Treatment of patients with IgA nephropathy: a call for a new paradigm

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IgA nephropathy (IgAN), the world's most common primary glomerular disease, carries a significant lifetime risk for kidney failure as well as an enormous socioeconomic burden. In the past, studies in patients with IgAN largely focused on optimizing so-called supportive care, that is, blockade of the renin-angiotensin system, blood pressure control, and lifestyle modifications. The effectiveness of immunosuppressive measures, particularly high-dose corticosteroid therapy, has been reported variably, but there is considerable evidence for an increase in serious adverse effects with such therapies. This disappointing situation has changed dramatically with a better understanding of the pathogenesis of IgAN, and with regulatory agencies accepting changes in proteinuria and the estimated glomerular filtration rate loss or slope over 2 to 3 years as surrogate outcome markers. A multitude of new therapies are now being evaluated in IgAN, and several drugs, such as sodium-glucose transporter-2 inhibitors, sparsentan (a dual endothelin-1 and angiotensin II receptor blocker), nefecon (a targeted release formulation of budesonide), and iptacopan (a complement factor B inhibitor), have been approved, with more to come in the next few years. In this review, we propose a new treatment paradigm that combines therapies with different mechanisms of action to target the immune components and the chronic kidney disease components of IgAN in parallel to preserve long-term kidney survival.

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IgA nephropathy (IgAN) is the world's most common primary glomerular disease and a significant cause of kidney failure among adults, particularly in East and South Asia.[1] Recent data from the UK Registry of Rare Kidney Diseases (RaDaR) show that most adults have a considerable lifetime risk of developing kidney failure, largely based on young age at presentation and already impaired kidney function at the time of diagnosis.[2] Similar findings have been reported from a Swedish registry and the German prospective German Chronic Kidney Disease cohort.[3,4] Treatment for IgAN has been limited for many years to optimized supportive kidney care. Although IgAN is an immune-mediated glomerular disease, there has been little evidence that many of the drugs commonly used to treat autoimmune glomerular diseases such as lupus nephritis, antineutrophil cytoplasmic autoantibody–associated vasculitis, and membranous nephropathy are effective in IgAN.[5] Until recently, immunologic treatment for IgAN was limited to prolonged high-dose systemic glucocorticoids. In contrast, in lupus nephritis, antineutrophil cytoplasmic autoantibody–associated vasculitis, and membranous nephropathy, the reliance on systemic glucocorticoids has decreased considerably, and now, due to the effectiveness of B-cell depletion therapies and the emergence of anticomplement therapies, may become avoidable. This, in tandem with the ability to reliably monitor pathogenic immunoglobulin levels (antineutrophil cytoplasmic autoantibody, double-stranded DNA, and phospholipase A2 receptor antibodies), has enabled a far more sophisticated approach to treatment than is currently possible in IgAN. However, things are changing rapidly for IgAN management. In this review, we summarize current developments, provide a vision of current management, and report how management may evolve over the next 5 to 10 years.

ASSESSING PROGNOSIS

Predictors of IgAN progression include clinical, histopathologic, and biomarker-based factors (recently reviewed by Cattran *et al.*[6]). Historically, the initiation of immunosuppressive therapies has been based on the level of proteinuria.[7] Although proteinuria has consistently been recognized as a risk factor for disease progression, a significant portion of adult individuals with proteinuria levels below 1 g/d may still progress to kidney failure.[2] The Oxford Classification

MEST-C score predicts IgAN prognosis based on biopsy features and is the most widely validated histopathologic score for IgAN.[8] Various validation studies support mesangial hypercellularity (M) and glomerular segmental sclerosis (S) as independent predictors of kidney survival, but tubular atrophy and interstitial fibrosis (T) were the only consistent outcome predictors in meta-analysis.[9] Endocapillary hypercellularity (E) and crescents (C) were rarely associated with clinical outcomes in validation cohorts.[9,10] In part, this may relate to the reproducibility of MEST-C scores among different pathologists, which is relatively poor for endocapillary hypercellularity and, notably, crescents.[11] Furthermore, the MEST-C score is based mostly on the presence or absence of a histologic finding (0 or 1 for M, E, and S) or relatively crude levels of severity (0, 1, or 2 for T and C). A more granular continuous measure of each MEST-C component would likely be more informative for clinical decision-making, but this remains to be tested.[12]

The International IgAN Prediction Tool combines clinical features at the time of biopsy or 1 to 2 years after the biopsy, along with the Oxford MEST-C score, to estimate the risk of a 50% decline in glomerular filtration rate (GFR) or kidney failure up to 6.7 years after the biopsy.[13,14] Limitations include its foundation on retrospective data, lack of consideration of the choice of treatment and response to therapy, and relatively limited follow-up beyond 80 months after biopsy.[13] In addition, further validation is required in non-White and East Asian populations.

A crucial limitation of the MEST-C score and the International IgAN Prediction Tool is that they have not been prospectively studied for treatment decision-making in a clinical trial. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines therefore explicitly discourage their use for this purpose. All these concerns plus the relative insensitivity of the IgA Prediction Tool to even large changes in laboratory parameters have limited the widespread use of the Prediction Tool in clinical practice.

ASSESSING RESPONSE TO TREATMENT AND MEASURING DRUG EFFICACY IN IgAN CLINICAL TRIALS

Proteinuria

The recognition by regulatory agencies of proteinuria reduction as a likely surrogate endpoint for the traditional clinical outcomes of kidney failure or doubling of serum creatinine marked a significant milestone for drug development in IgAN.[12] Surrogate outcomes, such as proteinuria reduction and estimated GFR (eGFR) slope (discussed later), have several advantages over time-to-clinical event endpoints for phase 2 and 3 clinical trials of IgAN. They require shorter follow-up and often fewer participants by allowing all trial participants to contribute to the measurement of treatment effect, regardless of whether they reach study completion or meet one of the clinical events. In a disease with relatively preserved kidney function at diagnosis and slow progression, such as IgAN, development of many novel therapies would otherwise not be possible. Proteinuria reduction is the primary outcome for all the new phase 2 and 3 trials discussed in this review and for most of the ongoing IgAN trials of novel therapies registered on ClinicalTrials.gov.

