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Advances in the Treatment of  
**IgA Nephropathy**

# Furthering Managed Care Through Advances in IgA Nephropathy Therapy

## Introduction

Immunoglobulin A nephropathy (IgAN), also known as Berger disease, is an autoimmune condition and the most common type of primary glomerulonephritis worldwide.<sup>1,2</sup> IgAN is characterized by the accumulation of IgA complexes in the kidney's glomeruli, which results in progressive damage that can lead to chronic kidney disease (CKD).<sup>3</sup> The deposition of these antibodies triggers chronic renal inflammation that manifests as hematuria and proteinuria.<sup>3</sup> The ongoing glomerular damage disrupts the filtration barrier; over time, scarring of the nephrons occurs, culminating in end-stage renal disease (ESRD).<sup>3</sup> Alarming, 40% to 53% of patients progress to ESRD within two decades of diagnosis.<sup>4,5</sup> This severe progression necessitates interventions such as dialysis or kidney transplantation; either of these interventions significantly impacts the patient's quality of life (QOL) and imposes substantial economic burdens.<sup>3</sup>

The landscape of IgAN treatment is rapidly evolving. As of September 2024, there are ongoing or recently completed phase 3 trials to investigate the safety and efficacy of at least 11 pharmaceutical agents to manage IgAN.<sup>6-16</sup>

This supplement reviews the clinical and economic impact of IgAN, the treatment landscape including guideline recommendations and investigational agents, and managed care considerations for the coming months, when results of several phase 3 trials of investigational agents are anticipated.

## Disease Overview

In the United States, the incidence of IgAN is approximately 1.29 cases per 100,000 individuals, amounting to over 4,000 diagnoses annually.<sup>5</sup> Genetic factors play a crucial role in the pathogenesis of IgAN.<sup>17,18</sup> The serum level of galactose-deficient immunoglobulin A1 (Gd-IgA1) is an inherited trait across various racial and ethnic groups.<sup>3</sup> In most families, IgAN is transmitted in an autosomal dominant manner with incomplete penetrance.<sup>3</sup> Prevalence varies considerably among ethnic groups; it is highest among those of Asian descent, lower among Caucasians, and lowest among persons of sub-Saharan African heredity.<sup>19</sup> The risk of developing IgAN is higher among males; in North America, the prevalence is twice as high among men as it is among women.<sup>19</sup> Confirmed diagnosis of IgAN requires a kidney biopsy; therefore, the true prevalence and incidence may be underestimated due to underscreening in subclinical presentations.<sup>19</sup>

## PATHOPHYSIOLOGY

In IgAN, the core mechanism of disease involves the formation and deposition of IgA complexes in the kidneys, triggering an inflammatory immune response that leads to tissue damage and clinical sequelae such as hematuria and proteinuria.<sup>20</sup> With sustained glomerular injury, chronic inflammation persists and leads to progressive glomeruli necrosis and kidney failure.<sup>3</sup>

The pathophysiology of IgAN has been characterized as a *multi-hit hypothesis* involving

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four steps that combine to result in irreversible damage to the kidney.<sup>20-22</sup> The first *hit* consists of increased circulating levels of Gd-IgA1, which is likely produced due to genetic factors.<sup>21</sup> The second involves the production of glycan-specific IgG or IgA1 autoantibodies; this is usually preceded by an immune-mediated event such as a viral or bacterial infection.<sup>3, 22</sup> Respiratory or intestinal infections may instigate the onset of the disease by triggering the production of these autoantibodies.<sup>3</sup> The third *hit* occurs when immune complexes form in the circulation and reach high serum levels.<sup>22</sup> When the immune complexes cross the glomerular filtration barrier to reach the mesangium, the complement cascade is activated and inflammatory mediators are produced, which constitutes the fourth *hit*.<sup>21, 22</sup> This multimodal attack results in the pathophysiologic environment for kidney injury but offers the potential for researchers and drug manufacturers to intervene at multiple stages in the inflammatory process.

## Disease Progression and Clinical Impact

The progression and clinical impact of IgAN can vary significantly among patients, ranging from a benign, asymptomatic condition to an aggressive form of the disease.<sup>17, 20</sup> In its mildest form, IgAN may be asymptomatic and can even resolve on its own.<sup>3</sup> Clinically, it most frequently presents as microscopic hematuria and moderate proteinuria with preserved kidney function, usually following an infection.<sup>3</sup> Microscopic hematuria with or without concurrent proteinuria may be detected during routine health screenings and urinalysis.<sup>17, 19</sup> Episodic, visible hematuria that manifests as pink or cola-colored urine is the hallmark of the disease.<sup>17, 19</sup> Less commonly, patients might experience nephrotic-range proteinuria that can lead to leg, foot, and ankle edema and foamy urine.<sup>3, 17</sup>

