The Treatment of Primary IgA Nephropathy: Change, Change, Change

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IgA nephropathy (IgAN) is the most common glomerular disease in the world. However, the approach to treatment remains controversial. There has been an explosion of clinical trials over the past decade both to further examine corticosteroid use and usher in additional treatment considerations, including 2 newly approved therapies for IgAN. Sodium glucose cotransporter 2 inhibitors are proving to be effective therapy across proteinuric chronic kidney diseases, and IgAN is not likely to be an exception. Further supportive agents are looking highly promising and so are novel agents that specifically focus on the pathophysiology of this disease, including endothelin blockade, complement inhibition, and B-cell targeted strategies. We suggest a present-day approach to treatment of individuals with IgAN, expose the limitations in our knowledge, and discuss new treatments that may arise, hoping they come with evidence about optimal utilization. Change appears to be inevitable for our approach to the treatment of IgA nephropathy. This is truly an exciting and optimistic time.

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Introduction

The treatment of primary IgA nephropathy (IgAN) is undergoing rapid change, based on new insights and novel approaches to care. Since its description by Hinglais and Berger, IgAN became established as the most common form of primary glomerular disease worldwide.[1-3] Though heterogeneous, it is increasingly recognized as a major cause of progressive kidney dysfunction and failure, which occurs in 20%-50% of affected patients over 10 to 20 years.[3] At highest risk are those with glomerular inflammation, interstitial fibrosis, increasing degrees of proteinuria, and kidney dysfunction.[4]

The pathogenesis of IgAN has become clearer over the decades as research findings accumulate. According to our current understanding, genetically predisposed individuals suffer multiple pathophysiologic changes, commonly referred to as "hits," to develop and progress the disease (Fig 1).[5-7] Galactose deficient IgA (GD-IgA) is produced in the mucosa after stimulation by various antigens, including microbes such as bacteria. Individuals prone to IgAN maintain higher systemic levels of GD-IgA, against which IgG- or IgA-directed auto-antibodies can be stimulated. This leads to circulating immune complexes containing the auto-antibody and the GD-IgA. Through specific and nonspecific interactions, these complexes accumulate in the glomerular mesangium. Once there, they are able to generate molecular and cellular responses, including cytokine-, chemokine-, and complement-mediated cellular inflammation and injury.[5-8] Over time, this process can lead to the characteristic findings of hematuria and proteinuria, and also drives glomerular and tubulointerstitial sclerosis. Ultimately, kidney dysfunction and failure ensue.

Historically, efforts to interrupt this process have focused on nonpharmacologic supportive care to generally reduce the risk of kidney injury, such as diet, exercise, weight control, and avoiding nephrotoxins (including tobacco). In addition to vigorous blood pressure control, supportive pharmacologic therapy includes non-immunosuppressive medications, traditionally agents that inhibit angiotensin II activity (renin angiotensin system [RAS] blockade), but also newer therapies that slow disease progression in proteinuric kidney disease, such as sodium-glucose cotransporter 2 (SGLT-2) inhibitors. More disease-specific therapies include utilization of immunosuppressive agents to reduce inflammation in IgAN.[9,10] Intervention has focused on the use of corticosteroids but also cytotoxic agents such as cyclophosphamide, azathioprine, and mycophenolate. These approaches have been controversial because their efficacy has not been well established and their side effects are clear and undesirable.[11]

More recently, efforts have been made to target therapy more specifically to the pathogenesis of IgAN. These efforts have been powerfully supported by collaboration among patients, physicians, the pharmaceutical industry, and regulators looking to find new ways to determine efficacy among therapies for this disease.[12] This has resulted in regulators accepting data on proteinuria reduction as a likely surrogate of hard kidney outcomes, including kidney failure, and allowing for a more economically viable and streamlined approach to discover treatments for IgAN.[13] Indeed, this approach appears to hold great promise. A variety of therapies for IgAN are now available or emerging, as discussed in further detail throughout this review (Table 1). Herein, we hope to provide a reasonable approach to the treatment of patients with IgA nephropathy as well as to set the stage for potential game-changing innovations in therapy on the immediate and near horizon.[14]

Prognosis

To determine the need for therapy, individuals need to be assessed for their risk of progression. Several risk factors

