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REVIEW
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New and future treatments for IgA nephropathy

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ABSTRACT

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis. The treatment for this disease has evolved over time, but results are often poor. In recent years, a large number of new drugs have been proposed in the treatment of IgAN. The disease develops according to four different hits. Any of these hits is the object of the newly proposed treatments. These treatments are divided into four groups. Agents acting by the inhibition of the endothelin A receptor and by the inhibition of angiotensin II subtype 1 receptor; agents acting by plasma cell depletion; agents acting by the signal induced by B Cell Activating Factor (BAFF) or by a proliferation-inducing ligand (APRIL); agents acting by the inhibition of complement activity. The aim of this review has been to highlight the new drugs available in the treatment of IgAN. The vast majority of these agents are still the object of clinical randomized trials, but many of them have already been the object of publication in relevant journals. The reader should pay attention because, over the months, new findings will appear.

Keywords: Drugs anti-complement, Drugs anti APRIL/BAFF, IgA nephropathy, New drugs

Introduction

IgA glomerulonephritis is the most common form of primary glomerulonephritis. Around 50% of patients with IgA nephropathy (IgAN) develop end-stage kidney disease (ESKD) and require dialysis.

IgAN is characterized by high heterogeneity and high unmet medical needs, including the best treatment (1,2).

Recently, a study by Floege et al. (3) reviewed IgA treatment and called for a new paradigm. The treatments should be divided into those addressing the generic chronic kidney disease (CKD) drivers of continued nephron loss and those addressing immune and inflammatory drivers of continued graft loss. The present study will address this second kind of treatment.

The present study is a narrative review. The literature utilized refers principally to the last 3 years, since 2024, and papers or studies on PubMed or on ClinicalTrials.gov were considered. Trials interrupted or not enrolling patients have been excluded.

Before discussing in detail all these agents, it should be highlighted which IgAN phenotypes may benefit from each therapeutic class.

A simple way is to distinguish the histologic phenotypes according to the Oxford classification.

Active or proliferative lesions have a good response to steroids and immunosuppressants, while phenotypes with fibrosis or atrophy have a poor response to these agents.

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A different way to distinguish the IgA phenotypes is the phenotype at risk.

Patients with abnormal IgA production have an improved response to agents that inhibit the BAFF/APRIL pathway, such as Atacicept or Sibenprelimab;

Patients with inflammation and complement activation are better treated with Iptacopan, a factor B inhibitor;

Patients with abnormal hemodynamics or hyperfiltration are better treated with endothelin and angiotensin II receptor antagonists such as Sparsentan and Atresentan.

It should be highlighted that in recent years many new possible treatments are the object of several randomized clinical trials in different steps of study. Many of them have already been studied in different papers documenting their efficacy. In addition, it should be highlighted that some of these agents have recently received regulatory approval or accelerated approval. This is the case of Sparsentan, a fully US Food and Drug Administration- and European Medicines Agency- approved dual endothelin A/angiotensin II receptor antagonist. Another approved agent is Iptacopan, which inhibits complement factor B and has received accelerated US Food and Drug Administration approval. The endothelin A receptor antagonist atrasentan and a proliferation-binding ligand inhibitor, sibenprelimab, have also received accelerated US Food and Drug Administration approval.

For a better understanding of the nature of these treatments and how and where they act, Figure 1 shows the potential therapeutic targets for IgAN, most of them based on recent findings from Genome-Wide Association Studies (GWAS).

IgAN develops through 4 different hits. In the first hit, there is an increased level of abnormal (galactose-deficient) IgA1. In the second hit, there is production of autoantibodies against galactose-deficient IgA1. In the third hit, circulating