Surrogate outcome validation requires biological plausibility, a strong and consistent association with "hard" clinical endpoints, and a demonstration that the intervention's effect on the surrogate predicts the intervention's effect on the "hard" clinical endpoint. Sustained proteinuria, typically greater than 1 g per day, was consistently associated with worse kidney outcomes in 7 IgAN cohorts from around the globe.[15] Furthermore, an individual-patient meta-analysis of 11 IgAN randomized controlled trials (RCTs) showed a continuous relationship between early reduction in proteinuria (median time 9 months) and the time to kidney failure, doubling of serum creatinine, or death across the interventions, such that for a 50% reduction in proteinuria, the hazard ratio for the composite outcome was 0.40 (95% confidence interval, 0.32–0.48).[16]

eGFR slope

Another surrogate outcome, the annual mean change in GFR over 2 or 3 years or the 2- or 3-year eGFR slope, has been approved so far by American, Chinese, and European regulatory agencies to predict kidney failure, the initiation of renal replacement therapy, or the doubling of serum creatinine in a wide range of kidney diseases, including IgAN (Figure 1a).[17–20] A difference in mean eGFR slopes of 0.5–1.0 ml/min per 1.73 m^2 per year was proposed as a threshold to provide a 97.5% positive predictive value of achieving a benefit on clinical outcomes (hazard ratio of approximately 0.7).[20]

An important issue arises when a drug has an acute negative effect on eGFR that opposes the drug's beneficial chronic effects, such as with renin-angiotensin system (RAS) and sodium-glucose transporter-2 inhibitors (SGLT2i) (Figure 1b). Similarly, an acute "improvement" of eGFR may relate to hemodynamic actions, for example, corticosteroid-induced pre- and postglomerular vasodilation,[21] or artifacts, for example, corticosteroid-induced muscle loss, which may not translate into better long-term outcomes. Therefore, whether the total GFR slope (i.e., from baseline to the end of the intervention) or the chronic slope (i.e., ignoring the first 1.5–3 months) should be used in these situations remains debated. Although clinicians generally focus on improving the chronic decline in eGFR, the total slope was more strongly and precisely associated with the clinical endpoints in individual participant data meta-regression of 66 RCTs.[19] In simulations, when an acute negative effect was present, the chronic slope had a higher statistical power to detect an effect than the total slope. When the acute negative effect attenuated as eGFR declined, the chronic slope was biased in favor of the treatment (higher risk of false positive), and the total slope was biased against the treatment (higher risk of false negative). The reverse pattern was observed in the presence of a positive acute effect.[22] Therefore, despite the overall better performance of the total slope to predict clinical events, the chronic slope might be preferable in certain contexts.

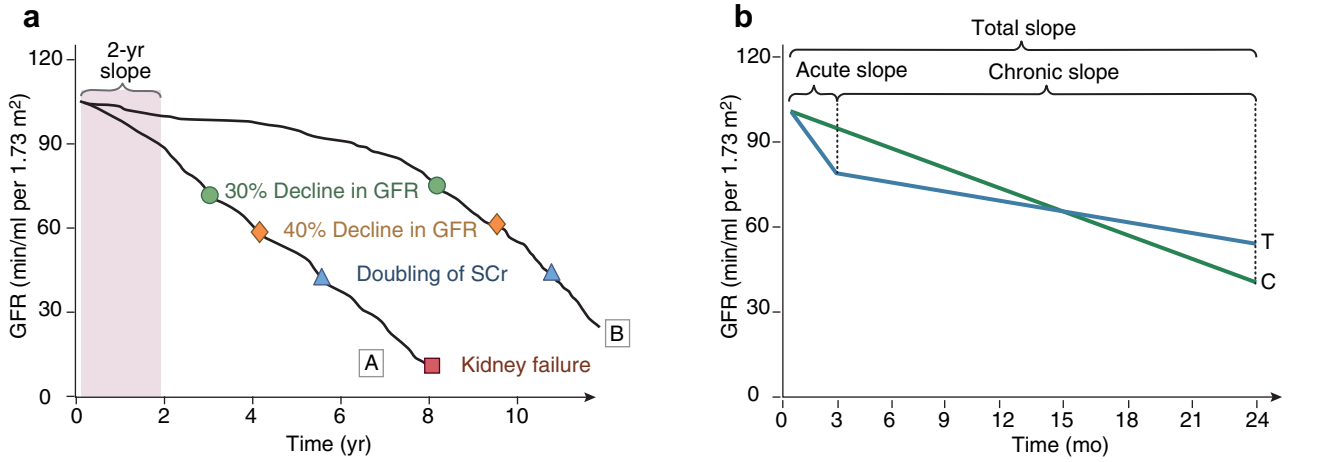

Figure 1 | (a) Demonstration of the time required to assess the estimated glomerular filtration rate (eGFR) slope as a surrogate outcome versus the other recognized surrogate outcomes of 30%, 40%, and 57% (doubling of serum creatinine [Scr]) decline in GFR and the clinical endpoint of kidney failure. Hypothetical examples of fast (*A*) and slowly (*B*) progressing kidney diseases are presented. (**b**) Graphical representation of the acute, chronic, and total GFR slope in the context of a hypothetical trial of a drug with an acute decline in eGFR (treatment arm, *T*) compared with placebo (control arm, *C*).

The controversy around the total versus chronic slope for drugs with acute effects on eGFR is particularly relevant to the 2 approved IgAN drugs: sparsentan and nefecon. In the PROTECT trial, sparsentan caused an acute drop in eGFR and improved the 2-year chronic eGFR slope but missed the statistical significance threshold for the total slope.[23] Unlike the previously mentioned simulated trial scenarios,[24] in PROTECT, both treatment arms displayed an acute decline in eGFR. Considering that the acute drop in eGFR was comparable across study arms, we may expect their respective effects to cancel out and result in a similar risk of type 1 error (false positive) for both the total and chronic slope. This reasoning, however, assumes similar attenuation of the acute drop for irbesartan and sparsentan and would require testing in simulations. In the NefIgArd trial,[25] nefecon led to an acute increase in eGFR at 3 months after randomization and improved the 2-year total eGFR slope compared with placebo. It is currently unknown whether the acute increase in eGFR is related to resolution of glomerular inflammation or is a hemodynamic effect (see above). In this situation, the chronic slope might offer a more conservative effect estimate.

