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COMMENTARY

An Expert Opinion on Current and Future Treatment Approaches in IgA Nephropathy

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Key Summary Points

Since multiple novel treatments for immunoglobulin A nephropathy (IgAN) have become available in recent years, with many more in development, the 2021 Kidney Disease: Improving Global Outcomes clinical practice guidelines are of limited relevance in modern practice

These novel agents specifically target the underlying disease pathophysiology of IgAN for improved efficacy and safety, but their place in the IgAN treatment approach has not been established

To address the need for updated guidance, this article proposes a novel approach to IgAN treatment based on the author's clinical expertise and interpretation of the available literature, which incorporates the established, recently approved, and late-phase-development pipeline agents

Although this approach may serve as a general guide for clinicians, it is most important to consider the clinical and pathologic characteristics of individual patients when making treatment decisions in IgAN

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INTRODUCTION TO THE MANAGEMENT OF IMMUNOGLOBULIN A NEPHROPATHY

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide, characterized by the presence of immune complexes

containing galactose-deficient (gd)-IgA1 and its associated immunoglobulin G (IgG) or IgA auto-antibodies in the glomerular mesangium [1, 2]. Accumulation of these immune complexes activates cytokine-, chemokine-, and complement-mediated inflammatory processes that produce the key clinical signs of proteinuria, hematuria, and impaired kidney function [1, 3–5], and contribute to disease progression.

Traditionally, IgAN management has involved initial optimization of supportive care to reduce the risk of disease progression. This encompasses controlling blood pressure using renin–angiotensin–aldosterone system (RAAS) inhibitors, implementing lifestyle modifications (e.g., weight management, smoking cessation, exercise, and a low-sodium diet) to mitigate risk factors, and addressing any potentially contributing comorbidities, such as hypercholesterolemia [2, 6]. The first-line RAAS inhibitors typically used in IgAN are angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, but these are not specifically approved for this indication by regulatory authorities [2]. Additionally, sodium–glucose cotransporter-2 (SGLT2) inhibitors are increasingly added to IgAN supportive care regimens following demonstration of their efficacy in reducing the risk of disease progression in patients with chronic kidney disease (CKD) and IgAN [7–9], but they have not yet been studied in an IgAN-dedicated clinical trial.

Patients with IgAN remaining at high risk of disease progression despite optimized supportive care may be candidates for systemic glucocorticoids to reduce glomerular inflammation [1, 2, 10]. Systemic glucocorticoids have long been used off-label in patients with IgAN, and the results of observational studies and meta-analyses of randomized trials generally support this [2, 11]. However, patient characteristics that may increase the likelihood of glucocorticoid treatment response have not yet been identified. Additionally, as observed in the STOP-IgAN and TESTING trials, outcomes with systemic glucocorticoids in IgAN may be inconsistent, and long-term, high-dose treatment may be associated with considerable toxicity [2, 12, 13].

To avoid glucocorticoid toxicity, the immunosuppressives mycophenolate mofetil (MMF) and hydroxychloroquine may be used as steroid-sparing agents in certain populations with IgAN [2, 14]. MMF effectively suppresses antibody production by B cells (acquired immunity), and hydroxychloroquine targets Toll-like receptors involved in the innate immune response [14]. These agents may help inhibit production of gd-IgA1 (hydroxychloroquine) and its auto-antibodies (MMF), which are key for IgAN pathogenesis [14]. In Chinese patients with IgAN, MMF has been shown to effectively reduce proteinuria and to improve renal survival compared with supportive care alone [15–17], although its effect was not superior to that of prednisone in a randomized trial [18]. Additionally, trials in North American and European populations did not consistently show significant benefits with MMF [19–21]. Hydroxychloroquine has demonstrated efficacy only in Chinese patients with IgAN [22, 23], with insufficient evidence in other populations [2]. It is recommended in published guidelines only for Chinese patients remaining at high risk of disease progression on optimized supportive care [2].