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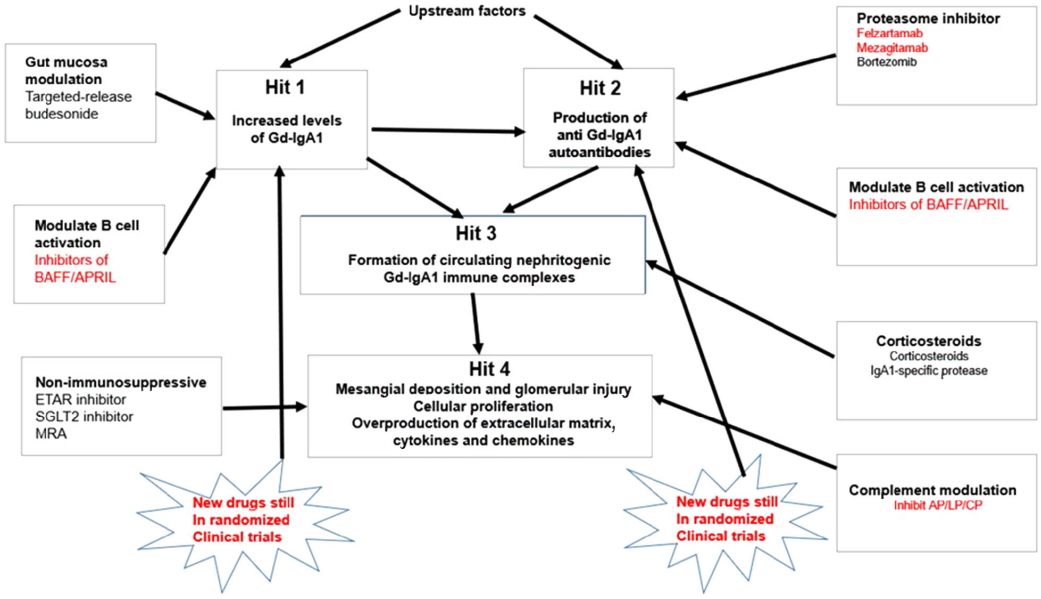


FIGURE 1 - Potential new and future therapeutic targets for IgAN (in red, the new ones).

nephrogenic galactose-deficient IgA1 immune complexes are formed. In the fourth hit, there is a mesangial deposition of such immune complexes with consequent glomerular injury. Each hit is the object of different treatments. The new therapies that will be treated in this study will act on hit one, hit 2, and hit 4.

Table 1 shows in detail the different investigational agents in clinical development for the treatment of IgAN, even if some of them have been definitively approved.

In general, according to the mechanism of action, these agents are divided into four groups.

- Agents acting by the inhibition of Endothelin A receptor and by the inhibition of the angiotensin II type 1 receptor
- Agents acting by plasma cell depletion
- Agents acting by the signal induced by B Cell Activating Factor (BAFF) or by a proliferation-inducing ligand (APRIL)
- Agents acting by the inhibition of complement activity

Agents acting by the inhibition of Endothelin A receptor

Sparsentan belongs to the first group, and it has been the object of two recently published papers (4,5). Sparsentan is a dual endothelin receptor antagonist and angiotensin receptor blocker. The PROTECT study assessed the effect of sparsentan on proteinuria reduction in a randomized, double blind, controlled study in 281 patients with biopsy-proven IgAN (6). In the PROTECT study, patients were randomized to either sparsentan or irbesartan. The double blind PROTECT study is ongoing to further evaluate the effect of sparsentan on the hard endpoint of estimated glomerular filtration rate (eGFR), kidney failure, or death. In a more recent study (5), the adverse events were evaluated in 504 IgAN patients. According to the study, sparsentan has a favorable safety profile.

Sparsentan was well tolerated, with no significant differences compared to irbesartan in fluid retention or rates of treatment-emergent adverse events.

Atrasentan is a selective endothelin A receptor antagonist. It is the other drug object of clinical trial in this group. In a study on 54 patients with IgAN already on treatment with maximal renin-angiotensin system inhibitor (RASi) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), atrasentan provided a significant further reduction in proteinuria, without significant adverse events (7). The beneficial effects of atrasentan were evaluated after 36 weeks of treatment, and the long-term effects are being evaluated after 136 weeks of treatment.

The second group of agents is represented by those inducing plasma cell inhibition.