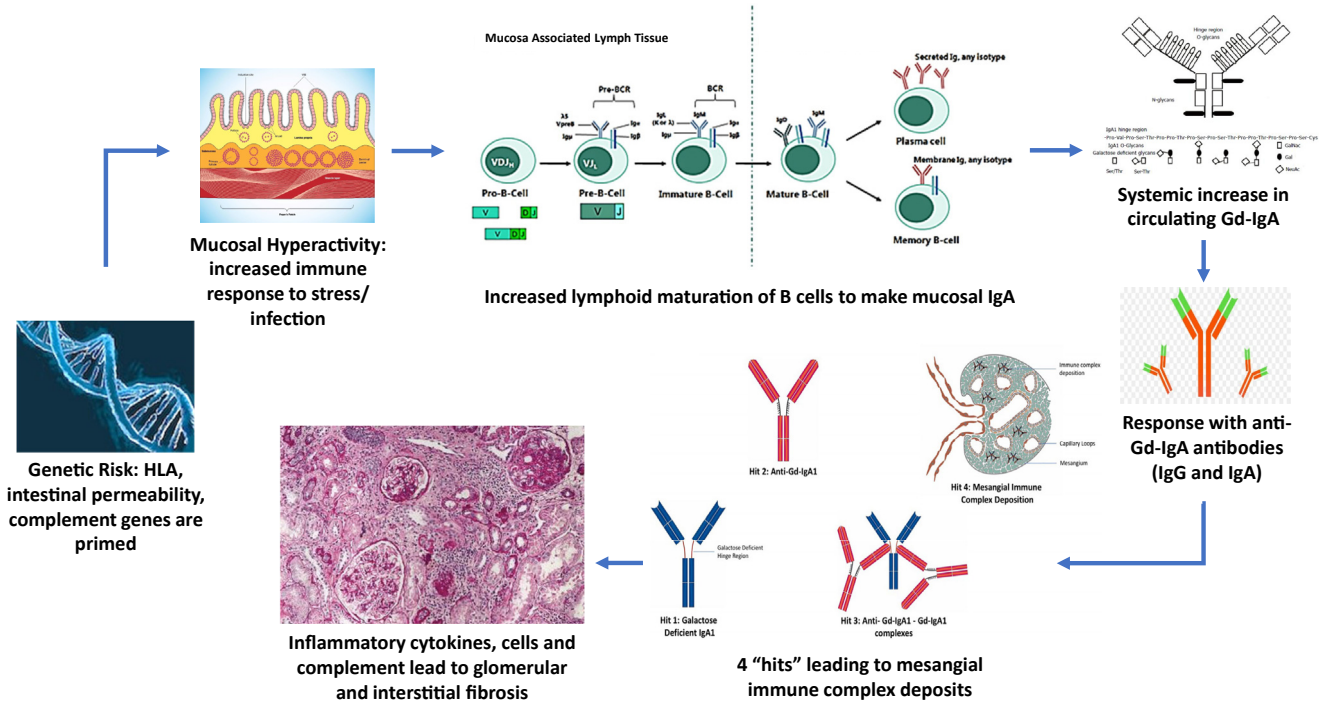

Figure 1. Pathogenesis of IgA nephropathy. As in the text, the pathophysiology of IgA nephropathy results from genetically predisposed individuals undergoing progressive pathophysiologic events, commonly referred to as "hits," setting up the patient for glomerular injury, inflammation, and scarring. As shown, genetic predisposition leads to mucosal immune hyperresponsiveness to stimuli. This leads to B lymphocyte class switching influenced by Toll-like receptor activation, and cytokines such as Blys (BAFF) and APRIL. Increased lymphoid production or systemic passage of plasma cells leads to increased circulating levels of mucosal IgA, generally known as galactose deficient IgA (hit 1). Again, genetic predisposition leads to increasing amounts antiglycan antibodies (hit 2), which causes circulating immune complexes of GD-IgA and antiglycan antibody (hit 3). These immune complexes deposit in glomerular mesangial areas (hit 4), leading in some individuals to glomerular inflammation. The inflammation leads to glomerular dysfunction with hematuria and proteinuria, eventually leading to glomerular and tubular fibrosis and progressive kidney dysfunction. Panel on 4 "hits" reproduced from Selvaskandan et al[7] under a CC-BY license. Panel on increased lymphoid maturation of B cells reproduced with permission of the copyright holder (SinoBiological, Inc). Abbreviations: APRIL, A proliferating ligand; BAFF, B-cell-activating factor; Blys, B-lymphocyte-stimulating factor; GD-IgA, galactose-deficient IgA; Ig, immunoglobulin.

have been identified for IgA nephropathy, including histology, race, gender, blood pressure, kidney function, and proteinuria.[15,16] The International IgAN Network risk prediction score has been validated for adults at time of biopsy, and an updated version can be used up to 2 years after biopsy.[17,18] Low-risk patients typically have normal blood pressure and kidney function, only low-grade proteinuria (generally less than 500 mg/day), and often do well for many years. However, if followed long enough, some of them will progress to kidney failure.[19] Whether to intervene pharmacologically at diagnosis or wait for evidence of progression is unknown, but conservative measures can still be undertaken. Individuals with greater degrees of proteinuria, hypertension, or reduced kidney function have a moderately poor prognosis over many years. Conservative and supportive pharmacologic measures should be undertaken to protect and maintain their kidney function. When the prognosis is more worrisome—proteinuria greater than 1 g/day or with diminishing kidney function or displaying poor prognostic features on kidney biopsy—certainly maximal supportive lifestyle and pharmacologic therapy are needed, and more disease-specific pharmacotherapy should be considered.

The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines focus on controlling proteinuria and suggest ongoing supportive therapy (including lifestyle modifications and RAS blockade) for patients whose prognosis appears improved by maintaining proteinuria < 1 g per day.[20] However, how strongly to consider other risk factors, such as kidney function, blood pressure, or histology, remains controversial. IgAN with rapidly progressive glomerulonephritis (RPGN) is marked by week-to-week or even day-by-day deterioration in kidney function and generally presents with more than 50% crescents on biopsy. Patients with IgAN and RPGN have very poor outcomes and should be considered separately because there are limited data on their care. Aggressive immunosuppression is generally used.[21] Secondary forms of IgAN include liver disease, infection, autoimmune disease, and IgA vasculitis. Treatment for patients with secondary forms of IgAN should also be considered separately because the disease pathophysiology

Table 1. Interventions to Consider in Patients With IgA Nephropathy

Intervention	Proteinuria Reduction	Kidney Function Preservation	Safety	Comments
Diet (low salt, protein)	Can help	May help	No concerns	
Tonsillectomy	Maybe	Maybe stabilizes GFR	Surgery/tolerability	Related to geography, genes
Fish oil	Probably no	Probably no benefit	Generally tolerable	Not recommended
RAAS inhibitors	Yes	Preserves function	Generally tolerated	Limited overall data, but standard of care
SGLT-2 inhibitors	Yes	Likely preserves function	Generally tolerated	
• *Trial:* DAPA-CKD substudy of IgAN.[36] Preplanned analysis of outcomes of patients with IgA nephropathy, with eGFR of 25-60, urine protein >500 mg/d, randomized to optimized RAAS inhibitor vs SGLT-2 inhibitor therapy; 270 patients. Median follow-up 2.1 years.	Mean urine albumin excretion reduced by 26% (−37% to 14%)	Reduced renal end point (50% eGFR decline, ESKD, renal or cardiac death), HR, 0.29 (0.12-0.73), regardless of baseline eGFR or proteinuria	Fewer SAEs than placebo, no DKA or major hypoglycemia	Awaits detailed analysis from empagliflozin study; concern for urogenital infections, especially for immunosuppressed patients
Endothelin blockade*	Yes	Still not clear	Newer agents appear well tolerated	
• *Trial:* PROTECT.[44] Randomized controlled trial, patients with IgAN, eGFR > 30 mL/min, urine protein >1 g/d, on optimized RAAS inhibition. Compared outcomes on sparsentan with irbesartan, with 9-mo proteinuria and 2-y eGFR; 404 patients randomized. Median follow-up 64 weeks (awaiting full report after 2 years of follow-up).	Week-36 reduction in proteinuria −49.8% compared with irbesartan, −15.1%. Complete remission in 21% vs 8%; partial remission in 70% vs 44%.* No differences based on baseline eGFR or proteinuria.	No data	Increased overall AEs (mildly increased edema, hypotension, dizziness) and discontinuations, but SAE rate was similar; BP only minimally lower, mainly diastolic	Ready for use as conservative therapy or need to await eGFR data, should be available soon
Corticosteroids				
Systemic	Can lower proteinuria, temporary	May preserve function in certain patients	Steroid side effects common and can be severe, even at reduced doses	May be better alternatives
ACTH[57]	Lowered proteinuria	Stable eGFR, no comparator	Can have steroid side effects	Needs further exploration, costly
Targeted-release budesonide	Lowered proteinuria	Less eGFR loss at early time points	Can have steroid side effects	Long-term outcomes pending, costly
• *Trial:* STOP IgA Nephropathy.[49] Europe-focused trial, patients with IgAN, maximal RAAS inhibition, eGFR > 30 mL/min/1.73 m^2, urine protein > 1 g/d; 162 patients randomized to conservative therapy vs immunosuppression. 95% completed 3 years follow-up.	Proteinuria went down from baseline in both groups, but immunosuppression group more often had proteinuria < 0.2 g/g.	No difference in eGFR decrease by >15 mL/min. No difference in mean absolute change in eGFR or rate of ESKD	Numerically greater AE and SAE ($P = 0.07$ for greater infections), significantly more weight gain, and impaired glucose tolerance	White European population; 10-y study follow-up disclosed no differences in kidney outcomes

(Continued)