Global clinical practice guidelines for IgAN covering these treatments were most recently published in 2021 by the Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group [2]. However, due to the availability of multiple new agents arising from prospective randomized trials, as well as emerging data from observational studies in IgAN [1, 24], application of these guidelines in current clinical practice is very limited. Of note, draft KDIGO guidelines for 2024 were made publicly available for review by healthcare providers in August 2024. Publication of the finalized guidelines is expected in the coming months, although additional regular updates will be needed moving forward to account for the continuously accumulating new evidence in this dynamic therapeutic area.

To address the need for updated guidance on IgAN management in the years following publication of the 2021 KDIGO guidelines,

recent reviews have suggested treatment approaches that incorporate novel therapeutic concepts and newly approved agents [1, 10, 24–26]. Although these algorithms are more relevant to current practice patterns, they may not remain viable with approval of the multitude of IgAN pipeline therapies.

To build on the concepts presented in these publications, this article proposes novel treatment approaches based on the author's clinical experience and interpretation of the available literature, incorporating established, recently approved, and late-phase-development (phase 2 or later clinical trials) pipeline agents for IgAN. The approaches presented here are intended to maintain clinical relevance as new IgAN therapies become available. However, the IgAN therapeutic landscape is rapidly evolving, and recommendations for the use of any agent may change depending on its efficacy and safety in clinical trials, as well as treatment outcomes observed in the real world. To date, most ongoing or completed IgAN clinical trials have short follow-up periods (e.g., ≤ 2–3 years) and rely heavily on surrogate endpoints to indicate treatment efficacy [27–30]. Longer-term follow-up is necessary to assess the therapeutic impact on hard outcomes such as progression to kidney failure or death due to complications of kidney disease [29, 30]. Thus, the therapeutic approach suggested here involves some degree of speculation and may require modification in the future as more research becomes available.

Importantly, although published algorithms may serve as general guides for clinicians, treatment decisions in IgAN should be based on the clinical and pathologic findings of each patient for a personalized medicine approach. The treatment pathway presented here incorporates detailed clinical and histologic criteria to facilitate individualization, but practitioners must still use careful clinical judgment, based on all available evidence, when making any treatment recommendations.

ASSESSMENT OF IgAN DISEASE ACTIVITY

Treatment decisions in IgAN may be influenced by clinical and histologic evidence of inflammatory and/or fibrotic disease in each patient [27]. Novel therapies that specifically target these underlying disease processes (most often, steps in the "multi-hit" model of IgAN pathogenesis [4, 5]) are desirable to prevent disease progression, while minimizing systemic adverse events [1, 24]. However, application of the "multi-hit" hypothesis to clinical therapeutics requires the use of biomarkers, many of which lack validation, to evaluate disease activity [27, 31]. Furthermore, few biomarkers (except complement components C3, C4, and factor H) are approved for commercial use [31, 32]. At present, proteinuria, blood pressure, hematuria, estimated glomerular filtration rate (eGFR), and kidney biopsy findings are most clinically useful to estimate the degree of inflammation and/or fibrosis in each patient [27, 33].

Proteinuria (measured as total urinary protein or total urinary albumin) is an indicator of kidney damage and the strongest known risk factor for disease progression in IgAN [28]; as such, the KDIGO 2021 guidelines recommend RAAS inhibitor treatment for patients with total proteinuria > 0.5 g/day [2]. It should be noted that even proteinuria levels as low as 0.5–1.0 g/day have been associated with an increased risk of disease progression in IgAN [34–36]. However, proteinuria alone may not be the most useful indicator of the level of glomerular inflammation in IgAN, as it is associated with both inflammatory and fibrotic lesions [37]. Hematuria, which results from glomerular damage in IgAN, may be a more reliable biomarker of inflammation, although it is not specific to IgAN [33, 38]. Hematuria that is both persistent and moderate to high-grade [≥ 25 red blood cells (RBCs) per high-power field (HPF) on sediment examination of a fresh urine sample, or hemoglobinuria ≥ 2 + by dipstick] usually indicates glomerular inflammation [33]. Despite the potential utility of these measures, neither should be considered in isolation when making treatment decisions.