Agents acting by plasma-cell depletion

The inhibition of the production of galactose-deficient IgA1 (Gd-IgA1) or of antibodies against Gd-IgA1 through the depletion of early B-cells with rituximab has been shown to be ineffective (8). A more effective therapeutic strategy for IgAN is represented by targeting CD38, which is highly represented in plasma blasts (9,10). Felzartamab is a fully human IgG1 monoclonal anti-CD38 (11-16). IGNAZ (NCT05065970) is a randomized, double blind, placebo-controlled phase 2a study assessing efficacy and safety of felzartamab in 54 patients with IgAN (17). The study documented an important reduction of proteinuria with disease improvement. These results with anti-CD38 were recently confirmed by a study by Floege et al. (18), who also reported two more studies (19,20) that documented decreased proteinuria and a reduced rate of GFR decline. The most common treatment-emergent AEs in the IGNAZ study reported with a greater incidence in the combined felzartamab arms versus the placebo arm were COVID-19, IRRs, diarrhea, nasopharyngitis, and upper respiratory tract infection (17).

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TABLE 1 - Investigational agents in clinical development for the treatment of IgAN

Agent	Phase	Registration No	Mechanism of action
Inhibition of Endothelin A receptor and Angiotensin II subtype receptor inhibitor			
Sparsentan	Approved	NCT03762850	Endothelin A receptor and Angiotensin II subtype 1 receptor inhibitor
Atrasentan	Approved	NCT04573478	Endothelin A receptor antagonist
Plasma Cell Depletion			
Felzartamab	II	NCT05065970	Monoclonal IgG1 antibody targeting CD38
Bortezomib	NA	NCT05383547	Proteasome inhibitor that depletes plasma cells
Inhibition of BAFF/APRIL Signaling			
Sibenprelimab	Approved	NCT052248646	Monoclonal IgG2k antibody targeting APRIL
Blisibimod	II/III	NCT02062684	Monoclonal antibody against both soluble and membrane BAFF
Atacicept	IIb/III	NCT04716231	BAFF/APRIL dual inhibitor
Telitacicept	II/III	NCT04905212	BAFF/APRIL dual inhibitor
Povatacicept	II/III	NCT05034484	BAFF/APRIL dual inhibitor
Zigakibart	II/III	NCT05852938	Monoclonal IgG4 antibody targeting APRIL
Inhibition of Immune Complex-Activated Complement Activity			
Iptacopan	Approved	NCT04014335	Small-molecule inhibitor of complement factor B
Avacopan	II	NCT02384317	Anti-C5ab receptor antagonist
Ravulizumab	III	NCT04564339	Long-acting C5-blocking antibody
Cemdisaran	II	NCT03841448	Small interfering RNA-targeting C5
APL-2	II	NCT03453619	Cyclic peptide inhibitor of C3 and C3b
IONIS-B-LRx	II	NCT04014335	Antisense inhibitor of complement factor B messenger ribonucleic acid
Narsoplimab	III	NCT03608033	Human monoclonal antibody against MASP-2

Another drug targeting plasma cells is mezagitamab (TAG-079). This drug is currently under evaluation in phase II IgAN studies. Even if this is a promising agent, nothing has been published, but it has been the object of an international meeting presentation (21).

APRIL and BAFF inhibitors

The tumor necrosis factor superfamily includes, among others, the cytokines B cell (BAFF) and APRIL. Both bind to two receptors, B cell maturation antigen (BCMA) and transmembrane activator, calcium modulator, and cyclophilin ligand interactor (TACI). BCMA is expressed on plasma cells, while TACI is expressed on mature B cells and activated plasma cells (22). BAFF and APRIL are important for mucosal B cell survival, maturation, and proliferation. Serum levels of APRIL and BAFF are increased in IgAN and when upregulated, stimulate B cells to increase the production of Gd-IgA1 and autoantibodies (23,24). Hence, the role of APRIL and BAFF in the pathogenesis of IgAN and the fact that targeting APRIL with or without BAFF is emerging as a viable strategy for the treatment of IgAN. New data from global clinical trials are showing very promising results (25). Table 2 shows the principal agents targeting APRIL and/or BAFF in patients with IgAN.

Several of these treatments seem to be effective, representing a new treatment approach. This is the case of atacicept and sibenprelimab, whose efficacy has been highlighted in an editorial in the New England Journal of Medicine by Tonelli (26). The author highlights two studies. The ORIGIN 3 evaluates atacicept, a soluble fusion protein that binds both BAFF and APRIL (27). The other study is VISIONARY, which evaluates the efficacy of sibenprenlimab, a monoclonal antibody directed against APRIL alone (28). Both of these interim analyses document the efficacy and safety of these drugs, supporting an accelerated approval to the Food and Drug Administration (FDA) (29).