These examples demonstrate the importance of selecting the slope outcome *a priori* based on previous knowledge of the intervention's acute effects on eGFR relative to the disease-specific expected rate of progression. Fortunately, for many interventions, no acute effect will be expected, and the total slope will be the surrogate outcome of choice given its better prediction accuracy for clinical events overall. If acute negative effects are expected, options include the following:

- Use the total slope for its greater robustness in predicting "hard" clinical endpoints, but to avoid prematurely dismissing a treatment, consider a longer trial duration to allow any initial acute decline to be offset by a long-term slowdown in eGFR decline.
- Choose the chronic over the total slope (decided *a priori*) and consider a lower threshold for the *P* value to reduce the risk of type 1 error (false positive). A 3-month cutoff for acute effects used in validating the GFR slopes as surrogate outcomes will not be appropriate for all interventions and should preferably be tailored to the specific intervention studied.
- Use trial designs that negate the acute effect. Drawbacks include the extra time and cost of conducting run-in and withdrawal phases and potential extra assumptions on the integrity of the randomization.
- In certain situations, traditional clinical endpoints will be more efficient than the total eGFR slope, such as when there is an important acute negative effect and the chronic mean eGFR decline is slow.[22]

For acute positive effects (initial eGFR improvement), the chronic slope offers a more conservative assessment of the treatment effect. However, accurately determining the point at which genuine improvement in kidney function begins, as opposed to hemodynamic or artifactual changes, can be challenging. To date, phase 2 and 3 IgAN trials have reported eGFR slopes as secondary outcomes,[23,25,26] and a trial based on eGFR slopes as the primary outcome is yet to come. Given the inherent trade-offs between total and chronic eGFR slopes, reporting both may be prudent when acute effects of an intervention on eGFR are anticipated.

AIMS OF THERAPY IN PATIENTS WITH IgAN

Historically, the goal of therapy was to decrease proteinuria to ≤1 g/d, considered the threshold for high risk of progressive loss of kidney function.[5] However, this goal needs to be revised in view of recent data and should rather be as low as possible.[2–4] Practically speaking, the aim of therapy should be complete proteinuria remission. Although there is no universally accepted definition of full remission in IgAN, we suggest a proteinuria goal of ≤0.3 g/d or a urine protein to creatinine ratio of ≤0.2 g/g.[2] In contrast to urine protein to creatinine ratio, target ranges for urine albumin to creatinine

Table 1 | Components of an integrated approach to treat CKD in patients with IgAN[3]

Category	Measures	Target
Blood pressure	• Initiate lifestyle measures (see below), antihypertensive therapy	Sitting systolic blood pressure <120 mm Hg
Proteinuria	• Initiate renin-angiotensin system inhibitor (RASi) and uptitrate as far as tolerated or allowed • Consider replacing RASi with sparsentan • Avoid dihydropyridine calcium channel blockers (e.g., amlodipine and nifedipine) as first-line therapy in antihypertensive therapy	Reduction of proteinuria as far as possible, ideally <0.3 g/d
Diet	• Restrict sodium intake and/or initiate diuretic • Restrict fluid intake unless medically indicated for other reasons	Sodium intake <2 g/d (9 mmol/d) Fluid intake 1.5–2 liters/d
Lifestyle	• Counsel about nicotine, weight loss, and exercise where appropriate	No nicotine consumption, normalize body weight, and initiate regular endurance sports (avoid strenuous types of exercise)
Additional measures	• Initiate SGLT2 inhibitor unless contraindicated • Avoid chronic intake of nonsteroidal anti-inflammatory drugs • Avoid prolonged hypokalemia	

CKD, chronic kidney disease; IgAN, IgA nephropathy; SGLT2, sodium-glucose transporter-2.

ratios in patients with IgAN are currently less well established. Future RCTs should focus on including patients with lower proteinuria than 1 g/d (0.8 g/g) and should test the validity of a full remission endpoint.

Beyond proteinuria, full remission of IgAN includes stability of eGFR with annual losses not exceeding the physiological loss of approximately 1 ml/min per year in older adults or nil in younger adults. Finally, the third target to fulfill the definition of complete remission should be the absence of persistent microhematuria, given the emerging evidence that the extent of hematuria is another important progression indicator in IgAN.[27] Indeed, recent clinical trials demonstrated that the disappearance of microhematuria can become a realistic goal in IgAN,[25] and complete remission of proteinuria with stabilization of eGFR has been seen in recent trials in a significant proportion of patients.[23,26] Importantly, an absence of hematuria does not mean that there is no ongoing IgA immune complex–mediated glomerular and tubulointerstitial injury, mediated through direct activation and injury to podocytes and tubular epithelial cells. An absence of hematuria should, therefore, not be a reason to deny patients access to treatment with drugs designed to reduce the synthesis of pathogenic forms of IgA (see later). Indeed, patients in the NefIgArd trial gained benefit from targeting pathogenic IgA production irrespective of whether they had hematuria at study inclusion. However, vice versa, there is currently no evidence that persistent microhematuria in the absence of significant proteinuria is associated with a poor prognosis and technical issues related to the quantification of hematuria (i.e., dipstick, automated analyses, and manual counts) need to be considered.

TREATING CHRONIC KIDNEY DISEASE

Patients with IgAN have an immune-mediated glomerular disease that often leads to the development of chronic kidney disease (CKD). Thus, CKD therapy, which is not specific to IgAN, constitutes a key component of the care of such patients. It relies on managing the generic intrarenal responses to IgAN-induced nephron loss (glomerular hypertension/hyperfiltration, the tubulointerstitial response to persistent proteinuria, and the initiation and/or worsening of systemic hypertension). This so-called optimized supportive kidney care encompasses an array of measures ranging from lifestyle modification, smoking cessation, and tight blood pressure control to pharmacologic therapy, as discussed below.[5] A full discussion of the measures (Table 1) is beyond the scope of this review, and the reader is referred to other recent publications.[5,28]

Renin-angiotensin system antagonists

The efficacy of RAS inhibition to attenuate progressive CKD has been examined across a range of IgAN clinical phenotypes. An early study examined ramipril in 60 Asian adults with long-standing IgAN who had proteinuria <0.5 g/d, normal blood pressure, and normal kidney function.[29] Half of the patients were given 2.5 mg/d ramipril, and half received no treatment besides non-RAS inhibiting antihypertensives as needed. Over 60 months of follow-up, the decline in eGFR was –0.39 ± 2.57 ml/min per 1.73 m^2 per year in the ramipril group compared with –0.59 ± 1.63 ml/min per 1.73 m^2 per year in the placebo group and not statistically different. In contrast, when the angiotensin-receptor blocker (ARB) valsartan was compared with placebo in 109 Asian adults with more severe IgAN, the ARB afforded significant protection.[30] In the ARB-treated group, median proteinuria fell from 1.5 g/d to 0.9 g/d, whereas no change was seen in the placebo patients (1.7 g/d at baseline and 1.6 g/d at study end). The chronic eGFR slopes (12 weeks after study entry to week 104) were –4.6 ± 9.6 and –6.9 ± 7.9 ml/min per 1.73 m^2 ($P = 0.025$) in the treatment and placebo groups, respectively. Importantly, despite an attenuation in the loss of kidney function with ARB therapy and a reduction in proteinuria to below 1 g/d, the patients continued to have GFR loss that could conceivably result in kidney failure within their