Histologic parameters, such as those defined in the Oxford MEST-C classification system, may help to define the degree of inflammation and/or fibrosis at a particular moment in time and predict a patient's likely prognosis [39]. Within the MEST-C system, the presence of crescents on biopsy (C1 or C2 score) is generally accepted as a sign of glomerular inflammation in IgAN and has been associated with a faster rate of kidney function decline [39–41]. Although endocapillary hypercellularity (E1 score) and mesangial hypercellularity (M1 score) have often been associated with glomerular inflammation in IgAN [10, 39, 42], the evidence in the literature is inconsistent [10, 43, 44]. Additionally, although segmental glomerulosclerosis (S1 score) has traditionally been considered a sign of fibrotic disease [10, 42], recent studies suggest that S1 lesions with concurrent diffuse podocyte abnormalities may indicate active glomerular injury and be associated with worse kidney outcomes [42, 45, 46]. Tubular atrophy or interstitial fibrosis (T1 or T2 scores) are associated with IgAN chronicity and indicate an unfavorable prognosis and poor response to immunosuppressive therapy [10, 44, 47].

Although MEST-C lesions may be useful to gauge the level of inflammation and/or fibrosis and inform future prognosis in IgAN [39], this system may not have sufficient granularity to serve as a therapeutic guide. For example, MEST-C does not capture some potentially clinically important histologic lesions in IgAN, like interstitial inflammation [48] or thrombotic microangiopathy [49], because these showed poor scoring reproducibility during their initial evaluation for the classification system [50]. As recognized in the 2021 KDIGO guidelines, the MEST-C classification system was designed as a prognostic tool and not as a vehicle upon which treatment decisions could be reliably based [2, 27]. Of note, only one randomized trial of IgAN therapy (the TESTING trial) has incorporated histologic findings from a recent kidney biopsy (at or near the time of study enrollment) into its eligibility criteria [12]. Instead, MEST-C scores used to qualify patients for clinical trials have often been from kidney biopsies performed years before enrollment. This delay between MEST-C scoring and clinical trial enrollment complicates analysis of the influence of histology on patient outcomes, since histologic characteristics in IgAN can change over time [51]. This limitation is important when considering clinicians' desire to use recent kidney biopsy findings to guide real-world therapy, highlighting a disconnect between clinical trial design and contemporary practice. Refinement of the Oxford MEST-C system to enhance its utility in distinguishing inflammatory and fibrotic disease in IgAN would facilitate clinical decision-making at the time of kidney biopsy.

NEWLY APPROVED THERAPIES FOR IgAN

Several new agents relevant to IgAN pathophysiology have been approved by regulatory bodies since publication of the 2021 KDIGO treatment guidelines. Sparsentan (Filspari®, Travere Therapeutics, San Diego, CA, USA) a dual endothelin A (ETA) and angiotensin II receptor blocker, received full approval by the US Food and Drug Administration (FDA) in September 2024 to slow kidney function decline in adults with primary IgAN who are at risk for disease progression [52]. Targeted-release formulation budesonide (TRF-budesonide; Tarpeyo®, Calliditas Therapeutics, Stockholm, Sweden), a locally acting corticosteroid formulation, received full FDA approval in 2023 to reduce the loss of kidney function in adults with primary IgAN at risk of disease progression [53]. TRF-budesonide was formulated to act on mucosal B cells in Peyer's patches of the ileum with the intent to minimize systemic toxicity while retaining clinical efficacy [53]. Of note, the labels for these two agents do not specify a magnitude of proteinuria warranting treatment [52, 53]. In August 2024, iptacopan (Fabhalta®, Novartis Pharmaceuticals, East Hanover, NJ, USA), an inhibitor of factor B of the alternative complement pathway, received accelerated FDA approval for reduction of proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a urine protein-to-creatinine ratio ≥ 1.5 g/g [54]. The approval followed its demonstration of efficacy and

safety for patients with IgAN having persistent proteinuria despite optimized supportive care after 9 months in the phase 3, randomized, double-blind, placebo-controlled APPLAUSE-IgAN trial [55]. Lastly, dapagliflozin (Farxiga®, AstraZeneca Pharmaceuticals, Wilmington, DE, USA) and empagliflozin (Jardiance®, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA) are SGLT2 inhibitors approved in 2021 and 2023, respectively, to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization in adults with CKD at risk of progression [56, 57].