Examining in detail all the cited drugs evaluated for the treatment of IgAN, we found as follows.

Sibenprelimab

Sibenprelimab is a humanized IgG2 monoclonal antibody that binds APRIL. It has been the object of two different clinical trials: ENVISION and VISIONARY (28). It blocks the APRIL biological activity, thereby reducing the production of pathogenic IgA and decreasing the deposition of IgA-related immune complexes in the kidney (30,31). An advantage of sibenprelimab is that it requires a monthly subcutaneous injection. Currently, sibenprelimab has entered phase III

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clinical trials. In these studies, sibenprelimab has demonstrated efficacy, reducing proteinuria and stabilizing renal function with a favorable safety profile (32). These results have been most recently confirmed by the results of two studies examining the interim analysis of the trials (28,33). The VISIONARY trial in particular confirmed the clinical promise, showing a favorable safety profile, with lower rates of serious adverse events compared to placebo.

Blisibimod

Blisibimod is a human protein that binds to soluble and membrane-bound BAFF. Because of its high affinity, it blocks all three forms of BAFF (soluble BAFF trimer, soluble 60-mer, and membrane BAFF) (34). The drug has been principally studied in patients with systemic lupus erythematosus. More recently, it has been studied in patients with IgAN, with poor results. Indeed, the phase II/III trial (BRIGHT-SC) has been concluded, but the results are still unpublished. Moreover, the phase III (BRILLIANT-SC) was terminated prematurely (35). The most common side effects in the treatment with Blisibimod after 60 weeks of treatment were upper respiratory infection, nasopharyngitis, and injection site reactions.

Current research on BAFF/APRIL biologics in the treatment of IgAN has moved toward both monotherapy with APRIL antibodies or dual inhibition of BAFF and APRIL antibodies.

Atacicept

Atacicept is a fully humanized soluble protein leading to dual APRIL/BAFF inhibition. It is an innovative TACI-Fc fusion protein whose molecular structure comprises the extracellular domain of the transmembrane activator and calmodulin-binding ligand (TACI) fused to the human IgG1 Fc segment (36,37). It is administered once weekly and has the advantage that inhibiting the activity of the two cytokines reduces the production of pathogenic IgA1 and immune complexes. Therefore, atacicept improves proteinuria and stabilizes the eGFR in IgAN patients (38,39). In a phase 2b study (40), atacicept versus placebo was administered in 116 patients with IgAN. At week 24, the mean protein-to-creatinine ratio was reduced, with stabilization of eGFR. In addition, galactose-deficient IgA1 levels significantly decreased.

In a different phase 2b trial, 113 IgAN patients received atacicept (41). After two years, atacicept was well tolerated, with reduction of proteinuria and stabilization of eGFR. In this study, the authors verified that stopping atacicept after 96 weeks of treatment results in an inversion of the beneficial effects. Indeed, there was an inversion in the reduction of Gd-IgA1 and in all types of autoantibodies. The strength of the trial was that most (90%) participants completed the entire 96-week trial; the weakness was that only a small percentage of participants were taking sodium-glucose transport inhibitors, making it difficult to assess atacicept's effect in combination with this common therapy.

Finally, in the already-completed phase 3 trial (ORIGIN 3) (27), these results were confirmed in 203 IgAN patients. In all the mentioned trials, the therapy was well tolerated, with fewer serious adverse events than placebo (0.5% vs 5.1%).

Telitacicept

Telitacicept is a fusion protein that binds to APRIL and BAFF (42). Telitacicept reduces levels of Gd-IgA1 and IgA-containing immune complexes, thus reducing proteinuria (43,44). In addition, by reducing IgA deposition and formation of immune complexes, it inhibits inflammation in the glomeruli (45,46). These results have been confirmed in recent studies. Weng et al. (47) documented the reduction of Gd-IgA1 and autoantibody-producing B cells in IgAN. Li et al. (48), in a retrospective study on 68 IgAN patients, documented the reduction of proteinuria and the stabilization of eGFR. Yang et al. (49) documented the improved efficacy of telitacicept when associated with steroids. The interim analysis of phase 3 (50) on 318 patients confirmed that after 39 weeks of treatment with telitacicept, there was a greater reduction in