Table 2 | Annual loss of eGFR from baseline in the control and treatment arms of recent randomized trials in patients with IgAN

Trial	Control arm	Annual eGFR loss, ml/min per 1.73 m^2	Treatment arm	Annual eGFR loss, ml/min per 1.73 m^2	Reference
STOP-IgAN	Optimized supportive care	−1.5	Immunosuppressants	−1.4	33
PROTECT	Irbesartan	−3.8	Sparsentan	−2.7	23
MAIN	Losartan	−3.8	Mycophenolate mofetil	−1.2	34
Dapa-CKD	Placebo	−4.7	Dapagliflozin	−1.2	35
TESTING	Placebo	−5.0	Methylprednisolone	−2.5	36
ENVISION	Placebo	−5.9	Sibeprenlimab	−1.5	26
NEFIGARD	Placebo	−6.0	Nefecon	−3.1	25
ORIGIN phase II trial	Placebo	−4.9 at 9 mo	Atacicept	−0.8 at 9 mo −0.6 at 22 mo[b]	37 38
Italian phase IV trial	Ramipril[a]	−6.17[a]	Ramipril[a] plus corticosteroid	−0.56[a]	39
Iptacopan phase II trial	Placebo	−3.2 at 6 mo	Iptacopan highest dose	−1.2 at 6 mo	40
Chinese phase II trial	Placebo	−4.3 at 6 mo	Endothelin A antagonist SC0062 highest dose	−3.4 at 6 mo	41
SANCTUARY	Placebo	−4.5 at 6 mo	Ravulizumab	+0.2 at 6 mo	42
Telitacicept phase II trial	Placebo	−7.3 at 6 mo	Telitacicept highest dose	+2.3 at 6 mo	43

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; MDRD, Modification of Diet in Renal Disease.
[a]GFR estimated using the MDRD formula; treatment with ramipril started at a dose of 2.5 mg/d and was then increased by 1.25 mg/d every month depending on blood pressure.
[b]Patients included in an open-label extension study who received atacicept 150 mg for an additional 60 weeks.[38]

lifetimes. Similarly, European patients with IgAN (n = 44) with proteinuria ≥0.5 g/d and normal or only modestly decreased GFR were randomized to enalapril or no RAS inhibitor and followed prospectively for a mean of over 70 months.[31] Enalapril was started at 5 mg/d and titrated to a maximum of 40 mg/d to reach a blood pressure target of <140/90 mm Hg. The control group received other antihypertensives to achieve the same blood pressure goal. Proteinuria in the angiotensin-converting enzyme (ACE) inhibitor–treated patients fell significantly from an average of 2 g/d at trial entry to 0.9 g/d at last visit, whereas there was no change in the control group (1.7–2 g/d). Creatinine clearance declined slightly but not significantly in enalapril-treated patients during the study (102 ± 25 to 95 ± 30 ml/min) but fell significantly in the control group (99 ± 22 to 64 ± 31 ml/min). Although these studies may not have optimized RAS inhibitors and blood pressure to present-day targets (Table 1), the results suggest that patients with IgAN and impaired kidney function and/or modestly high levels of proteinuria do have an attenuation of GFR loss with RAS inhibitor treatment. Importantly, the full antiproteinuric effect of RAS blockers in patients with IgAN may require 6 or more months of therapy.[32] Patients with little proteinuria and normal kidney function may not benefit or may need a longer time to show benefits.

In contrast to the early studies of RAS inhibition in IgAN, contemporary clinical trials provide insight into the decline of kidney function of patients with IgAN who have not responded adequately to RAS inhibition. Although adequate response was defined differently in each trial, the general approach to patient recruitment was to inhibit the RAS for a minimum of 3 months at maximally allowed or tolerated dose and then enroll only patients still at high risk for a bad outcome (based on the level of persistent proteinuria) who could potentially benefit from the addition of immunosuppression. These trials' placebo or control arms yield a glimpse of the decline in kidney function of patients with IgAN receiving optimized RAS inhibition (Table 2) who have residual proteinuria.

Three messages emerge from these data. First, despite prolonged and intense RAS inhibition, at least two-thirds of the patients may not experience a reduction of proteinuria below 0.75 g/d.[33] Second, patients with persistent proteinuria greater than 0.75 to 1 g/d after adequate RAS inhibition lose GFR at an annual rate sufficient to result in kidney failure within their lifetimes despite continuing RAS inhibition. Finally, in trials requiring the control arm to receive a specific ARB at the maximum recommended (not simply maximum tolerated) dose, annual GFR loss was less than in trials that relied on optimized RAS inhibition according to the site principal investigator.[23,34]

Endothelin-1 receptor antagonism

To leverage the beneficial effects of RAS inhibition in IgAN and further attenuate GFR decline, the PROTECT trial compared sparsentan, a dual endothelin type A and angiotensin II type 1 receptor blocker, with the ARB irbesartan.[23] The rationale for dual blockade stemmed from the observations that endothelin-1 expression is increased in the kidneys of patients with IgAN and that acting via the endothelin A type receptor (ET_AR) endothelin-1 can mediate intrarenal vasoconstriction, inflammation, fibrosis,

and cell proliferation.[44,45] As these effects are similar to the effects of angiotensin II on the kidney,[46] it seemed reasonable to block potentially redundant systems of injury together to enhance the already clear protective effects of RAS inhibition in IgAN. Sparsentan use resulted in a significantly greater fall in proteinuria at the trial's primary 36-week endpoint than irbesartan (49.8% vs. 15.1%, $P < 0.0001$, respectively).[47] The patients receiving sparsentan also showed an attenuated annualized decline in eGFR at the 110-week secondary endpoint (Table 2). eGFR decline was measured as the total slope (trial day 1 to week 110) and the chronic slope (trial week 6 to week 110) because both sparsentan and irbesartan cause an acute hemodynamic decline in eGFR. Although the eGFR benefit conferred by sparsentan was not different whether the slope was calculated as chronic or total, the total slope did not quite reach statistical significance ($P = 0.058$ vs. $P = 0.037$ for the chronic slope), demonstrating the relevance of *a priori* selection of slope analysis (see above).

