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REVIEW

Novel Treatment Paradigms: Primary IgA Nephropathy

Haresh Selvaskandan[1,2], Jonathan Barratt[1,2] and Chee Kay Cheung[1,2]

[1]Mayer IgA Nephropathy Laboratories, Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; and [2]John Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, UK

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Approximately 30% to 45% of patients progress to kidney failure (KF) within 20 to 25 years of diagnosis, and there has long been a lack of effective treatments. The therapeutic landscape in IgAN is rapidly evolving, driven in large part by the acceptance of the surrogate clinical trial end point of proteinuria reduction by regulatory authorities for the accelerated approval of new therapies. Two drugs, targeted release formulation (TRF)-budesonide (nefecon) and sparsentan, have recently been approved under this scheme. Advancing insights into the pathophysiology of IgAN, including the roles of the mucosal immune system, B-cells, the complement system, and the endothelin system have driven development of therapies that target these factors. This review outlines current, recently approved, and emerging therapies for IgAN.

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First described in 1968, IgAN represents the most common primary glomerulonephritis worldwide.[1] Patients present with a wide spectrum of clinical manifestations, including isolated nonvisible hematuria, progressive chronic kidney disease (CKD), nephrotic syndrome, or rapidly progressive glomerulonephritis.[2] An estimated 30% to 45% progress to KF within 20 to 25 years of diagnosis.[3–6] However, in a UK registry study of 2299 adults with IgAN, higher rates were reported: over 80% developed KF within 30 years, and a high rate of disease progression was observed even in those with proteinuria <1 g/day.[7] Life expectancy with IgAN is reduced by 6 to 10 years, mainly due to complications of KF.[5,8,9] IgAN often recurs following kidney transplantation and is a common cause of graft loss.[10]

In the 2021 Kidney Disease Improving Global Outcomes guidelines for glomerular diseases, it was acknowledged that no specific therapies for IgAN were available.[11] The historical lack of drug development in IgAN was largely attributable to the requirement by regulatory authorities for "hard" kidney outcomes (e.g., doubling of serum creatinine or KF) when assessing drug efficacy, and the typical slow progression of IgAN made clinical trials unattractive. In 2019, the Kidney Health Initiative performed an analysis of 13 controlled trials that demonstrated a clear association between an early treatment effect on proteinuria and a composite of time to doubling of serum creatinine, KF, and death.[12] Regulatory authorities now accept proteinuria reduction as a reasonably likely surrogate end point for progression to KF and as a basis for the accelerated approval of new treatments in IgAN. This has transformed the IgAN clinical trial landscape, leading to an explosion in clinical trial activity (179 trials registered on clinicaltrials.gov as of August 2023) and the approval of the first 2 drugs specifically for treating IgAN.

Current Guidelines

Diagnosis, Risk Stratification, and Treatment Selection

IgAN can only be diagnosed with a kidney biopsy, which will demonstrate dominant or codominant mesangial IgA deposition.[11] Risk stratification should be undertaken using the international IgAN prediction tool, which integrates validated prognostic factors (Table 1) to produce a personalized risk of progression (50% reduction in estimated glomerular filtration rate [eGFR] or development of KF) for up to 7 years from the date of kidney biopsy.[13] Despite its value in risk stratification and patient counselling, it is yet to be validated as at tool for guiding treatment. Risk stratification after this period is generally based on

Correspondence: Chee Kay Cheung, John Walls Renal Unit, Leicester General Hospital, Gwendolen Road, Leicester, LE4 5PW, UK. E-mail: ckc15@le.ac.uk

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Table 1. Parameters required by the international IgA nephropathy prediction tool to predict 50% decline in eGFR or kidney failure up to 80 months from biopsy

Parameters required by the IIgANPT
eGFR at biopsy
Systolic blood pressure at biopsy
Diastolic blood pressure at biopsy
Proteinuria at biopsy
Age at biopsy
Race
ACE inhibitor or ARB at biopsy
MEST score[a]
Immunosuppression at or prior to biopsy

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IIgANPT, international IgA nephropathy prediction tool.
[a]MEST score refers to the Oxford Classification scoring for IgA nephropathy, excluding crescents: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T).

proteinuria, blood pressure (BP), and eGFR, each of which are independent prognostic factors.[14] Treatment decisions are currently dictated by the extent of proteinuria (after optimization of supportive care) and eGFR (<30 ml/min per 1.73 m^2 usually being regarded as the limit below which immunomodulatory treatment would not be used outside a rapidly progressive glomerulonephritis). Traditionally, proteinuria >1 g/day has been used to identify patients at higher risk of KF and suitable for either a clinical trial or immunomodulator. Currently, there are no biomarkers to inform the choice of immunomodulator and the Oxford Classification has not been validated as a tool for treatment selection.

First Line Management

The 2021 Kidney Disease Improving Global Outcomes guidelines recommend optimized supportive care as initial management, aiming to reduce proteinuria by optimizing BP and maximizing single agent renin-angiotensin system inhibition (RASi), and to address lifestyle and cardiovascular risk factors (e.g., body weight, dietary salt restriction to <2 g/day, smoking cessation, lipid management).[11] RASi is recommended when proteinuria is >0.5 g/day, regardless of BP.

