological burden on affected children [5]. Consequently, the development of novel targeted agents for pediatric IgAN represents an urgent unmet clinical need.

In recent years, as research into the pathogenesis of IgAN has advanced, B cells and B-cell-mediated immune dysregulation within the "four-hit hypothesis" have been increasingly recognized as a key pathogenic driver, leading to the emergence of targeted therapies directed against B cell activation, proliferation, and antibody production [6]-[8]. B cell-targeted therapies, such as telitacicept and atacicept, have shown promising efficacy and safety in adult IgAN [9] [10] and have begun to be evaluated in pediatric IgAN.

2. Pathogenesis of IgAN

The "four-hit hypothesis" remains the predominant framework for IgAN pathogenesis. In brief, B cells overproduce galactose-deficient IgA1 (Gd-IgA1) (hit 1); autoantibodies are generated against Gd-IgA1 (hit 2); Gd-IgA1 and anti-Gd-IgA1 IgG antibodies form immune complexes (hit 3); and these complexes deposit in the glomerular mesangium (hit 4), leading to mesangial cell activation, inflamma-

tory cell recruitment, and complement activation, all of which culminate in podocyte injury and disruption of the filtration barrier [6]. In this four-hit hypothesis framework, B cells play a central role in initiating the pathogenesis by producing Gd-IgA1 and generating anti-Gd-IgA1 IgG autoantibodies that contribute to the second hit.

3. B-Cell- and Plasma-Cell-Targeted Therapies for IgAN

3.1. B-Cell-Activating Factor (BAFF)/A Proliferation-Inducing Ligand (APRIL) Inhibitors

IgA-producing B cells are believed to arise in mucosa-associated lymphoid tissue (MALT) and to be induced through both T cell-dependent and T cell-independent pathways. In the T cell-dependent pathway, TLR ligand recognition on dendritic cells drives the differentiation of naive T cells into follicular helper T cells, which in turn assist IgA class switching in B cells. The T cell-independent pathway, by contrast, requires BAFF and APRIL, both members of the tumor necrosis factor (TNF) superfamily [6] [11] [12].

BAFF and APRIL are homologous members of the TNF superfamily that signal through the shared receptors B cell maturation antigen (BCMA) and transmembrane activator and calcium-modulating and cyclophilin ligand interactor (TACI). In addition, the BAFF receptor (BAFF-R) is a receptor specific for BAFF [12]. BAFF primarily signals through BAFF-R and is essential for B cell maturation, differentiation, and survival, acting mainly on mature B cells and early plasma cells while providing only limited support for long-lived plasma cells. Notably, elevated BAFF levels in patients with IgAN have been shown to correlate with disease severity [13] [14]. Although BAFF inhibition is theoretically expected to ameliorate clinical symptoms in patients with IgAN, BAFF blockade reduces not only IgA but also total serum IgM and IgG levels, indicating that its effect on immunoglobulins is broad rather than IgA-specific. In spontaneous mouse models of IgAN, treatment with anti-BAFF agents did not inhibit the production of Gd-IgA1 or its autoantibodies, potentially indicating that BAFF has a limited contribution to pathogenic IgA production [15]. These findings suggest that anti-BAFF agents may offer limited therapeutic benefit to patients with IgAN. APRIL exerts its effects mainly through interaction with TACI and BCMA, thereby regulating B cell differentiation and plasma cell survival. Given its essential role in sustaining long-lived plasma cells, APRIL may contribute to the persistent production of Gd-IgA1 [14]. Furthermore, in animal experiments, anti-APRIL treatment decreased serum IgA levels and reduced immune complex deposition in ddY mice, leading to attenuated kidney injury [16], indicating that APRIL-targeted agents can reduce circulating Gd-IgA1 and immune complex levels in IgAN, thereby exerting a therapeutic effect.

Recent years have witnessed substantial advances in dual-targeting inhibition of the BAFF/APRIL pathway in patients with IgAN. A systematic review of the efficacy and safety of dual BAFF/APRIL inhibitors in adult IgAN showed that

BAFF/APRIL pathway inhibition significantly reduced proteinuria in adult patients with IgAN, with a favorable short-term safety profile [17].

Overall, current therapeutic approaches targeting the BAFF/APRIL pathway consist mainly of anti-APRIL agents and dual BAFF/APRIL inhibitors, which are designed to intervene at the source of the disease.