Atrasentan is an ET_AR antagonist that is being evaluated for treating IgAN in the ALIGN study (NCT04573478). A key differentiator of atrasentan compared with sparsentan is the ability to titrate the ET_AR antagonist and the RAS inhibitor independently. Interim data of ALIGN were recently published, showing greater proteinuria reduction with atrasentan (–38%) than with placebo (–3%) and a good safety profile of atrasentan. Fluid retention was reported by 11% of the patients in the atrasentan group and 8% in the placebo group.[48]

Another selective ET_AR antagonist, SC0062, also reduced proteinuria in patients with IgAN by approximately 50% at week 24 with a good safety profile.[41] There was also a modestly better protection of eGFR over the short study period (Table 2).

Sodium-glucose transporter-2 inhibitors

SGLT2i slow progressive loss of GFR in patients with diabetic and nondiabetic kidney disease. The DAPA-CKD and EMPA-KIDNEY trials enrolled a reasonably large proportion of IgAN patients with CKD and, in preplanned *post hoc* analyses, examined the effects of dapagliflozin and empagliflozin on outcomes in IgAN.[49] Unlike PROTECT, these trials were not designed to compare SGLT2i plus RAS inhibition with optimized RAS inhibition alone. Nonetheless, most of the patients were taking an ACE inhibitor or an ARB, so the effect of adding SGLT2i to RAS inhibition could be assessed. Administration of SGLT2i with RAS inhibition attenuated the annual decline in eGFR more than RAS inhibition alone (Table 2).[35,50] The addition of dapagliflozin and empagliflozin to background RAS inhibition also resulted in a reduction of albuminuria (measured as urine albumin to creatinine ratio) by 26% and 15%, respectively, compared with the RAS inhibitor alone.[35,50]

Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists (MRAs) may also affect the progression of CKD. Although MRAs have yet to be specifically studied for preserving kidney function in IgAN, it is reasonable to consider that they may provide benefits when combined with ACE inhibitors or ARBs. A meta-analysis of MRA effects in diabetic and nondiabetic proteinuric CKD concluded that relative to background therapy and/or placebo, MRAs result in a significant decline in proteinuria and albuminuria with a small early fall in eGFR.[51] Follow-up was too short to determine if this translated in long-term eGFR preservation. The meta-analyzed studies used various comparators to MRA treatment, including ACE inhibitors, ARBs, diuretics, and other antihypertensive medications. MRAs were added mainly to background RAS inhibitor therapy, but this was not the case in all studies. In a meta-analysis that evaluated the nonsteroidal MRA, finerenone, reaching a fixed 40% and 57% decline in GFR was significantly attenuated with finerenone compared with controls.[52] Control groups received either a placebo, or, in some cases, steroidal MRAs.

In summary, managing the generic intrarenal responses to IgAN-induced nephron loss with optimized CKD care does slow the annual rate of kidney function loss and is an essential component of the management of IgAN. However, it does not address the fundamental disease process, and, as might be expected, even multitarget therapy with combinations of RAS blockers, ET_AR antagonists, SGLT2i, and MRAs may not provide sufficient protection against kidney failure for patients with IgAN.[23,53] Unless patients already received the above drugs before the kidney biopsy, we feel that a short waiting period of 1 to 3 months with just "CKD therapy" is acceptable unless there are very active lesions in the biopsy, high-grade proteinuria (e.g., nephrotic range), or historical data suggesting relatively rapid GFR loss. We also acknowledge that most of the medications used to slow CKD also have various anti-inflammatory and/or immunomodulatory effects[54] that may be sufficient for some individuals with IgAN, but identifying such patients *a priori* is not possible given the current lack of IgAN biomarkers.

TREATING THE IMMUNOLOGIC DISEASE

Many immune-mediated glomerular diseases, including IgAN, follow a rather standard pathogenic scheme: deposition of antibodies or immune complexes leading to complement activation and cellular activation. During the latter, cells divide, attract leukocytes, and produce proinflammatory mediators and profibrotic signals unless the injury quickly subsides. In the case of glomerular diseases, another important consequence is the spreading of the primarily glomerular injury to the tubulointerstitium with subsequent tubular damage and interstitial fibrosis, that is, irreversible nephron loss. In this framework, one can arbitrarily define 3 goals of immunologic management of IgAN:

(i) Switch off the production of pathogenic forms of IgA and formation of IgA containing immune complexes as soon as the diagnosis is established to eliminate the presumptive origin of the disease.
(ii) Rapidly halt glomerular inflammation when present to prevent/attenuate irreversible parenchymal damage.

(iii) Halt the release of profibrotic signals in glomeruli and the tubulointerstitium to preserve every nephron possible.

Of course, these goals represent a simplification of pathogenesis, injury is rarely synchronized in all nephrons, and most therapeutic approaches address more than 1 goal. However, these goals frame a logical approach to treating the immune aspect of IgAN.

Goal 1: to switch off the production of pathogenic forms of IgA

B-cell/plasma-cell depletion. CD20 depletion strategies are commonly used in autoimmune glomerular diseases and have been shown to be highly effective in antineutrophil cytoplasmic autoantibody–associated vasculitis and membranous nephropathy. However, in a North American RCT, rituximab failed to reduce proteinuria and to affect the eGFR course over 1 year.[55] In that trial, CD20+ B-cell depletion with rituximab was confirmed, but serum levels of pathogenic IgA (commonly measured as galactose-deficient IgA1 [gd-IgA1]) did not change, suggesting that pathogenic IgA–producing plasma and B cells likely reside within discrete tissue microenvironments that are resistant to CD20 depletion approaches.[55]

CD38 depletion commonly used in the treatment of multiple myeloma is now being evaluated in IgAN and other glomerular diseases.[56] Data from phase II trials of the anti-CD38 antibodies felzartamab and mezagitamab in IgAN showed long-lasting proteinuria reduction and suppression of levels of gd-IgA1 (NCT05065970 and NCT05174221).[57] The most notable adverse event was the first-infusion reaction.