The STOP-IgAN trial included a run-in period when comprehensive supportive care was optimized; about one-third of participants responded with a reduction of proteinuria large enough to make them ineligible for the next phase of the trial, highlighting the value of this approach.[15]

Beyond Supportive Care

Options for those at high risk of progression (defined by Kidney Disease Improving Global Outcomes as having persistent proteinuria >1 g/day despite optimized supportive care) were limited in 2021 and enrolment into clinical trials was encouraged.[11] For those with preserved kidney function (i.e., an eGFR ≥30 ml/min per 1.73 m^2) and unable to participate in a trial, a course of glucocorticoids was suggested, but only after careful consideration of potential risks and benefits. Previous trials of glucocorticoids in IgAN reported benefit, but their interpretation was often limited by small sample sizes, BP, and RASi not being optimized according to current standards of care, and adverse events not being systematically captured. Two randomized controlled trials (RCTs), STOP-IgAN and TESTING, were designed to address these concerns.

STOP-IgAN (N = 337, from Germany) reported no benefit in terms of full clinical remission with glucocorticoids with or without other immunosuppression compared to supportive care, both within the 3-year study and after approximately 10 years of follow-up. Adverse events were more frequent in the immunosuppression group (Table 2).[15]

The TESTING study was halted early (total N = 504, predominantly from Asia) due to excess serious adverse events among those receiving methylprednisolone (0.6–0.8 mg/kg/day), mainly due to infection including 2 deaths.[16] TESTING was recommenced with a reduced methylprednisolone dose (0.4 mg/kg/day) given for 6 to 8 months with co-trimoxazole prophylaxis. Those treated with either dose of methylprednisolone had a lower rate of meeting the composite primary endpoint (40% reduction in eGFR, KF, or death due to kidney disease) compared to those receiving placebo (28% vs. 41.3%). Although adverse events were not systematically collected (e.g., through validated questionnaires), fewer events were reported with the lower methylprednisolone dose, although 1 death still occurred. Effects on proteinuria reduction were lost by 36 months, implying that potential benefits of systemic glucocorticoids are not sustained.[17]

Mycophenolate mofetil (MMF) was found to have no benefit beyond RASi in a collection of small RCTs (N = 32–52) performed in Belgium, Canada, and the USA.[18-20] Trials from Asia, however, have reported that MMF treatment is associated with a reduction in proteinuria and preservation of kidney function. An RCT from Hong Kong (N = 40) found that MMF produced a greater reduction in proteinuria compared to placebo, when used at 1.5–2 g/day.[21] These benefits were replicated in a recent, larger, open label RCT from China (N = 170); the MAIN trial incorporated a run-in period in which supportive care (RASi, BP control, salt restriction, and smoking cessation) was optimized, after which participants were randomized to receive MMF (1.5 g/day for 12 months, followed by 0.75–1 g/day for at least 6 months) or standard of care therapy only.[22] The MAIN trial reported that 7.1% of those receiving MMF met the primary composite outcome of doubling

Table 2. IgAN RCTs evaluating corticosteroids following a run-in period, during which supportive care was optimized

Trial	Majority ethnicity	Primary outcomes	Key exclusion criteria	Regimen	Outcome
STOP-IgAN	European	Complete remission: PCR <0.2 g/g and eGFR decrease <5 ml/min per 1.73 m^2 from baseline after 3 years	Creatinine clearance <30ml/min, rapidly progressive disease, IgAN variants (e.g., minimal change), secondary IgAN	eGFR ≥60 ml/min per 1.73 m^2: 1 g methylprednisolone i.v. for 3 days at month 1, 3, and 5. 0.5mg/kg per 48 h oral prednisolone for 6 months.	17% experienced remission with treatment vs. 5% with placebo. No difference in rate of eGFR decline. Steroid-related adverse events in treatment group.
		Progression: eGFR reduction ≥15 ml/min per 1.73 m^2 from baseline		eGFR <60 ml/min per 1.73 m^2: oral cyclophosphamide 1.5 mg/kg/day for 3 months, then azathioprine 1.5 mg/kg/day + oral prednisolone for 3 years (10 mg/day for 3 months, then 7.6 mg/day)	
TESTING	Asian	40% decline in eGFR, ESKD, or death due to kidney disease	IgAN variants (e.g., minimal change), secondary IgAN, >50% crescents on biopsy within 12 months	Original dosing: 0.8 mg/kg/day methylprednisolone	28% reached end point with treatment vs. 41.3% with placebo (pooled analysis of both doses). More steroid-related adverse events with treatment, including deaths. Benefits lost at 36 months of follow-up.
				Reduced dosing: 0.4 mg/kg/day methylprednisolone	

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; IgAN, IgA nephropathy; IIgANPT, international IgAN prediction tool; PCR, protein:creatinine ratio; RCT, randomized controlled trial.

of serum creatinine or KF, versus 21.2% receiving standard-of-care therapy only.[22] These results are consistent with a potential benefit of MMF in patients of Chinese origin.