TABLE 2 - Reports the clinical trials targeting APRIL and/or BAFF in patients with IgAN

Drug	Target	Mechanism of action	Trial Name and phase	NCT ID
Sibenprelimab (VIS649)	APRIL	Humanized IgG2 monoclonal antibody that binds APRIL	ENVISION (2) VISIONARY(3)	NCT04287985 NCT05248646
Blisibimod	BAFF	Human fusion protein that binds to soluble and membrane-bound BAFF	BRIGHT-SC (2 and 3) BRILLIANT-SC (3)	NCT02062684 NCT02052219
Atacicept	APRIL/BAFF	Fully humanized soluble fusion protein leading to dual APRIL/BAFF inhibition	JANUS (2) ORIGIN (2b) ORIGIN (3)	NCT02808429 NCT04716231
Telitacicept	APRIL/BAFF	Fusion protein that binds to APRIL and BAFF	(2) (3)	 NCT05799287
Povetacicept	APRIL/BAFF	Fc fusion protein including an engineered TACI receptor that acts as a decoy to inhibit both APRIL/BAFF	RUBY-3 (2) RAINIER (3)	NCT05732402 NCT06564142
Zigakibart (BION-301)	APRIL	Humanized IgG4 monoclonal antibody against APRIL	(1 and 2) BEYOND (3)	NCT03945318 NCT05852938

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TABLE 3 - Represents the same agents acting on BAFF/APRIL according to the mechanism of action, the research progress, the duration of treatment, the effects on proteinuria and eGFR, and the side effects

Medication	Mechanism of Action	Research Progress	Duration of Treatment	Proteinuria	Effect on eGFR	Side Effects
Blisibimod	Targets both soluble and membrane-bound BAFF	II/III	At least 60 weeks of treatment and up to 2 years	50% reduction from baseline at two consecutive visits	Annual improvement of +6.2 mL/min/1.73 m^2 per year	Upper respiratory infection, nasopharyngitis, and injection site reactions
Sibenprelimab	Humanized IgG2 monoclonal antibody binding and neutralizing APRIL	Approved	12 months, with follow-up continued until month 16	Reduction in the 24-h urinary protein-to-creatinine ratio of 58.8±6.1%	At month 12, the least-squares mean change in eGFR was 0.2 ± 1.7 mL/min/1.73 m^2	The incidence of adverse events was similar to the placebo group, with most being mild to moderate
Zigakibart	Humanized IgG4 monoclonal antibody reducing free APRIL levels	III	The maximum treatment duration was up to 124 weeks	Rapid and durable downward trend in proteinuria. The 24-h UPCR decreased by 60.4% compared to the baseline	eGFR remained sustained during treatment	Well tolerated, with no treatment-emergent adverse events
Atacicept	Novel dual-targeted fusion protein simultaneously inhibits BAFF and APRIL. It significantly reduces the production of Gd-IgA1 and its autoantibodies	Approved	For 36 weeks	The UPCR decreased by 31% from baseline	At week 36, the eGFR increased by 1% from baseline	The incidence of no treatment-emergent adverse events was lower than that in the placebo group
Telitacicept	Inhibiting the BLys/APRIL pathway reduces the production of Gd-IgA1 and its autoantibodies	III	Patients first underwent a 4-week run-in period, then were randomly assigned for 24 weeks	At week 24, the 24h proteinuria decreased by 49% from the baseline	At week 24, the eGFR increased by 2.34 mL/min/1.73 m^2	Overall safety was favorable; incidence of adverse events was mostly mild to moderate
Povetacicept	Inhibits BAFF and APRIL, blocks the production of pathogenic galactose-deficient IgA1	III	For a 24-week period	64.1% reduction in UPCR at 36 weeks.	eGFR assessment in the two groups showed stable renal function	Well tolerated with no reports of serious safety risks. No severe infections occurred

urinary protein-to-creatinine ratio than placebo. Additionally, the safety profile was favorable, with fewer serious adverse events than placebo (2.5% vs 8.2%) and a profile characterized by predominantly mild-to-moderate treatment-emergent events.