An alternative approach, almost exclusively adopted in Japan, is tonsillectomy to deplete a large reservoir of mucosal B and plasma cells. The role of the pharyngeal immune system, particularly the tonsils, in the production of pathogenic forms of IgA is uncertain, and outside of Japan, routine tonsillectomy is not recommended by the KDIGO guidelines.[5]

B-cell/plasma-cell modulation. *Nefecon.* Nefecon is a targeted-release formulation of budesonide designed to deploy the budesonide preferentially in the terminal ileum.[58] The therapeutic approach is based on accumulating evidence suggesting the existence of a gut-kidney axis in the pathogenesis of IgAN with mucosal lymphocytes releasing pathogenic forms of IgA into the systemic circulation instead of the gut lumen.[59] Indeed, serum levels of gd-IgA1 in patients with IgAN fell by approximately 20% with 16 mg of nefecon daily for 9 months.[60]

In the phase III NEFIGARD RCT,[61,62] 364 patients on RAS blockers, proteinuria above 1 g/d, and an eGFR of 35–90 ml/min per 1.73 m^2 were randomized to placebo or nefecon 16 mg/d for 9 months, followed by a noninterventional 15-month observation period. At 9 months, proteinuria fell approximately 50% with nefecon and eGFR remained stable, whereas the placebo group lost approximately 7.5 ml/min eGFR on average (Table 2).[61] Fifteen months later without continued nefecon treatment, proteinuria was increasing back toward baseline, and eGFR had declined in parallel to placebo but remained approximately 5 ml/min higher at the end of the observation period, suggesting that repeated cycles of nefecon may be needed to provide long-term kidney function protection.[25] Adverse events included well-known mild to moderate glucocorticoid-like side effects, including acne, weight gain, hypertension, edema, and mood changes. However, in contrast to systemic glucocorticoid therapy of IgAN, no increase in mortality or serious infectious events was observed with nefecon.[25,61] Nefecon became the first US Food and Drug Administration– and European Medicines Agency–approved treatment for primary IgAN. The initial restriction to patients with a urinary protein to creatinine ratio above 1.5 g/g was recently dropped by the US Food and Drug Administration and is under review by EMA.[63]

APRIL and/or BAFF inhibition. An approach being extensively investigated in IgAN is inhibiting B-cell proliferation and differentiation by targeting APRIL (a proliferation-inducing ligand) and BAFF (B-cell activating factor).[64,65] Conceptually, targeting APRIL has more selective effects on the immune system with a reduction of immunoglobulin class switching and plasma-cell survival, whereas combined BAFF and APRIL inhibition also affects peripheral B-cell survival and T-cell costimulation.[66] In phase II studies, anti-APRIL antibodies (sibeprenlimab, NCT04287985, and zigakibart, NCT03945318) and combined BAFF and APRIL inhibitors (atacicept EudraCT 2020-004892-41, telitacicept NCT05596708, and povetacicept NCT05732402) reduced proteinuria in patients with IgAN and levels of gd-IgA1 fell rapidly with a good safety profile despite parallel reductions in total serum IgA, IgG, and IgM.[37,43,67–69] In addition, in the open label extension phase of the ORIGIN trial, the annualized slope of eGFR was reduced to –0.6 ml/min per 1.73 m^2 in patients receiving atacicept.[38] When reported, levels of gd-IgA1 returned quickly to baseline on treatment cessation, suggesting that continued treatment may be required to maintain suppression of pathogenic forms of IgA.

Hydroxychloroquine. The antimalarial drug hydroxychloroquine exhibits some immunomodulatory action, in part via affecting the toll-like receptor system. A Chinese RCT noted a significant proteinuria reduction in patients with IgAN after 6 months of hydroxychloroquine.[70] The drug was well tolerated, but so far the efficacy of hydroxychloroquine has not been shown with respect to eGFR stabilization or in non-Chinese populations.

Inhibiting lymphocyte proliferation. *Mycophenolate mofetil.* The largest RCT to date was performed in China and randomized 170 patients with IgAN to receive either supportive care alone, including losartan, or with mycophenolate mofetil (MMF) (1.5 g/d for 12 months, followed by 0.75–1 g/d for at least 6 months).[34] The primary endpoint was a composite of doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular causes. After a median follow-up of 5 years, the endpoint occurred in 7.1% of the MMF group and 21.2% of the control group without increases in serious

adverse events with MMF. Two smaller RCTs from China also confirmed protection of eGFR with MMF, with one of them also suggesting that MMF can reduce the glucocorticoid dose.[71–73] However, a third trial in China had to be stopped early after 6 of 32 patients with IgAN developed pneumonia, mostly due to *Pneumocystis jirovecii*, requiring ventilation and 4 died.[74] These patients exhibited an eGFR below 60 ml/min.

In contrast to the above Chinese studies, 3 small trials in Caucasian patients failed to demonstrate any benefit from MMF,[75–77] and the KDIGO guideline therefore suggests restricting the use of MMF to Chinese patients with IgAN.[5] Particular care should be taken to add pneumocystis prophylaxis in such patients.

Cyclophosphamide and combination immunosuppression. A small British RCT randomized patients with IgAN and progressive loss of eGFR to either purely supportive therapy or prednisolone 40 mg/d (reduced to 10 mg/d by 2 years) plus oral cyclophosphamide for 3 months, followed by azathioprine up to 6 years.[10] Kidney failure developed within 5 years in 28% of the immunosuppressed group versus 94% of the control group. Supportive care did not allow angiotensin II receptor blockers, and ACE inhibitors could only be used if patients had received them before the study. Blood pressure was controlled to 160/90 mm Hg or less. The same regimen of immunosuppressants administered as part of the STOP-IgAN trial to patients with a baseline eGFR between 30 and 60 ml/min was ineffective in terms of eGFR preservation and led to a doubling of serious adverse events, including one infection-related death.[33,78] The addition of azathioprine for 6 months to a combined intravenous and oral glucocorticoid regimen[79,80] also did not improve kidney outcomes up to 7 years and rather was associated with more treatment-related adverse events.[81]

Goal 2: to halt glomerular inflammation

Systemic glucocorticoids. In the cell nucleus, glucocorticoids modulate a plethora of target genes and transcription factors, all of which are important for regulating inflammatory responses.[82] Systemic glucocorticoid therapy was one of the first treatment approaches for IgAN.