Outside of specific situations (nephrotic syndrome, rapidly progressive glomerulonephritis), evidence to support global use of other immunosuppressive agents is lacking. As with MMF, studies from China reported benefit with hydroxychloroquine; however, these data are yet to be replicated elsewhere.[23] Similarly, tonsillectomy is often performed in Japan based on favorable observational studies; however, there are no data outside of Japan supporting benefit.[11,24] These differences in treatment response could reflect a heterogeneity in the fundamental pathogenic pathways between races.

Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2is)

The DAPA-CKD and EMPA-KIDNEY studies of SGLT2is in CKD enrolled large numbers of patients with IgAN (Table 3).[25,26] Both were terminated early because of their clear efficacy in preventing kidney function decline, KF, or death. Prespecified analyses confirmed that these effects were equally seen in IgAN participants.[27] It should however be noted that DAPA-CKD and EMPA-KIDNEY were CKD-focused trials; baseline eGFR and proteinuria of patients included with IgAN were very different to those enrolled in ongoing or recently reported IgAN-specific trials. Supportive care, including RASi was not optimized during run-in, and the event rate in the placebo arm of the DAPA-CKD IgAN cohort was notably high.[28] Whether SGLT2is are as effective in those with preserved kidney function (compared to those with established chronic damage) is not yet clear. Nevertheless, SGLT2is have been shown to be safe and effective treatments for CKD and have emerged as an important addition to supportive care in IgAN.

Leveraging Novel Insights Into IgAN Pathophysiology

Central to the pathogenesis of IgAN is an increase in circulating IgA1 that lacks galactose at its hinge region (galactose deficient-IgA1 [Gd-IgA1], Hit 1). IgG and IgA autoantibody production occurs in susceptible individuals (Hit 2), with subsequent immune complex formation (Hit 3).[29–33] Deposition of Gd-IgA1-containing

Table 3. Summary of SGLT2i RCTs including IgAN participants. eGFR as CKD-EPI

Trial	Key Inclusion criteria	Primary outcomes	Key exclusion criteria	Regimen	Outcome
DAPA-CKD	eGFR ≥25 and ≤75 ml/min per 1.73 m^2, uPCR ≥200 and ≤5000 mg/g, stable + maximum tolerated single agent RAS blockade for 4 weeks	Sustained decline of eGFR by 50%, ESKD or death from cardio-renal causes	Immunosuppressive therapy, organ transplantation.	dapagliflozin 10 mg/day	Outcome occurred in 9.2% of treatment group vs. 14.5% in placebo group.
EMPA-KIDNEY	eGFR ≥20 and ≤45 ml/min per 1.73 m^2 OR eGFR ≥45 and <90 ml/min per 1.73 m^2 with uPCR ≥300 mg/g	Sustained decline of eGFR by 40% or to 10, ESKD, or death from cardio-renal causes	Immunosuppressive therapy, kidney transplant, dual RAS blockade.	empagliflozin 10 mg/day	Outcome occurred in 13.1% of treatment group vs. 16.9% in placebo group.

CKD-EPI, chronic kidney disease: epidemiology collaboration; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; IgAN, IgA nephropathy; RAS, renin-angiotensin system; RCT, randomized controlled trial; SGLT2i, sodium-glucose co-transporter-2 inhibitor; uPCR, urine protein-to-creatinine ratio.