Povetacicept

Povetacicept is an Fc fusion protein including an engineered TACI receptor that acts as a decoy to inhibit both APRIL/BAFF (51). This agent inhibits the synthesis of Gd-IgA1, reducing the renal damage caused by immune complex deposition (52). In the RUBY-3 study phase, treatment with povatacicept obtained a 69% decrease in Gd-IgA1 protein and a reduction in urinary protein-to-creatinine ratio, with disease remission in 67% of patients. Such results were confirmed in late-stage RUBY-3 trials, which, among other results, reported that the 240 mg dose group demonstrated efficacy comparable to the 80 mg dose used in the previous study. The safety profile of povetacicept has been favorable, with

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no evidence of opportunistic infections, immunosuppression, or hypogammaglobulinemia. This suggests that povetacicept achieves targeted immunomodulation without compromising systemic immune competence. Madan et al. reported these results, documenting the povatacicept efficacy both in IgAN and in primary membranous nephropathy (53).

Zigakibart

Zigakibart is a humanized IgG4 monoclonal antibody that inhibits interactions between APRIL and its receptors BCMA and TACI. In this way, it reduces B-cell activation and abnormal IgA production (54-56). Dulos et al. (57) conducted a preclinical characterization of zigakibart, documenting in vitro its activity against TACI and BCMA. In the same study, in vivo methods were used to characterize zigakibart in human APRIL transgenic mice and non-human primates. In a study by Kooienga et al. (58), zigakibart demonstrated efficacy and safety in a phase 1/2 trial on healthy volunteers and patients with IgAN. The effects of zigakibart on proteinuria and long-term kidney function in adults with IgAN are being evaluated in the ongoing phase III BEYOND study.

In a study up to 124 weeks, Zigakibart was well tolerated, with no treatment-emergent adverse events.

Agents acting by complement inhibition

In recent years, the central pathogenic role of complement activation in IgAN has been highlighted. Several drugs have been the object of clinical trials, and others are in development with the aim of preventing overactivation of the alternative, lectin, and/or terminal pathway of complement, as shown in Figure 2.

Inhibitors of the lectin pathway

Narsoplimab is a humanized monoclonal antibody targeting mannan-binding lectin-associated serine protease-2 (MASP-2) that selectively inhibits the lectin pathway. In a phase II study of 12 high-risk patients with IgAN, Lafayette et al. (59) found that proteinuria at 18 weeks was not different between the narsoplimab and control groups, even though the longer exposure revealed a significant decrease in proteinuria with narsoplimab. However, the recent phase III trial with narsoplimab (ARTEMIS-IGAN study) was terminated because of an insufficient antiproteinuric effect (60).

Inhibitors of the alternative complement pathway

Pegcetacoplan is a complement C3 inhibitor that binds to C3 and prevents its cleavage into active fragments. In a phase II clinical trial, pegcetacoplan reduced proteinuria in a small quantity, documenting a limited clinical effect (61).

Iptacopan is an oral selective factor B inhibitor that acts by blocking the amplification of the alternative complement pathway. In the phase II study of 112 patients with IgAN, iptacopan reduced proteinuria and was well tolerated (62). Two phase III studies (APPLAUSE-IgAN) have been conducted. Barratt et al. (63) included 477 patients who were randomly assigned to receive iptacopan or placebo. The iptacopan group had, at the 24-month data, a significantly slower decline in eGFR than the group treated with placebo.