Table 1 (Cont'd). Interventions to Consider in Patients With IgA Nephropathy

Intervention	Proteinuria Reduction	Kidney Function Preservation	Safety	Comments
• *Trial:* TESTING.[51] Randomized control trial of patients with IgAN; eGFR, 20-120 mL/min/1.73 m^2, urine protein >1 g/d, corticosteroids of methylprednisone 0.6-0.8 mg/kg (part 1), reduced to 0.4 mg/kg (part 2) after initial safety concerns; 503 patients randomized. Median follow up 3.5 years	Lower proteinuria during follow-up, between-group difference of 0.69g/d; difference no longer apparent by 3 y	Annual loss of eGFR 2.5 mL/min for the treated group, 5.0 mL/min for placebo. For loss of function (40% reduced eGFR, ESKD, death): HR, 0.5 (0.39-0.72)	SAEs (mostly hospitalization, infection) in 28 participants (10.9%) vs 7 (2.8%) placebo; difference greater in high dose vs reduced dose	Asian population, mainly in China; reduced dose similar efficacy, lower AEs but still more than double vs placebo.
• *Trial:* NeflgArd:[58] Randomized control trial of patients with IgAN with eGFR > 30, < 90 mL/min, urine protein > 1 g/d, 9 mo of targeted budesonide, followed by 15 mo follow-up for eGFR changes; 360 patients randomized. Initial report on 199 subjects at 9 mo; 87% provided 12 mo data as well.	Proteinuria reduced 27% at 9 mo and 48% at 12 mo after 9 mo of treatment; no difference based on baseline eGFR or proteinuria	7% Greater loss of kidney function in placebo compared with therapy at 9 and at 12 mo	AE and SAE numerically higher, no difference in infection, bleeding, but some increase in edema, acne, and blood pressure	Part B reported in press release only, shows sustained proteinuria benefits and eGFR preservation out to 2 y of study (9 mo treatment, 15 mo follow-up). No head-to-head comparisons but may well be lower side effects and safety concerns compared with nontargeted steroids.
Cytotoxics				
Azathioprine	Unclear	Likely no effect	Some safety issues	Limited number studied
Mycophenolate	Mixed results	Mixed results	Safety issues, tolerability	
Cyclophosphamide	Mixed results	Mixed results	Safety issues, tolerability	
• *Trial:* MAIN.[71] Open-label prospective study of mycophenolate in patients with IgAN, proteinuria >1 g/d, eGFR > 30, and either persistent hypertension or eGFR < 60 mL/min. All on optimal RAAS inhibition during run-in of 3 mo; 170 patients randomized. Followed for 3 years (92% followed median of 6 y).	57% Reduction in proteinuria in mycophenolate group compared with 28% in standard of care	Relative risk for end point (doubling creatinine, ESKD) HR, 0.31 (0.12-0.78); eGFR decline reduced 1.2 mL/min/y vs 3.8 mL/min/y with standard care	Numerically more adverse events, including infection (pneumonia) and GI upset	Only done in China, not replicated elsewhere; over time, proteinuria returning toward baseline
Disease-modifying Antirheumatics				
Hydroxychloroquine	Maybe	Maybe beneficial	Tolerable, but needs monitoring	Needs more study
Leflunomide	Maybe	Maybe beneficial	Possible safety issues, infection	Needs more study

(Continued)

Table 1 (Cont'd). Interventions to Consider in Patients With IgA Nephropathy

Intervention	Proteinuria Reduction	Kidney Function Preservation	Safety	Comments
B-Cell Agents				
Rituximab	Likely no effect	Likely no effect	Infusion reaction, infection risk	
Anti-April (± Blys)*	Early reductions seen in multiple programs	Early eGFR stability	Possible infections, injection reactions	Awaits phase 3 result, effectively reduces Gd-IgA; needs more study
Anti-plasma cell*	Unknown	Unknown	Possible infections, infusion reactions	
Complement Inhibition				
Common pathway*	Mixed results	Unknown	Infection, infusion reactions	Awaits phase 2 results
Antilectin*	Substantial reduction	Relatively stable	Generally tolerable	Awaits phase 3 results
Alternate pathway*	Reduced	Relatively stable	Infections/vaccination	Awaits phase 3 results

*Limited data. Abbreviations: ACTH, adrenocorticotrophic hormone; AE, adverse event; APRIL, a proliferating ligand; Blys, B lymphocyte stimulator; BP, blood pressure; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; Gd-IgA, galactose deficient immunoglobulin A; GI, gastrointestinal; HR, hazard ratio; RAAS, renin angiotensin system; SAE, severe adverse event; SGLT-2, sodium-glucose cotransporter 2.

is likely to vary. Secondary causes need to be ruled out before embarking on therapy for primary IgAN as discussed further here.

Conservative/Supportive Care

Lifestyle Modifications

General lifestyle modifications to reduce cardiovascular risk—including smoking cessation, maintaining a healthy weight, and regular exercise—are encouraged. General principles of diet in glomerular disease should be adhered to including low-sodium (<2 g/day) diet and avoidance of high-protein diets.[20] For chronic kidney disease (CKD), there may be additional benefit from following a plant-based diet and minimizing animal sources of protein.[22] There are conflicting studies regarding fish oil supplementation and insufficient evidence to recommend use.[23,24] A gluten-free diet may reduce IgA immune complexes but has not shown any benefit for long-term kidney function in patients without celiac disease.[25]

Supportive Pharmacologic Therapy

Renin Angiotensin System Blockade

The use of RAS blockade is associated with increased kidney survival in patients with nondiabetic proteinuric kidney disease.[26] Multiple studies have demonstrated RAS blockade also improves kidney outcomes in IgAN.[27-29] Small studies have demonstrated that the combination of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) may lead to further reductions in proteinuria and inflammatory markers.[30,31] However, combined use of ACE inhibitors/ARB led to worse kidney outcomes (doubling of creatinine, end-stage kidney disease, and death) in a large trial of patients with vascular disease or diabetes with end-organ damage.[32] A 2011 Cochrane analysis of nonimmunosuppressive therapies including antihypertensives, fish oil, antiplatelet agents/anticoagulants, and tonsillectomy for IgAN concluded that antihypertensive therapy (primarily with RAS blockade) was the only nonimmunosuppressive therapy to demonstrate clinical benefit in IgAN.[24] Based on these studies, current guidelines recommend patients with IgAN with proteinuria > 500 mg/day be placed on maximally tolerated RAS blockade with ACE inhibitor or ARB, even when normotensive.[20]

Sodium-Glucose Cotransporter 2 Inhibitor Therapy

The Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE) trial demonstrated that addition of canagliflozin to standard of care improved kidney and cardiovascular outcomes in patients with type 2 diabetes and kidney disease.[33] The Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) trial demonstrated that addition of dapagliflozin slows the progression of CKD and reduces cardiac events in both diabetic and nondiabetic CKD.[34] The Empagliflozin in Patients with

Chronic Kidney Disease (EMPA-KIDNEY) trial demonstrated that the addition of empagliflozin slows CKD progression and reduces cardiovascular mortality in both diabetic and nondiabetic kidney disease.[35] Together, these studies suggest a class-wide benefit of SGLT-2 inhibitors on both diabetic and nondiabetic CKD. A subgroup analysis of IgAN patients in the DAPA-CKD trial demonstrated strong benefit in this population.[36] Approximately 25% of patients in EMPA-KIDNEY had glomerular disease.[35] These data support the use of SGLT-2 inhibitor therapy as part of the supportive therapy regimen in patients with IgAN, proteinuria, and CKD.