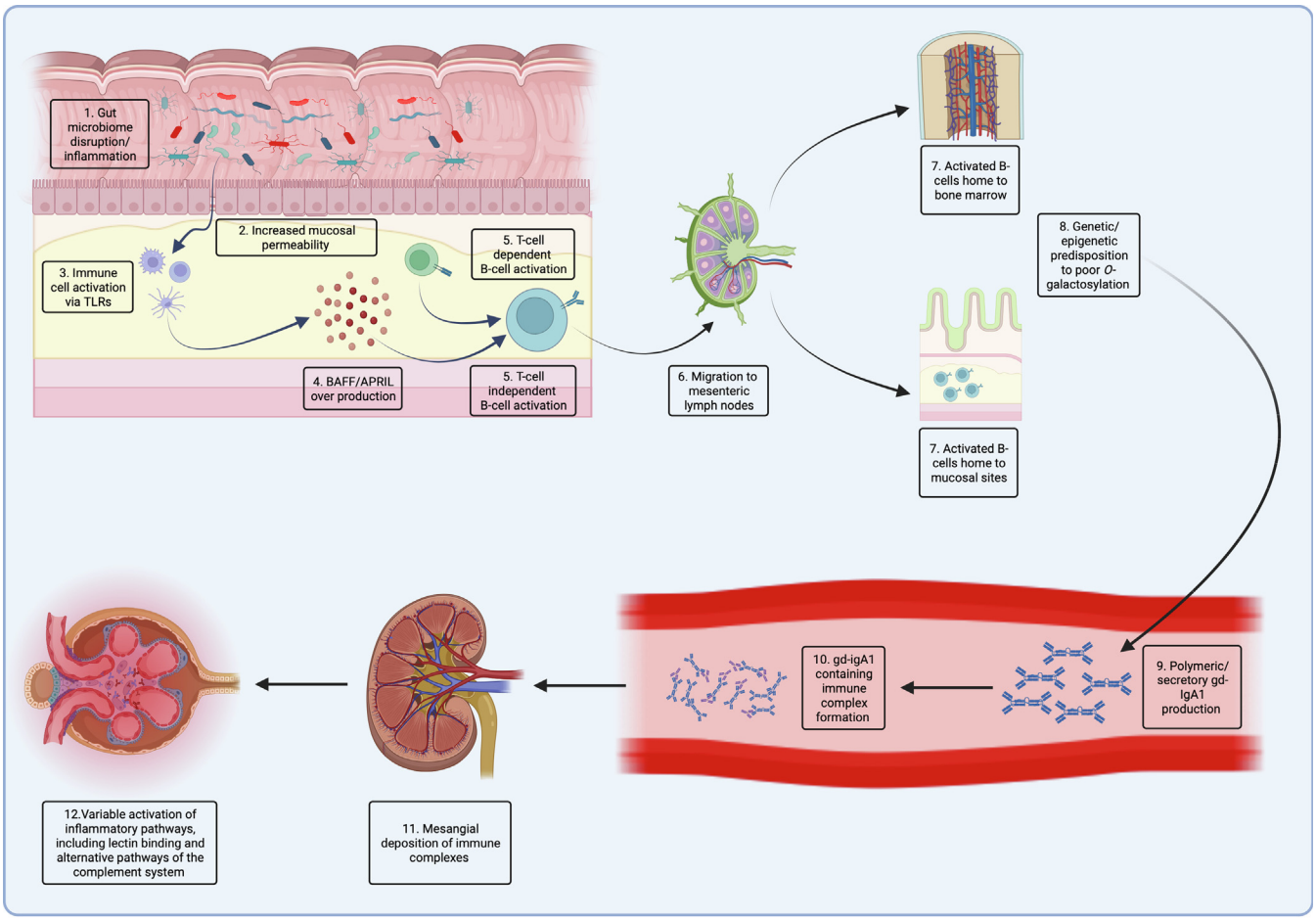

Figure 1. An overview of the pathophysiology of IgAN. (a) Infections, inflammation, or disruptions to host mucosal microbiota in conjunction with (b) increased mucosal permeability can lead to (c) mucosal immune cells being activated via toll like receptors. (d) This leads to an in increased production of BAFF and APRIL and (e) activation of mucosal B-cells via T-cell independent mechanisms, although these cells may also be activated by T-cells. (f) Activated B-cells traffic to central lymph nodes and (g) then traffic back to mucosal sites or mis-home to systemic sites such as bone marrow. (h) Mucosally-derived plasma cells produce Gd-IgA1 of which the magnitude is in part determined by genetic and epigenetic factors, which take up (i) polymeric and secretory forms. (j) Gd-IgA1 containing circulating immune complexes (k) deposit in the glomerular mesangium, (l) variably activating inflammatory pathways, including the lectin and alternative pathways of the complement system.
BAFF, B-cell activating factor; Gd-IgA1, galactose deficient-IgA1; IgAN, IgA nephropathy.

immune complexes induces mesangial cell activation and inflammation (Hit 4), driven by several mediators of inflammation, including cytokines, chemokines, and the complement system (Figures 1 and 2), leading to subsequent kidney damage.[34] Multiple lines of evidence indicate that circulating Gd-IgA1 originates from the mucosal immune system, particularly the gut-associated and nasal-associated lymphoid tissues.[35] Activation of the mucosal immune system can occur in response to environmental triggers such as infectious pathogens, autoinflammatory diseases, and interaction with the prevalent mucosal microbiota. Experimental evidence has shown that activation of mucosal immune cells via toll-like receptors, which may occur via extracellular vesicles produced by pathogens or resident microbiota, can upregulate expression of B-cell activating factor (BAFF) and A PRoliferation Inducing Ligand (APRIL), which are intimately involved in controlling IgA class switch recombination and IgA synthesis by mucosal B/plasma cells.[30,36–39] BAFF and APRIL activate mucosal B-cells via the BAFF receptor, B-cell maturation antigen, and T-cell activator and calcium-modulating ligand interactor.[40–42] Genetic and epigenetic alterations (including micro-RNA dysregulation) within B-cells have been shown to modulate synthesis of Gd-IgA1. Therapies targeting each of these pathways are now being tested in IgAN.