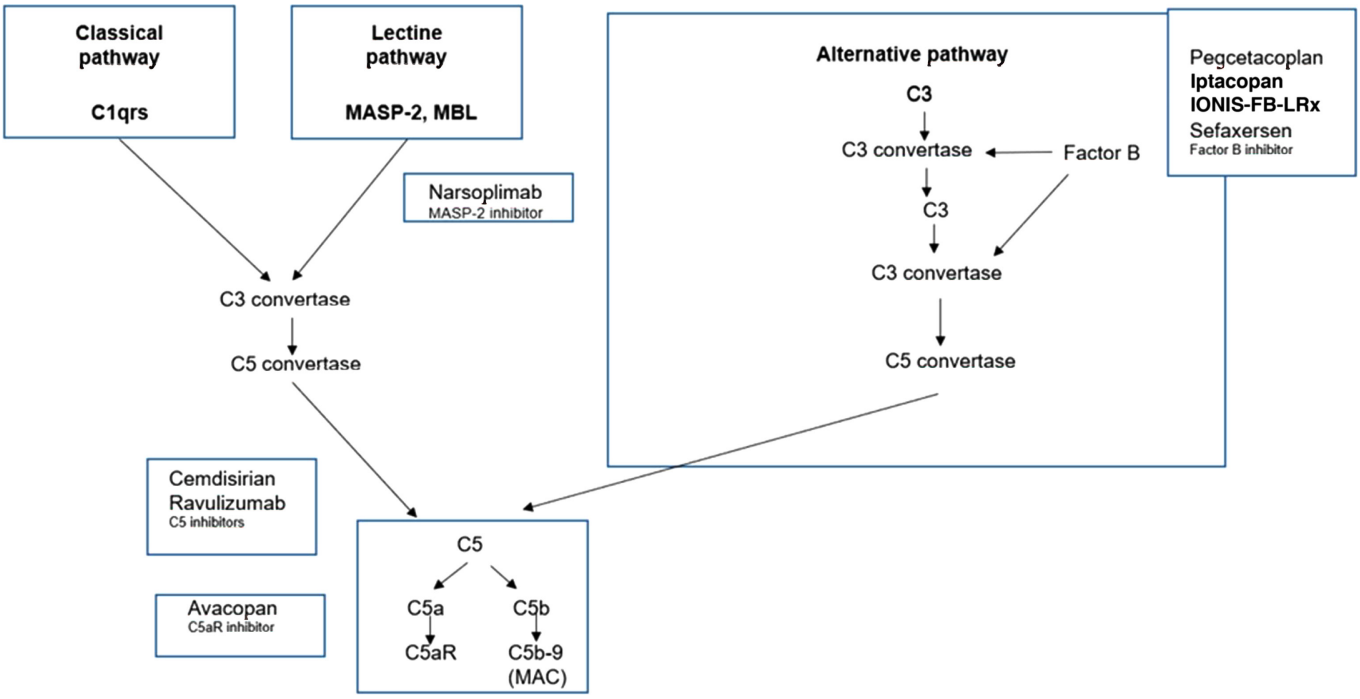


FIGURE 2 - Drugs targeting the complement system. Landscape of complement inhibitors tested or currently evaluated by ongoing trials for IgAN therapy and their site of action.

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Another factor B inhibitor is IONIS-FB-LRx. In a phase II study, 10 patients with IgAN were enrolled. By month 7, plasma levels of complement factor B had decreased significantly, and the urinary protein levels were significantly reduced. In addition, the treatment was well tolerated. The limitation of the trial is the small sample size (64).

The same molecule, with the name sefaxersen, entered a single-arm phase 2 trial for the treatment of IgAN. 23 patients with IgAN were enrolled, and the results at 29 weeks documented that sefaxersen inhibited the complement alternative pathway and reduced proteinuria with stable eGFR (65). These findings support further evaluation, and the phase III IMAGINATION trial is recruiting patients.

Inhibitors of the terminal complement pathway

Cemdisiran

Cemdisiran is an investigational RNA interference therapeutic that suppresses hepatic production of complement C5. In a phase 2 clinical trial (66), 31 IgAN patients were randomized to receive cemdisiran versus placebo. At week 32, cemdisiran patients had a significant reduction in proteinuria and a serum reduction of C5 of 98.7%. The only reported side effect was injection-site reaction.

Ravalizumab

Ravalizumab is a humanized monoclonal antibody inhibiting complement C5. In a phase 2 clinical trial, 43 patients were randomized to receive ravalizumab versus placebo (67). At week 50, there was a significant reduction in protein excretion rate associated with an eGFR stabilization. A phase III trial is to date enrolling patients.

Avacopan

Avacopan is an oral C5a receptor inhibitor that selectively blocks the effects of C5a through the C5a receptor. As a result of several studies, the drug has been approved for the treatment of antineutrophil cytoplasmic antibody-positive vasculitis. In a small study conducted by Bruchfeld et al. (68), 7 patients with IgAN were treated with avacopan and had an improvement in proteinuria after 22 weeks of treatment. The main limitation of the study is the small number of patients and the short duration.