An Italian trial randomized patients with IgAN to either usual supportive therapy or 1 g of methylprednisolone i.v. for 3 consecutive days in months 1, 3, and 5, each followed by oral prednisolone 0.5 mg/kg every second day for a total of 6 months.[80] Ten years later, 1 of 43 patients assigned to glucocorticoid versus 13 of 43 receiving usual care exhibited a doubling of serum creatinine, suggesting a legacy effect of the short corticosteroid treatment.[79] No serious adverse events were reported.[80] Only 14% of the patients had received an RAS blocker at the time of randomization.[80] The same glucocorticoid regimen was used in the STOP-IgAN trial, however, only after supportive care had been extensively optimized for 6 months.[33] Although proteinuria was transiently reduced in the glucocorticoid group of STOP-IgAN compared with supportive care alone, there was no evidence for better preservation of GFR either at study end (3 years) or after up to 10-year follow-up.[33,78,83] Serious infectious adverse events doubled with glucocorticoids, and impaired glucose tolerance or diabetes induction increased.[33,78]

Two early RCTs from Italy and China[39,84] used an RAS blocker alone or an RAS blocker plus a purely oral glucocorticoid regime (2 months of 0.8–1 mg/kg/d prednisone with tapering to zero over 4–5 months). In both RCTs, participants on prednisone lost significantly less kidney function than controls. Therapy reportedly was safe. In contrast to contemporary approaches, both RCTs required RAS blockers to be paused for at least 4 weeks before randomization, and then the RAS blocker was very slowly uptitrated.

In the recent TESTING trial, patients had to be on a stable RAS blocker for at least 3 months and were then randomized to placebo or 0.6 to 0.8 mg/kg/d methylprednisolone for 2 months with tapering over 6 to 8 months.[85] Methylprednisolone reduced the risk for a kidney endpoint (40% reduction in eGFR, end-stage kidney disease, or death due to kidney disease), but the study had to be halted given several infection-related deaths.[85] Subsequently, the study was continued at half the glucocorticoid dose, and there was a benefit for the kidney endpoint, but again one infection-related death occurred during the initial higher dose methylprednisolone phase.[36] The key difference between TESTING and STOP-IgAN is the almost exclusive inclusion of Southeast Asian patients in TESTING compared with 100% Caucasians in STOP-IgAN.[86] Indeed, there is some evidence that IgAN runs a more aggressive course in Asian than Caucasian patients.[87]

Three recent retrospective analyses from Romania, the UK, and Norway consistently found no benefit from a systemic glucocorticoid therapy for kidney endpoints (eGFR decline and kidney failure) in Caucasian patients with IgAN, but did observe an increase in adverse events.[88–90]

Targeting the complement system. There is ample evidence for the involvement of the alternative pathway of complement in the pathogenesis of IgAN and, in some patients, also of the lectin pathway (reviewed by Barratt *et al.*[91] and Duval *et al.*[92]). C1q, a component of the classical pathway of complement, is detected in <10% of IgAN biopsies, and evidence of lectin pathway activation is present in about a third of patients, suggesting that most complement activation in IgAN occurs via the alternative pathway. Many phase II and III RCTs are currently underway assessing interventions at multiple levels of the complement system.

An interim analysis of the APPLAUSE-IgAN phase III RCT evaluating iptacopan (LNP023) in patients with IgAN (NCT04578834) reported a 38% proteinuria compared with placebo after 9 months of treatment,[93] following a successful phase II RCT demonstrating a sustained proteinuria reduction and good safety profile.[40,94] Iptacopan is an orally administered small molecule inhibitor of factor B, which is needed for formation of the alternative pathway convertase and the C3-amplification loop. In an alternative approach, factor B is targeted by RO7434656, a complement factor B