3.2. Anti-CD38 mAb: Mechanism and Rationale

In many autoantibody-mediated diseases, disease refractoriness and relapse have been attributed to the persistence of long-lived plasma cells. CD38, a molecule highly expressed on the surface of plasma cells and long-lived plasma cells, is involved in immunometabolic regulation, and CD38-targeted therapies have demonstrated preliminary efficacy in various autoimmune diseases [18]. In a study involving four high-risk patients with IgAN who received the anti-CD38 agent daratumumab, a significant reduction in serum IgA levels was observed, while IgG and IgM exhibited only transient or non-significant declines. At a median follow-up of 13.5 months, all four patients demonstrated stable or improved eGFR, a 30% - 90% reduction in proteinuria, and complete disappearance of hematuria, with acceptable safety; infection occurred in only one kidney transplant recipient who was concurrently receiving immunosuppressive therapy [19]. Thus, anti-CD38 therapies may represent a promising therapeutic strategy for patients with IgAN.

3.3. Anti-CD20 mAb

As B cells occupy an upstream position in the pathogenesis of IgAN, their depletion may, in theory, prevent their differentiation into IgA-producing B cells, thereby lowering serum Gd-IgA1 and immune complex levels. Thus, anti-CD20 therapies may serve as a treatment option for patients with IgAN [20]. Rituximab, a representative anti-CD20 agent, was shown in a study of 34 patients with IgAN to be ineffective in significantly reducing proteinuria or stabilizing renal function, with no observed reduction in serum Gd-IgA1 or its autoantibody levels following treatment [21]. The reduced expression of CD20 and elevated expression of CD38 on plasma cells may account for the limited therapeutic efficacy of rituximab in patients with IgAN [22]. Notably, no pediatric clinical studies of anti-CD20 therapy in IgAN were identified in our search, and the evidence for anti-CD20 agents in this population therefore remains limited to adult data.

4. Efficacy and Safety of B-Cell- and Plasma-Cell-Targeted Therapies for Pediatric IgA Nephropathy

4.1. Dual-Targeting BAFF/APRIL Inhibitors

4.1.1. Telitacicept

As a biologic agent dual-targeting the BAFF/APRIL pathway, telitacicept suppresses pathogenic antibody production by B cells and plasma cells, leading to reduced levels of Gd-IgA1, IgG-IgA immune complexes, and polymeric IgA, which in turn ameliorates clinical manifestations including proteinuria and he-

maturia in patients with IgAN [23]. In a retrospective study of 10 pediatric patients with IgAN and proteinuria (baseline 24-hour urinary protein: 23.97 ± 26.63 mg/kg), 6 of 10 patients had normal renal function at baseline, and the remaining 4 patients had an eGFR of 50.8 - 63.3 mL/min/1.73 m^2. After a median follow-up of 3.75 months, proteinuria remission was achieved in 8 patients (four complete and four partial; complete remission: urinary protein excretion persistently < 150 mg/24h or urine protein-to-creatinine ratio < 200 mg/g; partial remission: ≥50% reduction in urinary protein excretion from baseline values), glucocorticoid tapering in 6, and glucocorticoid discontinuation in 4, accompanied by complete resolution of hematuria, with no serious adverse events reported [24]. In another retrospective study of 12 pediatric patients with IgAN, the median (IQR) 24-hour urinary protein excretion at baseline was 0.98 (0.64 - 1.88) g/day, and the median (IQR) estimated glomerular filtration rate (eGFR) was 112.74 (91.31 - 127.55) mL/min/1.73 m^2, over a median follow-up of 9 months, 7 patients (58.3%) achieved complete remission, although the study did not explicitly define complete remission; all patients exhibited significant improvement in urinary red blood cell counts. Corticosteroid tapering was achieved in all patients, with 3 discontinuing corticosteroids and 1 discontinuing immunosuppressive therapy. No serious adverse events were reported during follow-up [25]. Findings from both studies suggest that telitacicept was associated with reductions in proteinuria and hematuria in pediatric IgAN, and short-term safety appeared acceptable. Nevertheless, both were retrospective, single-arm studies with small sample sizes and short follow-up durations. Further validation through multicenter, large-scale randomized controlled trials is warranted. Because IgAN and IgA vasculitis with nephritis (IgAVN) share a common pathogenesis, some studies have included both IgAN and IgAVN patients. In a single-center retrospective study of 7 children with IgAN and 6 with IgAVN, the median (IQR) baseline urine protein-to-creatinine ratio (UPCR) was 1179.0 (795.5 - 1960.0) μg/mg, and the median (IQR) baseline eGFR was 109.5 (93.27 - 125.1) mL/min/1.73 m^2. Remission was characterized by the resolution of proteinuria (UPCR < 200 μg/mg) coupled with a normal eGFR (≥90 mL/min/1.73 m^2) or stable renal function; complete remission additionally required the resolution of hematuria, defined as <5 RBCs/HPF or a negative urine dipstick. Telitacicept treatment resulted in remission in 6 of 13 patients (46.15%) and complete remission in 4 (30.77%); 5 patients successfully discontinued steroids, and no severe adverse events were observed. Notably, of the 13 patients, 7 had persistent proteinuria despite having received corticosteroids plus at least one immunosuppressant. Of these, 6 experienced a reduction in proteinuria, and 2 achieved complete remission [26]. However, because this cohort included both IgAN and IgAVN patients and outcomes were not reported separately by diagnosis, these findings cannot be directly attributed to pediatric IgAN alone. In another multicenter study of 16 pediatric patients with refractory IgAN (n = 11) or IgAVN (n = 5), the median 24-hour urinary protein excretion at baseline was 1.83 g/1.73 m^2, and the mean eGFR was 97.0 mL/min/1.73 m^2. Refractory IgAN or IgAVN was defined as