Recently Approved Therapies

Nefecon

Nefecon (Tarpeyo [US]/Kinpeygo [EU]) comprises budesonide packaged within a pH-sensitive capsule, engineered to release active drug at peak concentration within the terminal ileum to act on the immune cells

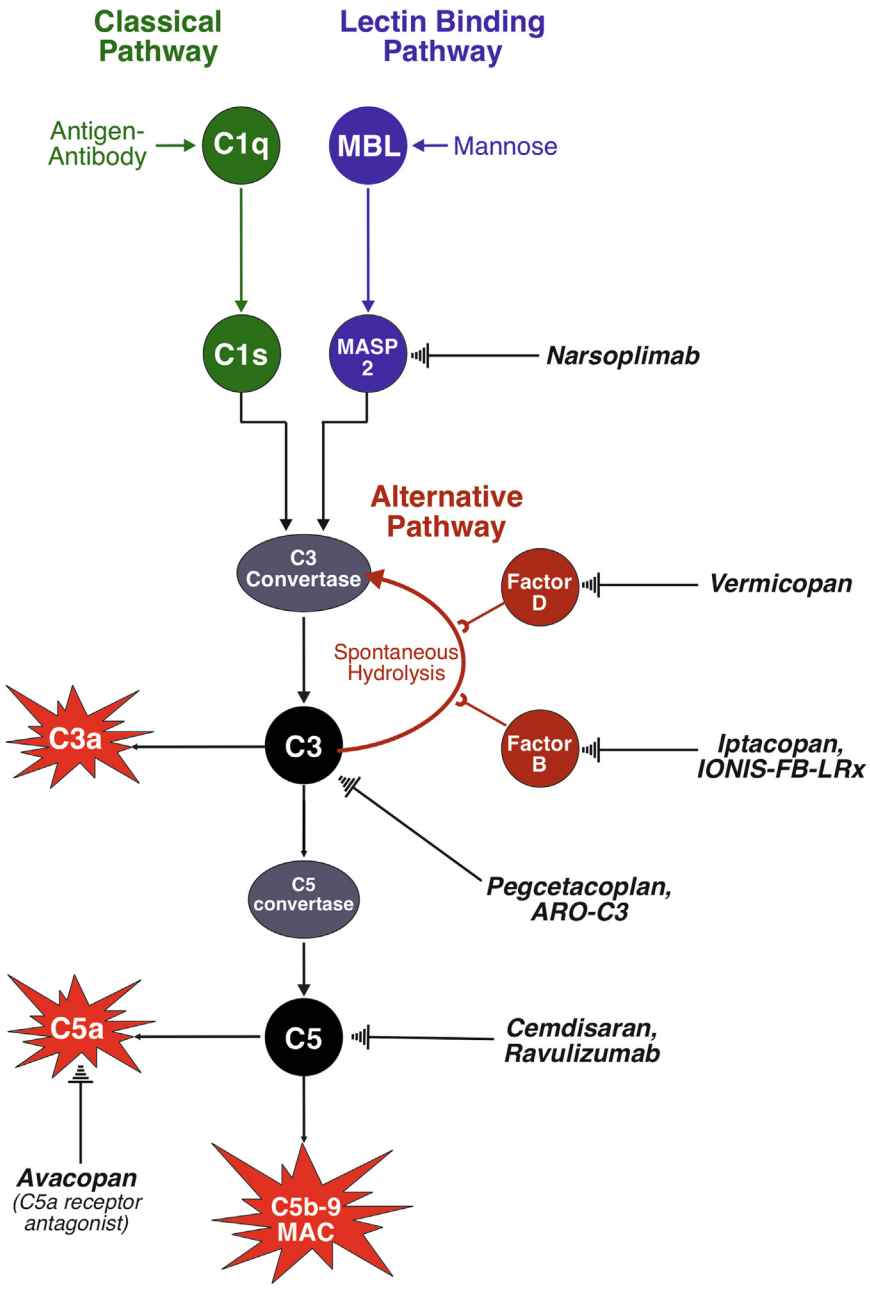

Figure 2. The complement system. The complement system can be activated by the classical, lectin, or alternative pathways. The classical pathway (green) is activated by antigen-antibody complexes, which bind C1q allowing C1r to cleave C1s which eventually leads to the formation of a C3 convertase downstream. There is little evidence of complement system activation via the classical pathway in IgAN. The lectin pathway (blue) is activated by mannose moieties commonly found on microbial surfaces, but also on Gd-IgA1, which bind mannose binding lectin to activate MASP1 and MASP2. MASP2 activation mirrors that of C1s, eventually leading to the formation of a C3 convertase. MASP2 is inhibited by narsoplimab. The alternative pathway (red) is constantly activated by the hydrolysis of C3; the pathway is promoted by factor B and factor D. Factor B is inhibited by iptacopan and IONIS-FB-LRx, whereas factor D is inhibited by vermicopan. The common pathway (black) is activated by any C3 convertase, cleaving C3 (inhibited by pegcetacoplan and ARO-C3) to C3a, an inflammatory mediator, and C3b. C3b is further acted upon by the C3 convertases to produce a C5 convertase, which cleaves C5 (can be inhibited by cemdisaran and ravuluzimab) to produce C5a, an inflammatory mediator (the C5a receptor can be blocked by avacopan), and C5b. This eventually leads to the formation of the membrane attack complex, which is capable of cell lysis. Gd-IgA1, galactose deficient-IgA1; IgAN, IgA nephropathy; MASP1, mannose-binding lectin serine protease 1; MASP2, mannose-binding lectin serine protease 2.