Current studies are assessing the safety of complement inhibitors, with particular focus on the risk of infections with encapsulated organisms that had emerged from use of terminal complement pathway inhibitors in other diseases. Per treatment guidelines in the United States, vaccination against *Neisseria meningitides* and *Streptococcus pneumoniae* are required prior to study entry. Vaccination against *Haemophilus influenzae* type B is also highly recommended. Current trials involving complement system-targeting therapies do not show an increased infection risk when these vaccinations are performed (22).

Discussion and Conclusion

An important point to be highlighted is the relationship between the Kidney Disease Improving Global Outcomes (KDIGO) and the new therapies for the treatment of IgAN. In 2021, KDIGO published a major revision of the Clinical Practice Guideline for the Management of Glomerular Diseases (69). In the case of IgAN, a number of important new insights and successful major randomized controlled clinical trials were published after 2021, prompting a new guideline update published by Floege et al. in 2025 (70). According to these findings, the targeted-release budesonide (Nefecon) is shown to have an effect on the production of pathogenic forms of IgA and IgA-containing immune complexes. Strategies to manage the general response to IgAN-induced nephron loss may also include the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, dual endothelin-angiotensin receptor antagonists, renin-angiotensin system inhibitors, and sodium-glucose cotransporter-2 inhibitors.

Many of the above-mentioned agents are not included in Floeges's paper. As the author highlights, suggested combinations of medications targeting different points in the IgAN pathogenic pathways may be more effective. In addition, trial experience shows that when some medications are stopped, proteinuria quickly returns. Therefore, the 2025 IgAN guideline will be appropriately updated, moving toward a fully evidence-based set of recommendations.

A different point to be discussed is combination therapy. Indeed, considering the different mechanisms of action of the new therapies is important to understand which combination therapy is the best one according to the clinical results expected.

- Mitigation of Nephron Loss
  Treatments: RAAS, SGLT2, Endothelin-1 blockers, Blood Pressure control
- Control of Glomerular Inflammation
  Treatments: Corticosteroids, Immunosuppressants, curtail acute glomerular injury
- Novel and Targeted Anti-Inflammatory
  Treatments: Complement inhibitors, block IgA-induced complement activation
- Reduction of Pathogenic IgA Production
  Treatments: B-cell and plasma cell therapies, targeted release budesonide

Independent of the large quantities of new agents to date in study for the treatment of IgAN, several unanswered questions remain.

Biomarkers predicting response

There is a gap in identifying reliable and well-validated biomarkers that can support individualized treatment planning. Serum Gd-IgA1 and anti-Gd-IgA1 autoantibodies, urinary Monocyte Chemoattractant protein 1 (MCP-1), CD89, and glomerular deposits of C3 and C4d have potential validity, but none of them is validated for clinical use. Additionally, new tools are being studied, such as urinary exosome profiles and genetic markers, but their use is still in its first stage (71).

Lack of Head-to-Head Comparative Trials

A persistent limitation in IgAN research is the absence of direct head-to-head randomized controlled trials. Although

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meta-analyses suggest that several agents, such as APRIL/BLys pathway inhibitors, complement factor B antagonists, and sparsentan, are effective compared with supportive care, there is no evidence establishing their relative superiority.

Absence of Long-Term Efficacy and Safety Data

Although newer therapies demonstrate promising short-to medium-term outcomes, long-term efficacy and safety remain insufficiently established. Given that IgAN typically progresses over 10-20 years, current follow-up durations are inadequate to assess the treatment potential. Hence, the use of surrogate endpoints is warranted.

Cost and accessibility of Novel Therapies

Despite clinical advances, new IgAN therapies remain costly and are not uniformly accessible across different healthcare systems. Consequently, disparities in access to advanced therapies may widen global treatment inequities in IgAN management (72).

Recently, several new agents have been found for the treatment of IgAN. The agents that have been previously used are either ineffective or partially effective. The studies that have been made with GWAS have allowed us to confirming that IgAN develops in four different steps. Different agents act on each step. The recently found new agents act in any phase of the disease, but the most important act on plasma cell inhibition, on the inhibition of APRIL and BAFF, and on the complement cascade. In particular, these agents are important because the complement is involved in all the phases of the disease.

Many of the agents described are still in different phases of randomized clinical trials, but several of these agents have already been described in articles in relevant medical journal.

In summary, the future is promising, and these new agents may add to the actions of the formerly used agents.

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