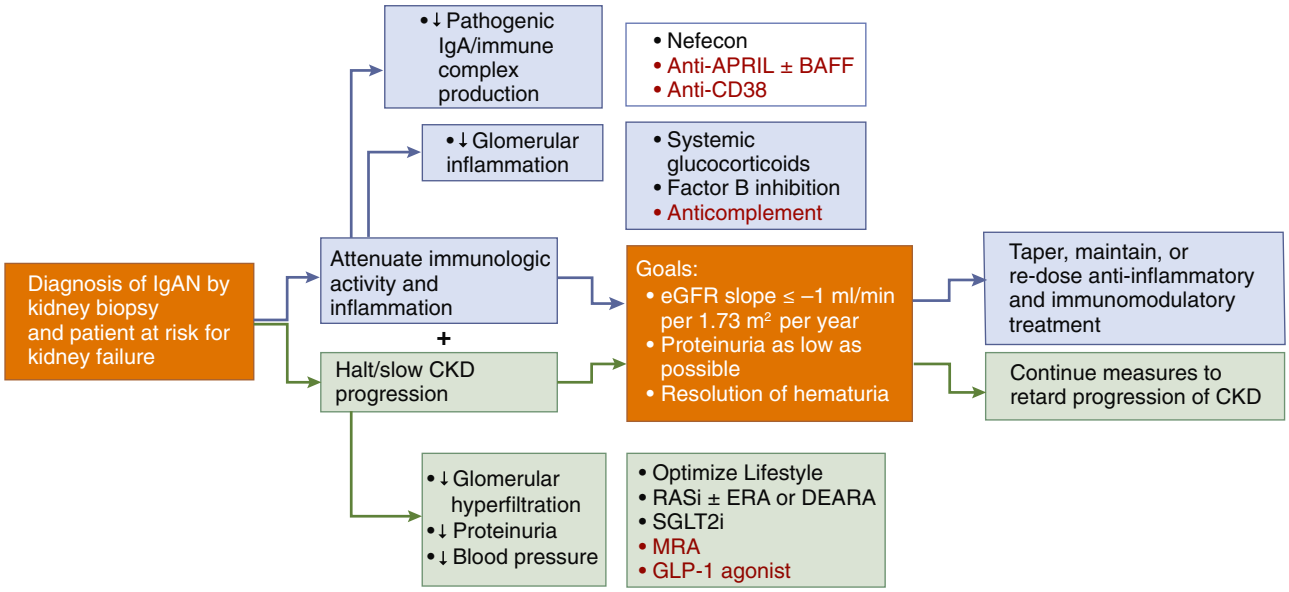

Figure 2 | Future treatment of immunoglobulin A nephropathy (IgAN) should focus on an integrated and targeted therapeutic approach, directed at those pathways driving continued nephron loss. This will require long-term suppression of pathogenic IgA synthesis, alongside immediate control of glomerular inflammation when present and ideally in the future inhibition of profibrotic pathways. This should be combined with a multifaceted approach to optimized supportive care, which is likely to involve targeting multiple intrarenal pathways, leveraging renin-angiotensin system inhibition (RASi), sodium-glucose transporter-2 (SGLT2) inhibition (SGLT2i), dual endothelin angiotensin receptor antagonism (DEARA), and endothelin and mineralocorticoid receptor antagonism (ERA and MRA). A glucagon-like peptide-1 (GLP-1) agonist can be considered in obese patients with IgAN. Whether the paradigm will be to add SGLT2i, ERA, and MRA on to maximal RASi or to target all pathways simultaneously with submaximal doses of each agent remains to be determined. Drugs in red are in phase II–III clinical trials in patients with IgAN or nondiabetic CKD. APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; CKD, chronic kidney disease.

antisense oligonucleotide, in a phase III RCT (IMAGINATION and NCT05797610). Various other approaches targeting components of the alternative pathway, including factor D, are in earlier stages of clinical development.[92]

The ARTEMIS phase III RCT evaluated narsoplimab, a fully human IgG4 monoclonal antibody targeting MASP2, the key enzyme of the lectin pathway (NCT03608033), after a small study showed that narsoplimab reduced proteinuria and stabilized eGFR in IgAN.[62] However, the trial was stopped after the interim analysis showed no effect of narsoplimab on proteinuria.[95]

Blockade of the common pathway of complement, namely, C3, C5, and C5a, is also being evaluated in patients with IgAN. Three phase 2 trials in patients with IgAN examining cemdisiran (NCT03841448), a C5 antisense oligonucleotide; ravulizumab (NCT04564339), a long-acting monoclonal antibody to C5; and avacopan (NCT02384317), a C5a receptor antagonist have reported significant proteinuria reductions.[96,97] In the phase II SANCTUARY trial, treatment with ravulizumab at week 26 proteinuria was reduced by 30% ravulizumab versus placebo, increasing to –45% in the open label phase at week 50.[42] Over the 50 weeks, patients receiving ravulizumab lost –3.9 ml/min per 1.73 m^2 in eGFR. A phase 3 trial of ravulizumab in IgAN is ongoing (NCT06291376).

A key challenge in studies targeting complement is the identification of noninvasive biomarkers that can guide therapy. In the case of iptacopan, first data of a phase II RCT suggest that urinary C5b-9 rapidly falls on initiation of complement blockade and could thus be used to monitor treatment efficacy and possibly in the future also the activity of IgAN.[40,94]

Goal 3: to halt the release of profibrotic signals

Many patients with IgAN come to medical attention when they have already lost significant kidney function, and it is common to find variable degrees of glomerulosclerosis and/or tubulointerstitial fibrosis in the first kidney biopsy. Thus, in addition to halting the immunologic disease and inflammation, conceptually it makes sense to also target progression of fibrosis. Indeed, many of the approaches discussed above, that is, RAS-blockade, endothelin-A antagonism, and complement inhibition, can be expected to exert antifibrotic actions based on preclinical data.[91,92,98] In addition, new approaches targeting key fibrosis mediators such as transforming growth factor β[99] signaling or platelet-derived growth factor[100] are being considered for clinical trials. At present, however, the key dilemma is the trial endpoint of such studies, as fibrosis progression may not be mirrored by changes in proteinuria or eGFR (e.g., if intact nephrons start to hyperfilter) and as currently, there are no routine methods to visualize and quantify kidney fibrosis. However, this is an active area of research and promising new imaging modalities are beginning to evolve.[101]

A CALL FOR AN INTEGRATED APPROACH

Most adult patients at the time of presentation have already developed more or less advanced CKD, with an eGFR on average between 50 and 60 ml/min at the time of kidney biopsy, meaning that they have lost at least 50% of their nephron mass before a nephrologist has the opportunity to intervene.[2] As the average age at presentation is between 30 and 40 years,[102] and typical life expectancy is 70 to 80 years,[103] there needs to be an immediate focus by the treating nephrologist to introduce therapies to preserve all remaining nephrons if kidney failure is to be avoided in the lifetime of the patient (Figure 2).

Treatment should be directed to those processes driving continued loss of nephrons, which necessitates 2 fundamental therapeutic approaches. The first is to manage the IgAN-specific pathogenic pathways leading to the production of pathogenic IgA, the formation of IgA immune complexes, glomerular IgA accumulation, and consequent activation of proinflammatory and profibrotic pathways within the kidneys.[28] The second is to manage the generic intrarenal responses to IgAN-induced nephron loss, which include the development of glomerular hypertension/hyperfiltration, the tubulointerstitial response to persistent proteinuria, and the initiation and/or worsening of systemic hypertension.[104]

As most patients already have established CKD at diagnosis, an immediate dual approach is warranted to target both the IgAN-specific and generic drivers of continued nephron loss simultaneously. This contrasts with current treatment guidelines that recommend all patients with IgAN commence goal-directed supportive care before disease-modifying therapies are considered. With the approval of new, safer, and better tolerated therapies, and a greater appreciation of the lifetime risk of kidney failure, even when residual proteinuria is less than 1 g/d on optimized supportive care, the "watchful waiting" treatment paradigm may only apply to patients with very mild disease manifestations and a full proteinuria remission within a few weeks in response to early generic CKD therapy. *Post hoc* analyses from existing trials will be critical to identify which patients may benefit from an immediate dual approach. Figure 2 outlines a multitargeted approach addressing nephron loss (IgAN-specific and generic) in IgAN that may be adopted into clinical practice now. There is also emerging evidence that continued maintenance or additional courses of immunomodulatory therapy will be necessary to obtain long-term control of IgAN.[25] However, at present, this is not firmly established, and future research will need to clarify the role of long-term immunomodulatory therapy.

Clinical practice will likely evolve rapidly over the coming 3 to 5 years as new drugs are approved for patients with IgAN. Critical to a reasoned and personalized approach to the treatment of IgAN in the coming years will be the introduction into clinical practice of validated biomarkers to allow treatment individualization with the best possible therapeutic combinations to maintain remission. This will be particularly important when novel therapies that are likely to be expensive and have distinct safety profiles are combined to maximize nephron preservation.

DISCLOSURE

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