responsible for mucosal IgA production within Peyer's patches.[43] The drug undergoes extensive first pass metabolism, minimizing systemic absorption and side effects. In the phase 2 NEFIGAN trial, nefecon treatment resulted in a 27.3% reduction in proteinuria at 9 months, with preservation of kidney function up to 12 months.[44-46] In parallel, reductions in serum levels of BAFF, APRIL, Gd-IgA1, secretory IgA, and IgA-IgG-immune complexes occurred.[45] The phase 3 NefIgArd trial evaluated TRF-budesonide 16 mg/day for 9

months versus placebo. Results from part A of the study ($N = 199$) demonstrated a 27% reduction in mean urine protein-to-creatinine ratio and preservation of kidney function (3.87 ml/min per 1.73 m^2 benefit) at 9 months. Based on these data, nefecon became the first disease-specific treatment to receive accelerated approval for IgAN.[47] Sustained and significant improvements in kidney function and proteinuria were recently reported at 24 months (including 15 months off treatment), although proteinuria rose and eGFR started to decline in both groups after 12 months.[48] The drug was generally well-tolerated; however, hypertension (15.% vs. 2%), edema (15.5% vs. 4%), muscle spasms (13.4% vs. 4%), and acne (11.3% vs. 2%) were reported more frequently with nefecon compared to placebo.

Sparsentan

Sparsentan (Filspari [US]) is a dual endothelin type A receptor (ETA-R) and angiotensin receptor antagonist. Endothelin receptors are widely expressed G-protein coupled receptors,[49] existing as either ETA-R or endothelin type B receptor subtypes, and are activated by endothelin 1, 2, or 3). ETA-Rs are mainly expressed on vascular smooth muscle and cause potent vasoconstriction. *In vitro,* ETA-R activation leads to mesangial cell activation and inflammation.[50] In the ddY mouse model of IgAN, ETA-R blockade suppressed the development of histological lesions and reduced proteinuria.[51] In humans, endothelin 1-related polymorphisms associate with IgAN, and glomerular ET1 expression correlates with a worse prognosis.[52,53] Sparsentan is being evaluated in the phase 3 PROTECT trial (NCT03762850). An interim analysis demonstrated a 49.8% mean proteinuria reduction at 9 months in those treated with sparsentan, approximately 3 times greater than that achieved with irbesartan (15.1%).[54] This effect was independent of changes in BP. Sparsentan was well-tolerated and there were no edema-related drug discontinuations, in distinction to the experience of endothelin receptor antagonism in SONAR, a diabetic kidney disease trial.[55] Nevertheless, the incidence of edema (14% vs. 9%), hypotension (14% vs. 6%) and dizziness (13% vs. 5%) were more frequent with sparsentan compared to irbesartan alone. Sparsentan was approved by the US Food and Drug Administration in 2023 for patients with IgAN at high risk of KF. Two-year eGFR data were recently reported.[56] Compared to irbesartan, treatment with sparsentan led to slower eGFR decline, with a reduction in the total 2-year eGFR slope (day 1 to week 110 of treatment) by 1.0 ml/min per 1.73 m^2/year ($P = 0.058$; −2.9 ml/min per 1.73 m^2/year with sparsentan vs. −3.9 ml/min per 1.73 m^2/year with irbesartan) and in the chronic 2-year eGFR slope (week 6–week 110 of treatment) by 1.1 ml/min per 1.73 m^2/year ($P = 0.037$, eGFR change = −2.7 ml/min per 1.73 m^2/year with sparsentan vs. −3.8 ml/min per 1.73 m^2/year with irbesartan). The difference in the 2 slope measurements (total vs. chronic) may be explained by the initial acute eGFR decrease after commencing either sparsentan and irbesartan due to their glomerular hemodynamic effects, and therefore chronic slope may be a better measure of nephroprotection with these classes of medications. The reduction in proteinuria with sparsentan observed in the interim analysis was maintained throughout the study period. In addition, the number of events in the composite kidney outcome of 40% eGFR reduction, end-stage kidney disease or all-cause mortality trended in favor of sparsentan treatment, although the study was not powered for this outcome.[56] An open-label experimental medicine study (SPARTAN; NCT04663204) is ongoing and is exploring the mechanistic actions of sparsentan in IgAN with repeat kidney biopsies, cardiac and kidney MRI, and extensive serum and urine biomarker studies.