It is as yet unclear whether SGLT-2 inhibitor therapy will benefit patients with preserved estimated glomerular filtration rate (eGFR > 90 mL/min/1.73 m^2) because these patients were not included in the DAPA-CKD or EMPA-KIDNEY trials. The mean eGFR among the DAPA-CKD IgAN cohort was 43.8 mL/min/1.73 m^2.[36] Further, the ideal timing of SGLT-2 inhibitor initiation is uncertain in the setting of IgAN; it appeared most effective as a late intervention in these trials. The mean age of the patients in the DAPA-CKD trial was 61.8 years (51.2 years among the IgAN subgroup) and in the EMPA-KIDNEYtrial was 63.8 years.[34-36] This, along with reduced eGFR, suggests that IgAN patients represented in these studies had significant disease chronicity at the time of entry into the study.

There also has been concern regarding concomitant use of SGLT-2 inhibitor with immunosuppressants (especially corticosteroids) due to the increased risk of urogenital infections seen in prior studies of SGLT-2 inhibitors in diabetic patients.[37,38] Although there was no increased risk of urogenital infection in the DAPA-CKD or EMPA-KIDNEY trials, patients receiving immunosuppressive therapy were excluded in the DAPA-CKD and limited in EMPA-KIDNEY trial.[34,35] Given the relatively short duration of immunosuppressive therapy regimens in IgAN (6-9 months), one approach may be to wait and add SGLT-2 inhibitor after completion of immunosuppression.

Novel Supportive Pharmacologic Therapy

Endothelin Receptor Antagonists

Multiple animal models have demonstrated that activation of endothelin A receptors by endothelin-1 (ET-1) contributes to cell injury, proteinuria, inflammation, and fibrosis in CKD.[39] Recent clinical trials evaluating endothelin receptor antagonists (ERAs) demonstrated improved kidney outcomes and decreased proteinuria in both diabetic and nondiabetic kidney disease.[40,41] However, fluid retention remains a concern for this therapeutic class.[42] Interestingly, the addition of an SGLT-2 inhibitor in combination with ERAs may help mitigate fluid retention.[43]

Atrasentan is currently being evaluated in a phase 3 trial of IgAN.[44] All participants are required to be on maximally tolerated RAS blockade at study entry, and the trial will also evaluate a subset of patients who are on stable SGLT-2 inhibitor therapy at study entry. Sparsentan, a dual ERA and ARB, is currently being evaluated in a phase 3 trial for IgAN.[45] For this study, patients are randomized to receive sparsentan versus active control (irbesartan). Interim analysis demonstrated statistically significant reductions in proteinuria in the treatment arm.[46] Based on the positive interim analysis, sparsentan received accelerated approval from the US Food and Drug Administration (FDA) for the treatment of proteinuria in patients with IgAN with high risk of disease progression.[47] Ongoing FDA approval will be contingent on the final results of the trial, including eGFR slope analyses.

Immunosuppressive Therapy

Corticosteroids

Since the initial description of IgAN, there have been ongoing efforts to treat it with immunosuppressants, given its nature as an autoimmune, immune complex disease. Most studies have focused on the use of corticosteroids, and the results remain highly mixed, with no clear consensus on the safety or efficacy of these agents.[48] Early experiences decades ago with steroids and cytotoxic agents were deemed unsuccessful in a review by Cameron.[9]

Understanding the impact of steroids on patients with IgAN is complex because many different regimens have been used in different populations and with different background therapy, which could have impacted the results, such as antihypertensive and RAS blocking agents. Generally, no advantage has been demonstrated for long-term (>1 year) compared with moderate-term (6-9 months) therapy,[49] thus most of the more recent trials have focused on short-term to moderate-term courses of steroids.

Indeed, it seemed that evidence had supported, even validated, the use of moderate length courses of steroids, either using about 1 mg/kg per day with a slow taper over 6 months or using pulse steroids on alternate months with moderate dose maintenance (0.5 mg/kg on alternate days) for approximately 6 months.[10,50] In fact, a large observational study supported immunosuppression for IgAN.[51] However, the STOP-IGAN study demonstrated no benefit on kidney function with corticosteroid treatment for IgAN patients with eGFR values of ≥60 mL/min/1.73 m^2 and no benefit of combined immunosuppression including corticosteroids when the eGFR was <60 mL/min/1.73 m^2.[52] In fact, this study demonstrated significant harm with immunosuppression. This was followed by the initial reports of the TESTING study showing such significant side effects—importantly, fatal and life-threatening infection—that it outweighed the early benefit seen in proteinuria reduction and kidney preservation, and the study was stopped for safety.[53] This led to renewed concerns regarding the value of corticosteroids in IgAN.

Although the TESTING II study demonstrated efficacy in preserving kidney function of a modestly reduced course

of corticosteroid (still 0.4 mg/kg per day of methylprednisolone tapered slowly over at least 6 months), the adverse events were still significant. Additionally, longer term follow-up of the patients suggested high rates of relapse and return to progressive kidney disease.[54] Thus, while steroids may have short-term benefits in some populations with IgAN, their side effects must be carefully considered; additional options are desired to ensure efficacy combined with safety. Patients considering immunotherapy should be well screened for chronic infection and well vaccinated for infectious risk. Steroid doses and durations should be limited.

Other Immunosuppression

Other immunosuppressives have included cyclophosphamide and azathioprine. The data remain mixed on these agents, with a small study suggesting benefit among high-risk patients given short-term cyclophosphamide and prednisone followed by longer term azathioprine.[55] This regimen appeared ineffective in other studies, including the STOP IgAN trial.[52]

Mycophenolate is of great interest as a steroid-sparing therapy and a means to prevent relapse. However, the trial results have been quite mixed, with studies in the People's Republic of China suggesting efficacy in slowing kidney disease progression, yet studies done in Europe and North America were unable to show a similarly significant effect.[56-58] The magnitude of benefit in the Chinese studies of mycophenolate seem impressive (kidney failure relative risk, 0.22 [95% CI, 0.05-0.9]), suggesting that race or geography may impact efficacy through genetic or environmental influences.

Other immunosuppressive agents have been tested in IgAN as well. This includes calcineurin inhibition, adrenocorticotropic hormone, hydroxychloroquine, mizoribine, and leflunomide. Each of these agents appeared promising in small studies. For calcineurin inhibition, there was proteinuria reduction but no favorable impact on kidney function.[59] For the others, studies are still limited in terms of number and general applicability, such that further investigation is warranted.[49,60]

A rather specific intervention for IgAN has been tonsillectomy. This has been studied over multiple decades. There have been suggestions of benefit in certain populations, especially in Japan (kidney failure relative risk, 0.25 [95% CI, 0.12-0.52]), but confirmatory studies have not replicated these results. Due to the invasiveness of adult tonsillectomy, it is difficult to recommend without adequate evidence.[20]

Novel Immunosuppression

It is essential to find well-tolerated, safe, and effective agents to inhibit the autoimmune activity of IgAN. Fortunately, there are many efforts underway to accomplish this goal.