PIPELINE THERAPIES FOR IgAN

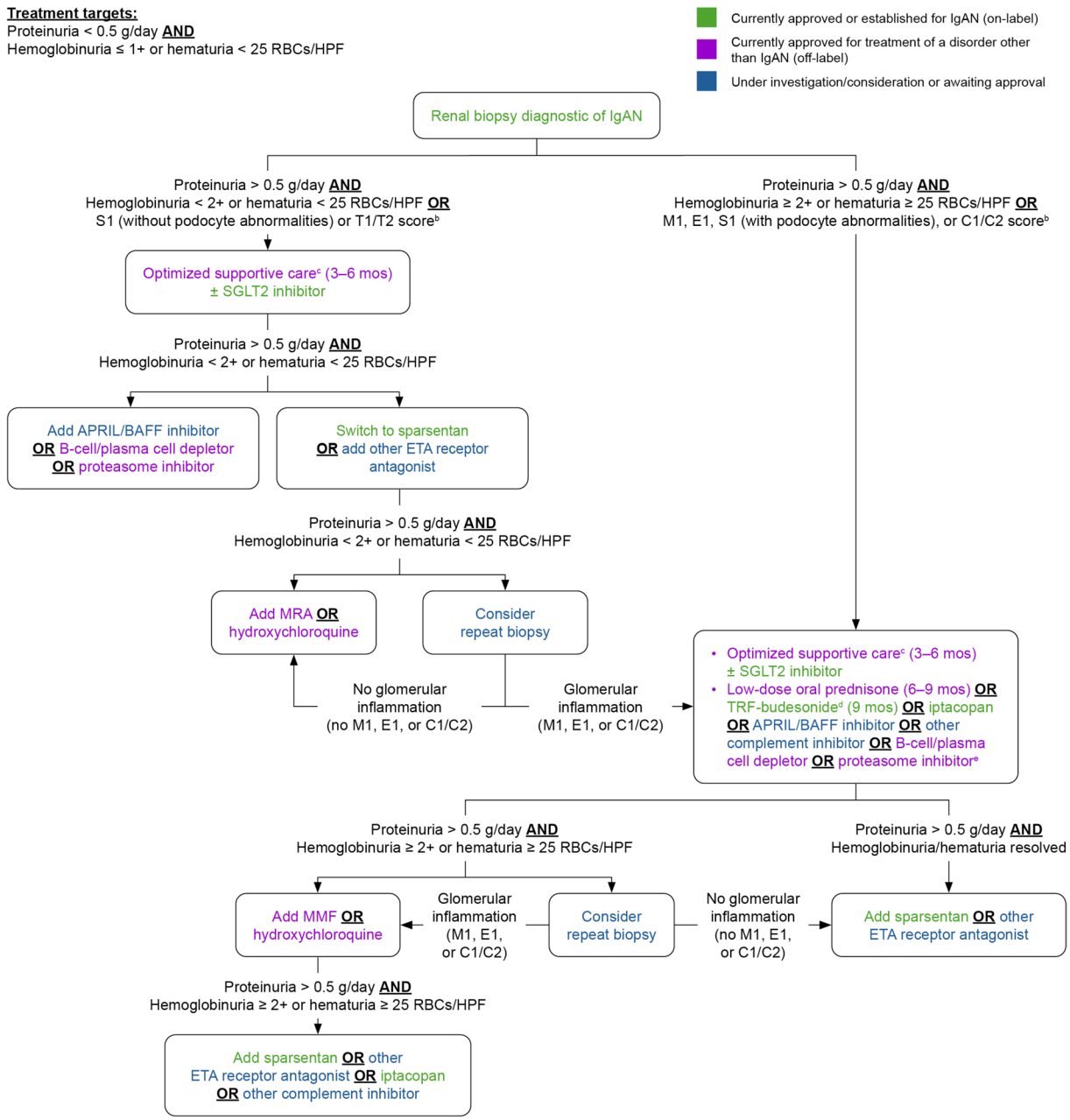
Many other therapies targeting various aspects of IgAN pathophysiology are currently in development. Pipeline drugs in phase 2 or later clinical trials for IgAN include ETA receptor antagonists, complement (C3, factor B, factor D, C5, or C5a receptor) inhibitors, a proliferation-inducing ligand (APRIL) inhibitors, combined APRIL and B-cell activating factor (BAFF) inhibitors, B-cell/plasma cell depletors, and proteasome inhibitors [1, 10, 24]. Fecal transplantation and various chemical agents have also been studied for IgAN [1, 58]. Investigative agents in late-phase clinical trials that have not yet been approved for IgAN or another indication are described in greater detail in Table S1 of the supplementary material [10, 59–85].