Therapies in Phase 2 and Phase 3 Studies in 2023

Endothelin Receptor Antagonists

In addition to sparsentan, atrasentan is an ETA-R antagonist being evaluated in a phase 3 trial (ALIGN), a phase 2 open-label basket study (AFFINITY; NCT04573478), and the ASSIST cross-over study examining combination of atrasentan with SGLT2is (NCT05834738). Interim analysis of AFFINITY demonstrated a 58.5% mean proteinuria reduction in patients with IgAN treated with atrasentan at 24 weeks, and a favorable safety profile.[57] ALIGN also met its primary endpoint on interim analysis, with treatment with atrasentan resulting in a statistically significant reduction in proteinuria compared to placebo at 36 weeks.[58]

B-Cell Directed Treatments

As the source of Gd-IgA1, B-cells are central to the pathogenesis of IgAN (Figure 1). Rituximab, an anti-CD20 chimeric monoclonal antibody that depletes peripheral B-cells, demonstrated no benefit in terms of proteinuria reduction, kidney function, or in reducing levels of Gd-IgA1 in an open-label study in IgAN. This may reflect the inability of rituximab to target tissue-resident (e.g., mucosal) B-cells or $CD20^-/CD38^+$ plasma cells.[59,60]

BAFF and APRIL play critical roles in IgA class switch recombination and B-cell proliferation and survival. Serum levels of BAFF and APRIL correlate with IgAN disease severity, and genome wide association studies identified the gene encoding APRIL

(*TNFSF13*) as an IgAN risk locus.[61-64] BAFF-overexpressing mice develop an IgAN-like phenotype, and blocking APRIL inhibits spontaneous IgAN in ddY mice.[65,66]

Sibeprenlimab (VIS649) and zigakibart (BION-1301) are APRIL-neutralizing monoclonal antibodies currently being evaluated in phase 3 studies (VISIONARY; NCT05248646 and BEYOND; NCT05852938 respectively). In the phase 2 ENVISION study, sibeprenlimab demonstrated rapid suppression of serum Gd-IgA1, IgA, and APRIL, and a 44% mean placebo-adjusted proteinuria reduction at 9 months, in a prespecified interim analysis of 72 participants.[67] Full results of the ENVISION study for 155 participants have recently been reported.[68] At 12 months, sibeprenlimab produced a dose dependent reduction in proteinuria of 47.2% to 62% compared to 20% by placebo, whereas eGFR remained stable in the sibeprenlimab-treated groups (change from baseline was -2.7 to 0.2 ml/min per 1.73 m^2) compared to a 7.4 ml/min per 1.73 m^2 reduction in the placebo group. Zigakibart is being evaluated in a single-arm open-label phase 1/2 study of up to 30 patients with IgAN. Interim results from 17 participants report that the drug is well-tolerated and suppresses Gd-IgA1, APRIL, and proteinuria, with a 67% mean proteinuria reduction at 52 weeks.[69]

Atacicept, telitacicept and povetacicept are fusion proteins containing extracellular portions of T-cell activator and calcium-modulating ligand interactor, which bind and inhibit both BAFF and APRIL. Atacicept is being evaluated in the phase 2b ORIGIN trial; interim results have demonstrated reductions in serum IgA and Gd-IgA1, a 43% reduction in mean proteinuria, and eGFR stabilization at 36 weeks (vs. 8.5% decline with placebo).[70] A phase 3 trial (ORIGIN 3, NCT04716231) is being initiated. Telitacicept was studied in a phase 2 IgAN RCT in China ($N = 44$) (NCT04905212); treatment produced a 49% mean proteinuria reduction at the 240 mg dose, with eGFR remaining stable.[71] Povetacicept is being studied in an open label basket trial (RUBY-3) including patients with IgAN (NCT05732402).

An alternative B cell targeting approach, utilizing monoclonal antibodies that bind $CD38^+$ plasma cells and being developed to treat multiple myeloma, is also being tested in IgAN. Felzartamab is being assessed in a phase 2 RCT for proteinuria reduction (IGNAZ; NCT05065970) and mezagitamab is being studied in a phase 1 trial (NCT05174221).

At present, there are insufficient data to determine if targeting APRIL alone, APRIL and BAFF, or CD38 is likely to be of greatest benefit in IgAN.

Modulating the Complement System

The complement system comprises over 20 proteins, capable of mediating inflammation as part of the innate immune response.[34] It is activated via the classical, lectin, or alternative pathways (Figure 2). Glomerular C3 codeposition occurs in >90% of IgAN cases and the absence of C1q in most cases implies that classical pathway activation does not play a role in IgAN.[34] Multiple therapies are being developed to block individual proteins of the complement cascade and many of these are being studied in IgAN (Figure 2; see Cheung *et al.*[72] for a comprehensive review). Complement inhibitors are likely to soon offer a realistic alternative to systemic glucocorticoids as a means to limit intrarenal inflammation and glomerular injury in IgAN.

Alternative Pathway Inhibition. There is evidence for alternative pathway activation in most cases of IgAN, and increased mesangial deposition of alternative pathway components is associated with a worse clinical outcome.[34] Drugs in development in IgAN target factor B (FB) and factor D (Figure 2).