A newly approved immunosuppressive agent (in the United States and Europe thus far) is targeted-release budesonide (Nefecon). The goal is to expose the intestinal mucosa (where GD-IgA production is plentiful) to significant concentrations of corticosteroid and then to limit systemic exposure as budesonide is extensively metabolized by the liver in first-pass removal. In this way, GD-IgA production and systemic delivery should be limited, and the disease quieted. In studies of IgAN patients receiving this agent for 9 months, significant reductions in proteinuria were seen in the first year.[61] Short-term observations on kidney function are promising, but longer term evaluation was still awaited at the time of this article.[61,62] The side effects were limited, although corticosteroid effects such as acne, sleep issues, and some hyperglycemia have been seen. More severe adverse events have not been detected thus far, making this agent an attractive alternate to systemic corticosteroids.

Another approach is B-cell inhibition. As B lymphocytes mature to become antibody-producing (including GD-IgA and anti-IgA antibodies) cells, there are multiple opportunities to block this process.[6,14] Efforts have been made with anti-CD19 antibodies. While small series of IgA vasculitis patients seemed to have a response, a small, randomized trial demonstrated no impact on proteinuria, let alone on reducing serum GD-IgA or autoantibodies.[63,64] The search for other inhibitors continues, with active programs underway with proteosome inhibition, efforts to block receptor ligands such as BLYS, APRIL, or plasma cell receptors.[65-69] Early reports suggested some efficacy in reducing GD-IgA and proteinuria, but larger scale studies are underway.[70]

There is an increasing body of evidence that complement plays an important role in the pathogenesis of IgAN.[71,72] Tissue markers of lectin pathway activation are associated with increased disease severity.[73] Multiple studies have identified alternative pathway proteins (properdin and factor H) and activation of the membrane attack complex (C5b-9) in IgAN glomeruli.[71,72] Promising results from the LNP023 phase 2 trial and OMS721 phase 2 trials have led to these agents being evaluated in phase 3 trials.[74,75] These phase 3 studies are expected to reach completion in the next 2 years.

Considerations and Challenges

As previously suggested, IgAN is a heterogeneous disease, and there are many unknowns. Rare patients spontaneously remit, but there are many others whose course changes from their initial risk assessment. The interplay between environmental exposures (diet, infection, other stresses) and genetic risk may be responsible for the diverse presentation of IgAN. Controversy continues regarding the optimal therapy for low-risk patients. Furthermore, IgAN is a chronic, lifelong disease. Thus, patients who respond well to short-term treatments, including steroids, often relapse after

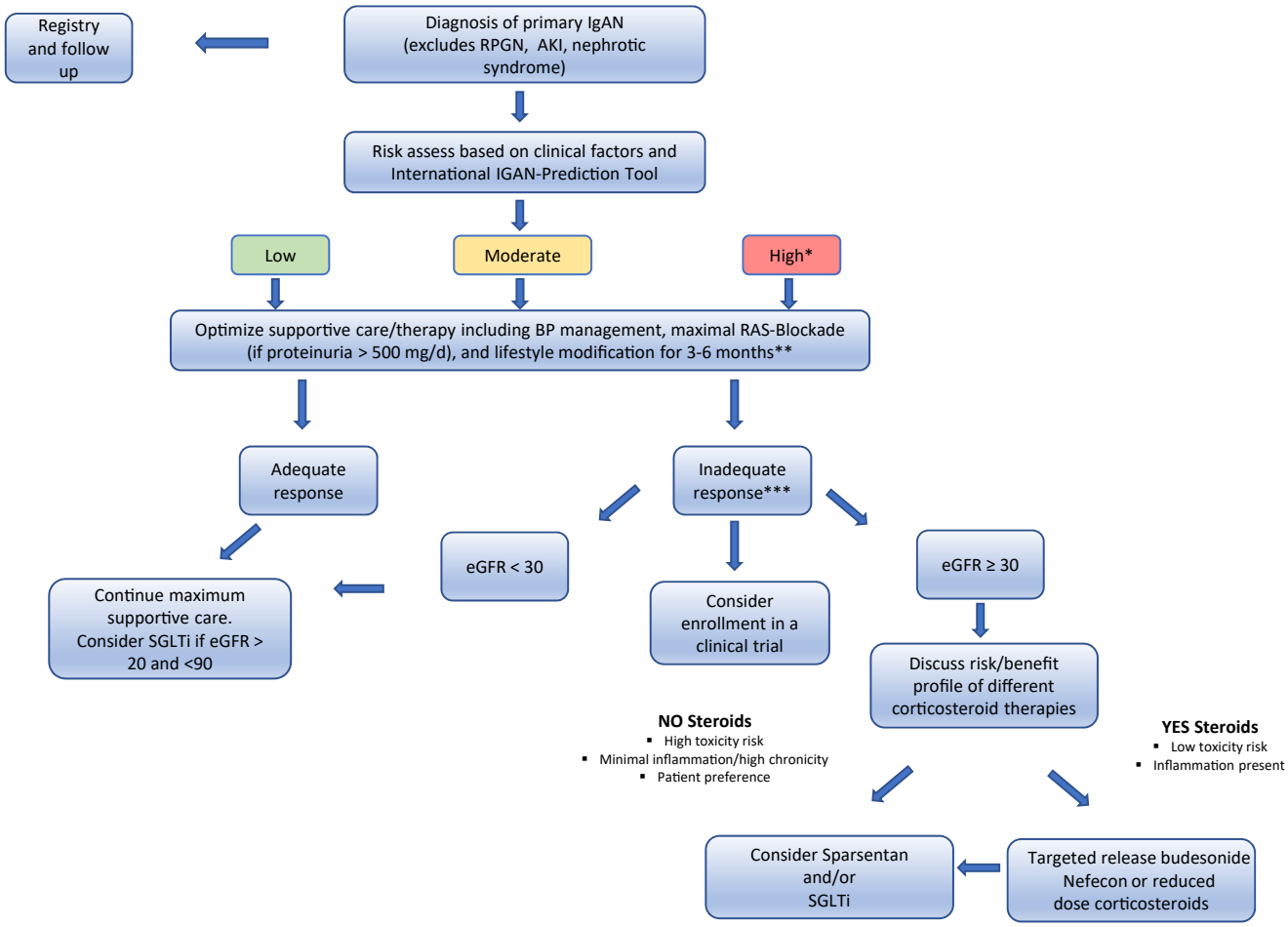

Figure 2. Treatment algorithm for IgA nephropathy. The International IgAN prediction tools are available on QxMD (https://qxmd.com).[17,18] Treatment is based on risk of progression, response to supportive therapy, and corticosteroid toxicity risk. The ideal timing of SGLT-2 inhibitor therapy is uncertain and may be given as part of supportive care or added on at a later time point. Corticosteroids (systemic or corticosteroid) may be considered early in high-risk patients with inflammatory lesions, but there remain insufficient data to base treatment decisions on biopsy alone. Based on information in KDIGO clinical practice guideline for the management of glomerular diseases.[20] *Consider shorter duration of supportive care prior to addition of corticosteroids in high-risk patients with significant inflammatory lesion. **SGLT-2 inhibitor may be considered as a component of maximal supportive care. ***Patients who remain at moderate or high risk of progression after trial of supportive care are considered to have inadequate response. Abbreviations: AKI, acute kidney injury; BP, blood pressure; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; RAS, renin angiotensin system; RPGN, rapidly progressive glomerulonephritis; SGLT2i: sodium-glucose cotransporter 2 inhibitor.