Key pipeline therapies for IgAN include two ETA receptor antagonists, atrasentan and SC0062 [10, 24], which prevent activation of the ETA receptor driving inflammation, proteinuria, and fibrosis [68]. Additionally, pipeline complement inhibitors in late-phase clinical development include agents blocking the alternative (IONIS-FB-LRx/RO7434656, vemircopan) or terminal (cemdisiran, ravulizumab) complement pathways, both the alternative and terminal pathways (KP104), complement protein C3 (pegcetacoplan, ARO-C3), or the C5a receptor (avacopan) [10, 24]. Multiple APRIL and/or BAFF inhibitors, which target these cytokines to prevent the differentiation, class switch, and survival of B cells and plasma cells producing gd-IgA1 and its auto-antibodies, are also being investigated for IgAN. These include sibeprenlimab, zigakibart, atacicept, telitacicept, and povetacicept [10, 24]. Preliminary findings of the clinical trials investigating these agents are highly encouraging. Felzartamab (anti-CD38 monoclonal antibody) and bortezomib (proteasome inhibitor) are other key IgAN pipeline agents that function by depleting plasma cells, possibly including those producing pathogenic gd-IgA1 and its auto-antibodies [86, 87]. The interim analysis of a phase 2 study of felzartamab, and a phase 4 study of bortezomib have demonstrated positive results in patients with IgAN [86, 87].

Since gut dysbiosis is hypothesized to promote gd-IgA1 production in IgAN [58, 88], fecal transplantation has also been investigated as a potential treatment option [89]. Results from two phase 2 clinical trials in China evaluating fecal microbiota transplantation in patients with IgAN are pending [60, 61].

Other therapies studied for IgAN include tonsillectomy, fish oil, and immunosuppressive agents, such as cyclophosphamide, the calcineurin inhibitors cyclosporine and tacrolimus, azathioprine, leflunomide, mizoribine, and adrenocorticotropic hormone [1, 2, 90]. Tonsillectomy is routinely performed in Japan based on multiple studies reporting remission of clinical signs, lower relapse frequency, and improved kidney survival with this procedure [2, 91, 92]; however, it is not currently recommended as a treatment for white patients [2]. Of the listed immunosuppressive agents, cyclophosphamide is currently recommended only in patients with rapidly progressive IgAN, which is characterized by quick eGFR decline and extensive crescents on biopsy [2]. The existing evidence for the other agents is not sufficient to support their use at this time [1, 2].

Availability of these many diverse agents, upon FDA approval, will likely alter the IgAN treatment paradigm substantially in the coming years and necessitate further changes to the therapeutic guidelines [24].



PROPOSAL FOR UPDATED TREATMENT APPROACHES IN IgAN

Updated treatment approaches for IgAN that incorporate existing guidelines for the established agents, as well as suggestions for use of the recently approved and pipeline drugs, are proposed in Fig. 1. It is important to note that recommendations for future use of the pipeline agents are speculative at this time, and their placements within the suggested approach are based on the therapeutic targets of each agent, their safety and efficacy in phase 2 or 3 clinical trials, and the patient populations in which each has been investigated.