Iptacopan, an oral small molecule FB inhibitor, was assessed in a phase 2 dose-finding study. Iptacopan inhibited alternative pathway activation and reduced proteinuria by 23% compared to placebo by month 3.[73,74] Iptacopan is being evaluated in a phase 3 RCT (APPLAUSE-IgAN, NCT04578834).[75] IONIS-FB-LRx is an antisense oligonucleotide which blocks hepatic FB production through RNA interference. Interim analysis of an ongoing single arm phase 2 IgAN study ($N = 10$) demonstrated reductions in plasma FB, serum alternative pathway activity, urine Ba, and 44% proteinuria reduction by week 29 (NCT04014335),[76] and a phase 3 trial is being initiated (IMAGINATION; NCT05797610). Vermicopan (ALXN2050), a small molecule factor D inhibitor, is currently being evaluated in a phase 2 study (NCT05097989).

Lectin Pathway Inhibition. Glomerular deposition of lectin pathway components, including mannose-binding lectin serine protease 1 and 2 (MASP1/2) and C4d, are detected in 30% to 40% of IgAN cases, and their presence correlates with a worse outcome.[34] Narsoplimab, a monoclonal antibody against mannose-binding lectin serine protease 2 (Figure 2), was tested in a small phase 2 trial. A 72% mean proteinuria reduction occurred by week 18 in those who entered the study on corticosteroids. Twelve patients continued with open-label extended narsoplimab treatment, which resulted in a 38% mean proteinuria reduction after 22 months, and preserved eGFR compared to a matched retrospective cohort.[77] Narsoplimab was subsequently assessed in the phase 3

ARTEMIS-IgAN trial (NCT03608033). A recent interim analysis found no statistically significant evidence of proteinuria reduction with narsoplimab treatment compared to placebo, and the trial has now been discontinued.[78] Further analysis of the ARTEMIS-IgAN trial is awaited.

Common Pathway Inhibition. Drugs targeting complement proteins in the common pathway (C3, C5, and C5a receptor) are also being evaluated in IgAN (Figure 2). C3 is being targeted in phase 2 studies with the peptide pegcetacoplan (NCT03453619), and with ARO-C3, an RNA interference treatment designed to suppress hepatic C3 production (NCT05083364). C5 inhibition is being studied in phase 2 studies with the monoclonal antibody ravulizumab (SANCTUARY; NCT04564339) and the RNA interference treatment cemdisiran, designed to suppress hepatic C5 production (NCT03841448). Interim results from the cemdisiran phase 2 study demonstrated a 37.4% reduction in mean proteinuria at 32 weeks, and stabilization of kidney function ($N = 22$).[79] An interim analysis of SANCTUARY at 6 months ($N = 43$ on ravulizumab vs. 23 on placebo) found a 40.3% reduction in proteinuria in those treated with ravulizumab compared to 10.9% with placebo, and no safety concerns.[80] Avacopan, a small molecule C5a receptor antagonist, was studied in a small open-label study. Three of 7 patients had a 50% reduction in proteinuria at week 12, and urinary monocyte chemoattractant protein-1-to-creatinine ratio was reduced by 30% by week 8, indicating suppression of renal inflammation.[81]

Future Directions

The increased understanding of IgAN pathogenesis and the development of new treatment options is transforming the therapeutic landscape for IgAN. The Kidney Disease Improving Global Outcomes 2021 guidelines are already in need of updating, and new treatment strategies have been proposed for the management of IgAN.[82] As more therapies become available, clinicians will soon be faced with having to select the most appropriate treatment strategy for their patients. Effective strategies are almost certainly going to involve combinations of drugs; however, there is likely to be limited trial data available on these approaches for the foreseeable future.

At present, initiation and escalation of treatment is guided by levels of proteinuria and eGFR, which are nonspecific and often late indicators of kidney damage. Wider use of the international IgAN prediction tool to define those patients most at risk of progression where intervention is needed, alongside identification of additional biomarkers to improve prognostic precision of the international IgAN prediction tool is required. Biomarkers are also needed to predict response to the new therapeutic approaches, and also to monitor response, so that those not responding can be switched to alternative treatments quickly. Each of the phase 3 trials in IgAN has generated a large biorepository of samples and the hope is that through collaboration between academia and industry, these samples can be studied to find the biomarkers we need to deliver truly personalized medicine to those living with IgAN.

DISCLOSURE

HS reports no competing interests. JB reports receiving consulting and speaker fees from Alnyam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Otsuka, Travere Therapeutics, Vera Therapeutics, and Visterra; reports receiving grant support from Argenx, Calliditas, Chinook, Galapagos, GSK, Novartis, Omeros, Travere Therapeutics, and Visterra; reports serving as scientific/medical advisor to Alnylam, Astellas, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Roche, Travere Therapeutics, UCB, and Visterra, Inc.; is a member of Kidney Health Initiative; and has lectured, chaired, or participated in symposia/panel discussions for Calliditas, Omeros, and Travere Therapeutics. CKC reports receiving consulting and speaker fees from Alpine Immune Sciences, Calliditas, Chinook, CSL Vifor, George Clinical, Novartis, Otsuka, Stada, Travere Therapeutics, Vera Therapeutics; receiving grant support from Travere Therapeutics; and being on a data monitoring committee for Roche.

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