persistent proteinuria > 0.5 g/1.73m^2/day or recurrent macrohematuria despite treatment with ACE inhibitors, corticosteroids, or immunosuppressants for at least 6 months, or glucocorticoid intolerance (e.g., ocular hypertension, cataracts). Proteinuria showed a downward trend in all patients during follow-up, and none of the 3 patients with recurrent gross hematuria experienced further episodes. By the end of follow-up, 10 patients (62.5%) had achieved complete remission, with corticosteroids gradually tapered and no serious adverse events reported [5]. Similarly, this study did not report outcomes separately for IgAN and IgAVN. Thus, in these uncontrolled retrospective studies, telitacicept was associated with reductions in proteinuria and hematuria in pediatric patients with refractory IgAN or IgAVN, with a favorable short-term safety profile. However, given the mixed IgAN/IgAVN cohorts and the lack of diagnosis-specific reporting, these findings should be interpreted with caution when applied specifically to pediatric IgAN.

Collectively, current evidence in pediatric IgAN consistently supports the favorable preliminary efficacy and short-term safety of telitacicept. All four studies demonstrated reductions in proteinuria and resolution of hematuria, together with the benefit of corticosteroid tapering or discontinuation, thus mitigating the impact of prolonged steroid exposure on growth and development in children. No serious adverse events were reported; only mild adverse reactions, including injection-site reactions, respiratory tract infections, and rash, were observed. Nevertheless, the importance of immunological monitoring during treatment warrants emphasis, and preventive measures, such as temporary avoidance of live attenuated vaccines, should be considered [26]. However, owing to the unique characteristics of the pediatric population, the current evidence is subject to several limitations. First, available studies are predominantly retrospective, with small sample sizes and short follow-up durations, and prospective randomized controlled trials with larger cohorts are lacking. Second, pediatric patients in these studies rarely received telitacicept as monotherapy; concomitant use of corticosteroids and immunosuppressants was common, precluding any assessment of the independent efficacy of telitacicept in pediatric IgAN. Finally, pediatric-specific pharmacokinetic data are absent, and the appropriateness of weight-stratified dosing regimens remains to be validated. Accordingly, the existing findings should be interpreted as exploratory evidence rather than a definitive basis for clinical recommendations. The definitive efficacy and long-term safety of telitacicept in pediatric IgAN warrant further validation through multicenter, large-sample, long-term follow-up randomized controlled trials.

4.1.2. Atacicept

Atacicept is a naturally occurring human TACI-Fc fusion protein that inhibits both BAFF and APRIL. In adults with IgAN, a phase III trial (n = 203) showed that at 36 weeks, atacicept reduced UPCR by 45.7% from baseline versus only 6.8% with placebo, and lowered Gd-IgA1 by 68.3% versus 2.9% with placebo; furthermore, hematuria resolved in 81% of patients receiving atacicept. Adverse reactions occurred in 59.3% of the atacicept group, predominantly mild to moderate, with

only one serious adverse reaction (0.5%) reported [27]. On the basis of these data, atacicept received FDA approval for adult IgAN in 2026. Nevertheless, to date, no published studies have evaluated its efficacy and safety in pediatric IgAN, leaving its applicability in children completely undetermined.