A kidney biopsy is required to diagnose IgAN [2], but consideration of all histologic, clinical, and laboratory findings is vital to determine an appropriate management strategy for each

◂**Fig. 1** Suggested treatment approach in IgAN[a]. [a]This approach was developed based on author perspectives in conjunction with recent treatment algorithms proposed for IgAN [1, 10, 24–26]. It is intended for use only in adults (≥ 18 years of age) with primary IgAN. It does not apply to patients with extensive crescentic disease (crescents present in > 50% of glomeruli on biopsy), concomitant minimal change disease with nephrotic syndrome, rapidly progressive glomerulonephritis, lgA vasculitis, or type 2 diabetes mellitus. [b]As based on the Oxford MEST-C histologic classification score using a recent (within days to weeks) biopsy diagnostic of IgAN [39]. [c]Optimized supportive care for IgAN involves using maximum tolerated doses of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers for best control of blood pressure and proteinuria, instituting lifestyle changes (weight management, smoking cessation, exercise, and a low-sodium diet), and treating any potentially contributing comorbidities (e.g., hypercholesterolemia). It should be implemented for all patients with proteinuria > 0.5 g/day [2]. [d]Treatment durations have been included for agents for which these are established. Duration of treatment for the other agents will depend on the patient's response to treatment and tolerability of the drug, and further research is required before recommendations can be made. [e]TRF-budesonide may be considered as an option in patients for whom oral prednisone is contra-indicated. [f]When approved, APRIL/BAFF inhibitors, complement inhibitors, B-cell/plasma cell depletors, or proteasome inhibitors may be used as first-line therapies in place of steroids. *APRIL* a proliferation-inducing ligand, *BAFF* B-cell activating factor, *C1* cellular crescents present in ≥ 1 glomerulus, *C2* cellular crescents present in > 25% of glomeruli, *E1* endocapillary hypercellularity present, *ETA* endothelin A, *HPF* high-power field, *IgA* immunoglobulin A, *IgAN* IgA nephropathy, *M1* > 50% of glomeruli showing mesangial hypercellularity, *MMF* mycophenolate mofetil, *mos* months, *MRA* mineralocorticoid receptor antagonist, *RBC* red blood cell, *S1* segmental glomerulosclerosis present, *SGLT2* sodium–glucose cotransporter-2, *T1* 26–50% of the cortical area affected by tubular atrophy or interstitial fibrosis, *T2* > 50% of the cortical area affected by tubular atrophy or interstitial fibrosis, *TRF-budesonide*, targeted-release formulation budesonide

patient. Distinct treatment approaches may be used for patients with predominant evidence of fibrotic/sclerotic disease (Fig. 1, left side) versus glomerular inflammation (Fig. 1, right side), as these phenotypes may convey differing risks of disease progression and responses to immunomodulatory therapy [10, 24].

Consistent with the 2021 KDIGO guidelines, supportive care in the form of RAAS inhibitor optimization and applicable lifestyle changes over 3–6 months should be the first step for all patients with IgAN showing proteinuria > 0.5 g/day [2]. Additionally, based on the reduced risk of disease progression noted in the pivotal DAPA-CKD and EMPA-KIDNEY trials of CKD [7, 8] and a prespecified analysis of patients with IgAN from DAPA-CKD [9], SGLT2 inhibitors may be added to the supportive care protocol for eligible patients.

In patients with persistently elevated proteinuria and/or hematuria despite optimized supportive care, advanced therapy is warranted to prevent disease progression [28, 33]. Of note, Fig. 1 includes both hematuria (based on urine microscopy) and hemoglobinuria (based on urine dipstick) as treatment criteria because urine sediment examination is not always clinically feasible. Multiple approved and/or pipeline agents may be utilized to address these persistent disease signs. For example, patients with proteinuria and minimal hematuria may be switched to an ETA receptor antagonist, or may have an APRIL/BAFF inhibitor, B-cell/plasma cell depletor, or proteasome inhibitor added to their treatment protocol in the future. Hydroxychloroquine, based on its efficacy in certain patient populations with IgAN [22, 23], or mineralocorticoid receptor antagonists, based on the approval of finerenone (Kerendia®, Bayer HealthCare Pharmaceuticals, Whippany, NJ, USA) to reduce the risk of sustained eGFR decline and end stage kidney disease in patients with CKD associated with type 2 diabetes [93], may also be considered as off-label therapies in these patients.