several months or a few years. We have limited data on second-line or repeat therapy for these individuals. Similarly, it is unclear whether post-kidney-transplant recurrences will behave like native kidney IgAN. Additionally, we need to know if proteinuria reduction is a reliable surrogate of disease response. For instance, if you achieve excellent proteinuria control with lifestyle modifications and blood pressure control, does it still matter that there is active inflammation and hematuria? The pediatric population with IgAN is more limited and more complex to study, and whether children should be treated the same as adults remains uncertain. Finally, there are many secondary forms of IgAN including IgA vasculitis, and evidence regarding an optimal therapy is limited.

Suggested Treatment Approaches

Ideally, the treatment for IgAN would be safe, curative, and cost-effective. Until now, our interventions appear only to be disease-modifying agents, which were often ineffective, of limited value, and side-effect laden. Of course, early diagnosis will give the best chance for effective disease control and prevention from irreversible kidney injury. Once diagnosed, accurate assessment of risk should allow a decision on which patients to observe, who to treat conservatively, and who to treat more aggressively.

Presently, the KDIGO approach to treatment is a reasonable start.[20] For patients at risk of progression, aggressive lifestyle changes are joined by ensuring

excellent blood-pressure control and maximally tolerated agents to control angiotensin II activity. However, for patients whose disease profile does not convert to low risk after this approach or for those with more aggressive disease presentation (very heavy proteinuria, increasing serum creatinine values, and high degree of acuity and/or injury on biopsy), it quickly becomes unclear how to proceed. We agree that offering patients clinical trials to learn more about the disease and obtain access to promising therapies is essential and ethical. However, thorough discussions about the appropriateness of a course of corticosteroids, including the individualized risk versus benefit ratio, consideration of SGLT-2 inhibitor therapy, and reviewing the options of targeted budesonide or sparsentan, all seem to be necessary. One can also discuss intervention with off-label medications, such as hydroxychloroquine, mycophenolate, and other interventions such as tonsillectomy in appropriate populations. Once therapy is started, monitoring of proteinuria, eGFR, and for side effects is necessary to determine whether the chosen path is working or another tack is needed (Fig 2). Unfortunately, there are no disease-specific biomarkers that can further guide therapy, and the utility of repeat kidney biopsy has not been studied.[76]

However, the research advances in IgAN increase the likelihood of new treatments emerging. Endothelin antagonists appear highly effective in reducing proteinuria, and complement inhibition has shown early evidence of disease protection as well. Some pathways of B-cell inhibition appear to effectively reduce GD-IgA and reduce proteinuria. Other anti-inflammatory therapies specifically addressing the pathophysiology of IgAN continue to be explored. There is great hope these treatments will prove themselves able to slow or even halt disease progression and, in some cases, lead to disease remission with improved safety, excellent tolerance, and reasonable costs.

As we have more interventions, we will need further evidence as well. What will be an adequate response—proteinuria reduction to what level, hematuria control or biopsy regression?[77,78] Presently, much of the focus is on proteinuria control. The work for better biomarkers of disease activity and risk must continue.[76]

Conclusions

Today, patients with IgAN and poor risk markers have a difficult road ahead. Basic science has led to an improved understanding of the underlying processes of disease. We can already intervene with conservative and supportive pharmacologic therapy, which has recently expanded to include SGLT-2 inhibitors and ERAs, an option for targeted rather than systemic steroids, and several approved, repurposed therapies that may be of value. In no small part thanks to changes in how we test novel therapies in IgAN utilizing validated surrogates, we have an increasing armamentarium to safely and effectively combat IgAN. Potentially, these advances can serve as a model of bench-to-bedside research fueled by industry, government, physician, and patient interactions and innovations.

Article Information

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References

1. Berger J, Hinglais N. Intercapillary deposits of IgA-IgG [in French]. *J Urol Nephrol (Paris)*. 1968;74(9):694-695.
2. Zaza G, Bernich P, Lupo A, Triveneto' Register of Renal B. Incidence of primary glomerulonephritis in a large North-Eastern Italian area: a 13-year renal biopsy study. *Nephrol Dial Transplant*. 2013;28(2):367-372. doi:10.1093/ndt/gfs437
3. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. *Kidney Int*. 2004;66(3):920-923. doi:10.1111/j.1523-1755.2004.00837.x
4. Barratt J, Feehally J. IgA nephropathy. *J Am Soc Nephrol*. 2005;16(7):2088-2097. doi:10.1681/ASN.2005020134
5. Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368(25):2402-2414. doi:10.1056/NEJMra1206793
6. Knoppova B, Reily C, King RG, Julian BA, Novak J, Green TJ. Pathogenesis of IgA nephropathy: current understanding and implications for development of disease-specific treatment. *J Clin Med*. 2021;10(19):4501. doi:10.3390/jcm10194501
7. Selvaskandan H, Shi S, Twaij S, Cheung CK, Barratt J. Monitoring immune responses in IgA nephropathy: biomarkers to guide management. *Front Immunol*. 2020;11:572754. doi:10.3389/fimmu.2020.572754
8. Yeo SC, Cheung CK, Barratt J. New insights into the pathogenesis of IgA nephropathy. *Pediatr Nephrol*. 2018;33(5):763-777. doi:10.1007/s00467-017-3699-z
9. Cameron JS. Immunosuppressant agents in the treatment of glomerulonephritis. 1. Corticosteroid drugs. *J R Coll Physicians Lond*. 1971;5(3):282-296.