4.2. APRIL Inhibitors

Sibeprenlimab, a humanized IgG2 monoclonal antibody, specifically binds to and inhibits APRIL. In adults with IgAN, an interim analysis of a phase III trial demonstrated that at 9 months, sibeprenlimab reduced 24-hour UPCR by 45.6% from baseline (95% CI, 37.2 to 52.9); at 48 weeks, Gd-IgA1 decreased by 67.1% in the sibeprenlimab group; adverse reactions were predominantly mild to moderate; and serious adverse reactions occurred in 3.5% of the sibeprenlimab group versus 4.4% of the placebo group. Compared with placebo, sibeprenlimab-treated patients achieved higher rates of proteinuria and hematuria remission, with evidence suggesting renal protection and a favorable safety profile. The final trial report will assess the long-term renal protective effects and safety of sibeprenlimab over 24 months [28]. Although sibeprenlimab has shown preliminary efficacy in adult IgAN, data in the pediatric population remain absent. Zigakibart, a humanized IgG4 monoclonal antibody, binds to APRIL. In a phase 1/2 trial, at week 100, zigakibart treatment resulted in a 60% reduction in proteinuria and a marked reduction in hematuria, accompanied by significant and sustained declines in free APRIL, IgM, and Gd-IgA1 levels; no serious adverse reactions were reported. Zigakibart has shown promising efficacy and a favorable safety profile in adult patients with IgAN [29]. As with sibeprenlimab, data regarding zigakibart in pediatric IgAN are also currently unavailable.

4.3. Anti-CD38 mAb: Available Evidence

Felzartamab is a fully human anti-CD38 monoclonal antibody. In a randomized, double-blind, placebo-controlled phase 2a trial, UPCR decreased rapidly within 3 - 6 months in the felzartamab group and continued to decline at 9 and 24 months after the end of treatment, with adverse reactions being predominantly mild to moderate. These findings provide preliminary evidence supporting the efficacy and safety of felzartamab in adult IgAN [30]. Further studies in larger phase III trials are therefore needed.

In a study of daratumumab in four adult patients with high-risk IgAN, urinary protein decreased by as much as 90% from baseline, hematuria resolved, renal function stabilized or recovered, and the treatment was generally well tolerated [19].

5. Conclusions and Future Directions

As our understanding of IgAN pathogenesis continues to deepen, B cell-targeted therapies are thought to act at the source of the disease by reducing the production of pathogenic IgA and its immune complexes. However, B cell-targeted therapy

for pediatric IgAN is still in its early stages of investigation. The available evidence has largely centered on telitacicept, with multiple small retrospective studies consistently showing that it effectively reduces proteinuria and hematuria, promotes corticosteroid tapering or discontinuation, and demonstrates a favorable short-term safety profile in pediatric IgAN. In a multicenter study by Xu *et al.*, 10 of 16 pediatric patients (62.5%) with refractory IgAN (n = 11) or IgAVN (n = 5) achieved complete remission, although the study did not explicitly define complete remission; complete corticosteroid discontinuation was achieved in 8 of 16 patients (50%). However, outcomes were not reported separately by diagnosis, and these findings should be interpreted with caution when applied specifically to pediatric IgAN. Several BAFF/APRIL-targeting agents, including atacicept, sibeprenlimab, and zigakibart, have advanced to phase III or phase 1/2 clinical trials in adult IgAN; however, data in the pediatric population remain lacking. Although anti-CD38 agents have demonstrated preliminary efficacy in adult IgAN, evidence in the pediatric population remains unavailable. Future large-scale, prospective, randomized controlled trials are warranted to further validate telitacicept in pediatric IgAN. Moreover, additional trials are needed to address the evidence gaps for anti-APRIL and anti-CD38 agents in this population, ultimately aiming to facilitate individualized B cell-targeted therapy for children with IgAN across different clinical phenotypes. Despite the currently limited evidence for B cell-targeted therapy in pediatric IgAN, preliminary findings with telitacicept support the biological rationale and short-term benefits of this approach in children. With an increasing number of agents advancing into clinical development and the continued progress of pediatric-specific research, B cell-targeted therapies hold promise for offering more precise and safer treatment options for pediatric patients with IgAN.

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Author Contributions

Conceptualization, writing—original draft preparation, C.C.; writing—review and editing, project administration, Q.F.; All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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