For patients with predominant evidence of inflammatory disease who are at risk of rapid disease progression, supportive care may be instituted concurrently with the appropriate anti-inflammatory medication(s) (Fig. 1, right side). Per the 2021 KDIGO guidelines, initial anti-inflammatory therapy may take the form of low-dose oral glucocorticoids [2]. Alternately, TRF-budesonide may be considered

in patients for whom systemic steroids are contra-indicated [10]. The recently approved complement inhibitor iptacopan may also be particularly useful in patients with evidence of glomerular inflammation for whom steroids are contra-indicated or refused. Those having persistent proteinuria and hematuria despite steroid (low-dose oral prednisone or TRF-budesonide) or complement inhibitor therapy may require long-term management with MMF or hydroxychloroquine, although the use of these drugs is not currently recommended in non-Chinese patients per KDIGO 2021 [2].

Pending their approval, APRIL/BAFF inhibitors, B-cell/plasma cell depletors, proteasome inhibitors, and/or other complement inhibitors may serve as first-line anti-inflammatory agents in place of steroid therapy in high-risk patients, to more specifically target IgAN pathophysiology and avoid the adverse effects associated with systemic glucocorticoids [10].

Since the morphologic features of IgAN can change over time with natural disease progression and/or response to treatment [51], repeat biopsy may be considered in patients with persistent disease signs to determine whether treatment adjustment is warranted. However, further research is needed to validate the clinical utility of repeat kidney biopsy in IgAN [1, 27, 51] and to establish which therapeutics may be most useful for patients with different histologic phenotypes.

To ensure that any ongoing inflammation is addressed and to minimize the risk of disease progression, providers should aim for treatment targets of proteinuria < 0.5 g/day and hemoglobinuria ≤ 1 + or hematuria < 25 RBCs/HPF.

Importantly, the treatment sequence proposed here is intended as a general guide based on the current and anticipated therapeutic landscape in IgAN. This approach is subject to change as IgAN research evolves and new agents are developed, approved, and established.

THE IMPORTANCE OF INDIVIDUALIZED TREATMENT IN IgAN

IgAN is associated with heterogenous clinical presentations and highly variable disease progression [2]; therefore, therapy should be individualized as much as possible to meet each patient's needs and optimize outcomes. Treatment guides, like the one presented in this article, may help to inform the overall approach, but each patient's clinical and pathologic findings and all available therapeutic options should be considered when making treatment decisions to ensure appropriate care [1, 2, 10]. For example, patients with IgAN and comorbidities like diabetes may be treated differently than described here.

Individualized approaches to IgAN treatment will likely become increasingly complex with approval of the multitude of new therapies expected in the coming years. Since the new targeted treatments address separate components of IgAN pathophysiology, combination therapy will likely be necessary for disease control in most patients, although these combinations will vary on a case-by-case basis [1, 10].

The most valuable future research goal for IgAN, in addition to the continued investigation of targeted therapies, will be to establish guidelines to better classify inflammatory and fibrotic disease on biopsy, since this will help to direct the initial therapeutic approach [10]. Additionally, finding reliable serologic or urinary biomarkers of disease activity in IgAN would be beneficial to provide less invasive options for monitoring the disease course and treatment response in each patient. For example, the development of a reliable commercial assay to detect gd-IgA1-specific IgG auto-antibodies would likely transform the treatment paradigm in IgAN [3, 94].

CONCLUSION

The comprehensive IgAN treatment approach proposed here uniquely incorporates existing, newly approved, and anticipated pipeline therapies, with the intent to maintain clinical relevance in the rapidly evolving therapeutic landscape. However, this approach should be used only as a general guide, since individualized treatment considering each patient's needs is most important to optimize therapeutic outcomes.

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Declarations

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