10. Pozzi C, Andrulli S, Del Vecchio L, et al. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. *J Am Soc Nephrol*. 2004;15(1):157-163. doi:10.1097/01.asn.0000103869.08096.4f
11. Oh GJ, Waldo A, Paez-Cruz F, et al. Steroid-associated side effects in patients with primary proteinuric kidney disease. *Kidney Int Rep*. 2019;4(11):1608-1616. doi:10.1016/j.ekir.2019.08.019
12. Inker LA, Mondal H, Greene T, et al. Early Change in urine protein as a surrogate end point in studies of IgA nephropathy: an individual-patient meta-analysis. *Am J Kidney Dis*. 2016;68(3):392-401. doi:10.1053/j.ajkd.2016.02.042
13. Thompson A, Carroll K, Al L, et al. Proteinuria reduction as a surrogate end point in trials of IgA nephropathy. *Clin J Am Soc Nephrol*. 2019;14(3):469-481. doi:10.2215/CJN.08600718
14. Gutierrez E, Carvaca-Fontan F, Luzardo L, Morales E, Alonso M, Praga M. A personalized update on IgA nephropathy: a new vision and new future challenges. *Nephron*. 2020;144(11):555-571. doi:10.1159/000509997
15. Lemley KV, Lafayette RA, Derby G, et al. Prediction of early progression in recently diagnosed IgA nephropathy. *Nephrol Dial Transplant*. 2008;23(1):213-222. doi:10.1093/ndt/gfm560
16. Coppo R. Clinical and histological risk factors for progression of IgA nephropathy: an update in children, young and adult patients. *J Nephrol*. 2017;30(3):339-346. doi:10.1007/s40620-016-0360-z
17. Barbour SJ, Coppo R, Zhang H, et al. Evaluating a new international risk-prediction tool in IgA nephropathy. *JAMA Intern Med*. 2019;179(7):942-952. doi:10.1001/jamainternmed.2019.0600
18. Barbour SJ, Coppo R, Zhang H, et al. Application of the international IgA nephropathy prediction tool one or two years post-biopsy. *Kidney Int*. 2022;102(1):160-172. doi:10.1016/j.kint.2022.02.042
19. Lee H, Hwang JH, Paik JH, et al. Long-term prognosis of clinically early IgA nephropathy is not always favorable. *BMC Nephrol*. 2014;15:94. doi:10.1186/1471-2369-15-94
20. KDIGO 2021 Clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4s):S1-s276. doi:10.1016/j.kint.2021.05.021
21. Tumlin JA, Lohavichan V, Hennigar R. Crescentic, proliferative IgA nephropathy: clinical and histological response to methylprednisolone and intravenous cyclophosphamide. *Nephrol Dial Transplant*. 2003;18(7):1321-1329. doi:10.1093/ndt/gfg081
22. Joshi S, Kalantar-Zadeh K, Chauveau P, Carrero JJ. Risks and benefits of different dietary patterns in CKD. *Am J Kidney Dis*. 2023;81(3):352-360. doi:10.1053/j.ajkd.2022.08.013
23. Coppo R, Amore A, Peruzzi L, Mancuso D, Camilla R. Angiotensin antagonists and fish oil for treating IgA nephropathy. *Contrib Nephrol*. 2007;157:27-36. doi:10.1159/000102285
24. Reid S, Cawthon PM, Craig JC, Samuels JA, Molony DA, Strippoli GF. Non-immunosuppressive treatment for IgA nephropathy. *Cochrane Database Syst Rev*. 2011;3:CD003962. doi:10.1002/14651858.CD003962.pub2
25. Coppo R, Roccatello D, Amore A, et al. Effects of a gluten-free diet in primary IgA nephropathy. *Clin Nephrol*. 1990;33(2):72-86.
26. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet*. 1997;349(9069):1857-1863.
27. Coppo R, Peruzzi L, Amore A, et al. IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. *J Am Soc Nephrol*. 2007;18(6):1880-1888. doi:10.1681/asn.2006040347
28. Praga M, Gutiérrez E, González E, Morales E, Hernández E. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. *J Am Soc Nephrol*. 2003;14(6):1578-1583. doi:10.1097/01.asn.0000068460.37369.dc
29. Li PK, Leung CB, Chow KM, et al. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis*. 2006;47(5):751-760. doi:10.1053/j.ajkd.2006.01.017
30. Horita Y, Tadokoro M, Taura K, et al. Low-dose combination therapy with temocapril and losartan reduces proteinuria in normotensive patients with immunoglobulin a nephropathy. *Hypertens Res*. 2004;27(12):963-970. doi:10.1291/hypres.27.963
31. Nakamura T, Inoue T, Sugaya T, et al. Beneficial effects of olmesartan and temocapril on urinary liver-type fatty acid-binding protein levels in normotensive patients with immunoglobin A nephropathy. *Am J Hypertens*. 2007;20(11):1195-1201. doi:10.1016/j.amjhyper.2007.06.003
32. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372(9638):547-553. doi:10.1016/s0140-6736(08)61236-2
33. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744
34. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. doi:10.1056/NEJMoa2024816
35. Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388(2):117-127. doi:10.1056/NEJMoa2204233
36. Wheeler DC, Toto RD, Stefánsson BV, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int*. 2021;100(1):215-224. doi:10.1016/j.kint.2021.03.033
37. Zheng Z, He D, Chen J, et al. Risk of urinary tract infection in patients with type 2 diabetes mellitus treated with dapagliflozin: a systematic review and meta-analysis of randomized controlled trials. *Clin Drug Investig*. 2023;43(4):209-225. doi:10.1007/s40261-023-01256-9
38. Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and safety of canagliflozin used in conjunction with sulfonylurea in patients with type 2 diabetes mellitus: a randomized, controlled trial. *Diabetes Ther*. 2015;6(3):289-302. doi:10.1007/s13300-015-0117-z
39. Kohan DE, Barton M. Endothelin and endothelin antagonists in chronic kidney disease. *Kidney Int*. 2014;86(5):896-904. doi:10.1038/ki.2014.143
40. Heerspink HJL, Parving HH, Andress DL, et al. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. *Lancet*. 2019;393(10184):1937-1947. doi:10.1016/s0140-6736(19)30772-x
41. Trachtman H, Nelson P, Adler S, et al. DUET: a phase 2 study evaluating the efficacy and safety of sparsentan in patients with FSGS. *J Am Soc Nephrol*. 2018;29(11):2745-2754. doi:10.1681/asn.2018010091
42. Smeijer JD, Kohan DE, Webb DJ, Dhaun N, Heerspink HJL. Endothelin receptor antagonists for the treatment of diabetic

and nondiabetic chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2021;30(4):456-465. doi:10.1097/mnh.0000000000000716
43. Heerspink HJL, Kohan DE, de Zeeuw D. New insights from SONAR indicate adding sodium glucose co-transporter 2 inhibitors to an endothelin receptor antagonist mitigates fluid retention and enhances albuminuria reduction. *Kidney Int*. 2021;99(2):346-349. doi:10.1016/j.kint.2020.09.026
44. Chinook Therapeutics US, Inc. Atrasentan in Patients With IgA Nephropathy (ALIGN). Identifier NCT04573478. ClinicalTrials.gov. updated May 30, 2023. Accessed October 9, 2023. https://clinicaltrials.gov/study/NCT04573478
45. Travere Therapeutics, Inc. A study of the effect and safety of sparsentan in the treatment of patients with IgA nephropathy (PROTECT). Identifier NCT03762850. ClinicalTrials.gov. updated September 6, 2023. Accessed October 9, 2023. https://clinicaltrials.gov/study/NCT03762850
46. Heerspink HJL, Radhakrishnan J, Alpers CE, et al. Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. *Lancet*. 2023;401(10388):1584-1594. doi:10.1016/s0140-6736(23)00569-x
47. US Food and Drug Administration. Novel Drug Approvals for 2023. Updated October 2, 2023. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023
48. Lv J, Zhang H, Chen Y, et al. Combination therapy of prednisone and ACE inhibitor versus ACE-inhibitor therapy alone in patients with IgA nephropathy: a randomized controlled trial. *Am J Kidney Dis*. 2009;53(1):26-32. doi:10.1053/j.ajkd.2008.07.029
49. Natale P, Palmer SC, Ruospo M, et al. Immunosuppressive agents for treating IgA nephropathy. *Cochrane Database Syst Rev*. 2020;3(3):CD003965. doi:10.1002/14651858.CD003965.pub3
50. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric IgA nephropathy. *Nephrol Dial Transplant*. 2009;24(12):3694-3701. doi:10.1093/ndt/gfp356
51. Tesar V, Troyanov S, Bellur S, et al. Corticosteroids in IgA nephropathy: a retrospective analysis from the VALIGA Study. *J Am Soc Nephrol*. 2015;26(9):2248-2258. doi:10.1681/ASN.2014070697
52. Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med*. 2015;373(23):2225-2236. doi:10.1056/NEJMoa1415463
53. Lv J, Zhang H, Wong MG, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. *JAMA*. 2017;318(5):432-442. doi:10.1001/jama.2017.9362
54. Lv J, Wong MG, Hladunewich MA, et al. Effect of oral methylprednisolone on decline in kidney function or kidney failure in patients with IgA nephropathy: the TESTING randomized clinical trial. *JAMA*. 2022;327(19):1888-1898. doi:10.1001/jama.2022.5368
55. Ballardie FW, Roberts ISD. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. *J Am Soc Nephrol*. 2002;13(1):142-148. doi:10.1681/asn.V131142
56. Tang SC, Tang AW, Wong SS, Leung JC, Ho YW, Lai KN. Long-term study of mycophenolate mofetil treatment in IgA nephropathy. *Kidney Int*. 2010;77(6):543-549. doi:10.1038/ki.2009.499
57. Maes BD, Oyen R, Claes K, et al. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. *Kidney Int*. 2004;65(5):1842-1849. doi:10.1111/j.1523-1755.2004.00588.x
58. Hogg RJ, Bay RC, Jennette JC, et al. Randomized controlled trial of mycophenolate mofetil in children, adolescents, and adults with IgA nephropathy. *Am J Kidney Dis*. 2015;66(5):783-791. doi:10.1053/j.ajkd.2015.06.013
59. Song YH, Cai GY, Xiao YF, et al. Efficacy and safety of calcineurin inhibitor treatment for IgA nephropathy: a meta-analysis. *BMC Nephrol*. 2017;18(1):61. doi:10.1186/s12882-017-0467-z
60. Zand L, Canetta P, Lafayette R, et al. An open-label pilot study of adrenocorticotrophic hormone in the treatment of IgA nephropathy at high risk of progression. *Kidney Int Rep*. 2020;5(1):58-65. doi:10.1016/j.ekir.2019.10.007
61. Barratt J, Lafayette R, Kristensen J, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney Int*. 2023;103(2):391-402. doi:10.1016/j.kint.2022.09.017
62. Fellstrom B, Barratt J, Floge J, Jardine A. Targeted-release budesonide therapy for IgA nephropathy—authors' reply. *Lancet*. 2017;390(10113):2625-2626. doi:10.1016/S0140-6736(17)32138-4
63. Donnithorne KJ, Atkinson TP, Hinze CH, et al. Rituximab therapy for severe refractory chronic Henoch-Schonlein purpura. *J Pediatr*. 2009;155(1):136-139. doi:10.1016/j.jpeds.2008.12.049
64. Lafayette RA, Canetta PA, Rovin BH, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. *J Am Soc Nephrol*. 2017;28(4):1306-1313. doi:10.1681/ASN.2016060640
65. RemeGen Co., Ltd. A study of telitacicept for injection (RC18) in subjects with IgA nephropathy. Identifier NCT04905212. ClinicalTrials.gov. updated August 30, 2023. Accessed October 9, 2023. https://clinicaltrials.gov/study/NCT04905212
66. HI-Bio. Clinical trial to assess efficacy and safety of the human anti-CD38 antibody felzartamab (MOR202) in IgA nephropathy (IGNAZ). Identifier NCT05065970. ClinicalTrials.gov. updated September 28, 2023. Accessed October 9, 2023. https://clinicaltrials.gov/study/NCT05065970
67. Vera Therapeutics, Inc. Atacicept in subjects with IgA nephropathy (ORIGIN 3). Identifier NCT04716231. ClinicalTrials.gov. updated July 19, 2023. Accessed October 9, 2023. https://clinicaltrials.gov/study/NCT04716231
68. Chinook Therapeutics, Inc. Safety and tolerability of BION-1301 in healthy volunteers and adults with IgA nephropathy (IgAN). Identifier NCT03945318. ClinicalTrials.gov. updated May 24, 2023. Accessed October 9, 2023. https://clinicaltrials.gov/study/NCT03945318
69. Ruijin Hospital. Bortezomib for treating glomerular diseases. Identifier NCT05383547. ClinicalTrials.gov. updated October 31, 2022. Accessed October 9, 2023. https://clinicaltrials.gov/study/NCT05383547
70. Barratt J, Tumlin J, Suzuki Y, et al. Randomized phase II JANUS study of atacicept in patients with IgA nephropathy and persistent proteinuria. *Kidney Int Rep*. 2022;7(8):1831-1841. doi:10.1016/j.ekir.2022.05.017
71. Rizk DV, Maillard N, Julian BA, et al. The emerging role of complement proteins as a target for therapy of IgA nephropathy. *Front Immunol*. 2019;10:504. doi:10.3389/fimmu.2019.00504

72. Medjeral-Thomas NR, Cook HT, Pickering MC. Complement activation in IgA nephropathy. *Semin Immunopathol*. 2021;43(5):679-690. doi:10.1007/s00281-021-00882-9
73. Roos A, Rastaldi MP, Calvaresi N, et al. Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. *J Am Soc Nephrol*. 2006;17(6):1724-1734. doi:10.1681/asn.2005090923
74. Lafayette RA, Rovin BH, Reich HN, Tumlin JA, Floege J, Barratt J. Safety, tolerability and efficacy of narsoplimab, a novel MASP-2 inhibitor for the treatment of IgA nephropathy. *Kidney Int Rep*. 2020;5(11):2032-2041. doi:10.1016/j.ekir.2020.08.003
75. Webb N, Haraldsson B, Schubart A, et al. LNP023: a novel oral complement alternative pathway factor b inhibitor for the treatment of glomerular disease [abstract MO042]. *Nephrol Dial Transplant*. 2020;35(suppl 3):gfaa140.MO042. doi:10.1093/ndt/gfaa140.MO042
76. Suzuki H. Biomarkers for IgA nephropathy on the basis of multi-hit pathogenesis. *Clin Exp Nephrol*. 2019;23(1):26-31. doi:10.1007/s10157-018-1582-2
77. Reich HN, Troyanov S, Scholey JW, Cattran DC; Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol*. 2007;18(12):3177-3183. doi:10.1681/ASN.2007050526
78. Lafayette RA, Reich HN, Stone AM, Barratt J. One-year estimated GFR slope independently predicts clinical benefit in immunoglobulin A nephropathy. *Kidney Int Rep*. 2022;7(12):2730-2733. doi:10.1016/j.ekir.2022.09.017