Within 20 years of diagnosis, up to half of patients with IgAN will progress to ESRD.<sup>5</sup> Signs and symptoms of ESRD include hypertension, edema, fatigue, reduced urine output, weight loss, sleep disturbances, difficulty concentrating, darkened skin and muscle cramps.<sup>3</sup> Advanced stages of IgAN can lead to complications that include hypertension, chronic or acute renal disease, cardiovascular disease, nephrotic syndrome and Henoch-Schönlein purpura.<sup>3</sup> Similar to other chronic nephritic diseases, IgAN is associated with an increased risk of mortality.<sup>3</sup> In a 2018

study, researchers identified a 10.1-year reduction in life expectancy relative to predicted age of death at the time of kidney biopsy in patients with IgAN.<sup>23</sup> Not surprisingly, 82.5% of the deaths occurred after progression to ESRD, underscoring the high burden of mortality associated with disease progression.<sup>23</sup>

### Economic Impact

Although economic data on IgAN are limited, the management of ESRD remains a significant cost burden to the U.S. healthcare system, highlighting the need for treatments that slow kidney disease progression and maintain health-related QOL (HRQOL).<sup>24-26</sup> Approximately 15% of the U.S. population, or about 51 million people, are living with CKD.<sup>27,28</sup> Healthcare expenditures for patients with CKD are high compared to those for their matched non-CKD cohorts, with significant increases in costs associated with each advance in the stage of the disease.<sup>24,26</sup> A large-scale retrospective analysis of health plan electronic medical records from 2007 to 2012 in the U.S. demonstrated that for patients with CKD who were younger than 65 years, the average annualized cost per patient increased at least 57% with each CKD stage. For patients 65 years or older, costs increased by at least 68% when disease progressed to ESRD or stages 4 or 5 CKD but by no more than 45% when disease progressed to stage 3a or 3b CKD. Inpatient admissions accounted for the bulk of increased costs in ESRD and stages 3b or 4 to 5 CKD; at least 80% of the cost increase was propelled by rising inpatient costs.<sup>26</sup>

In addition to inpatient expenses, healthcare costs in CKD are inflated by spending for dialysis treatment. In 2019, Medicare costs for CKD were estimated to exceed \$87 billion with more than \$37 billion spent on treating ESRD.<sup>29</sup> Adjusted for inflation to July 2024 costs, this represents Medicare costs of more than \$108 billion for CKD and \$46 billion for ESRD.<sup>30</sup> For patients needing dialysis, the average annual Medicare expenditure is around \$85,000 for outpatient-based hemodialysis and \$69,000 for home-based peritoneal dialysis.<sup>24</sup>

Patients with IgAN experience a substantial symptom burden with pain and fatigue being the most commonly reported issues.<sup>3</sup> In a systematic literature review of IgAN that evaluated eight studies on HRQOL, proteinuria was linked to lower HRQOL and higher rates of mental

depression.<sup>5</sup> Additionally, patients with glomerulonephritis reported poorer mental health compared with healthy individuals.<sup>5</sup>

These findings emphasize the need for early detection and treatment to minimize CKD progression, reduce healthcare costs and improve QOL for patients with IgAN.

### Treatment Landscape

The primary aim of IgAN treatment is to prevent or delay progression to ESRD and preserve kidney function.<sup>17,31</sup> In its 2021 clinical practice guideline for the management of glomerular diseases, Kidney Disease: Improving Global Outcomes (KDIGO) issued guidance for the management of IgAN absent any FDA-approved treatments.<sup>31</sup> Recent advancements in understanding the pathogenesis of IgAN as an immune-mediated disease and the acceptance of surrogate outcomes for accelerated drug approval have led to a rapid increase in clinical trials exploring new therapeutic strategies that target specific disease pathways.<sup>22,32-33</sup> In December 2021 and February 2023, respectively, the FDA granted accelerated approval to budesonide (Tarpeyo; Calliditas Therapeutics) and sparsentan (Filspani; Traver Therapeutics) for reduction of proteinuria in adults with IgAN to reduce disease progression.<sup>34,35</sup> In December 2023, the FDA granted full approval to budesonide to reduce loss of kidney function in all patients with IgAN who are at risk for disease progression; this marked the first drug approval for IgAN.<sup>36</sup> In August 2024, the FDA granted accelerated approval to iptacopan (Fabhalta; Novartis) for reduction of proteinuria in adults with primary IgAN at risk of rapid disease progression.<sup>37,38</sup> In September 2024, the FDA granted full approval to sparsentan to slow kidney function decline in adults with primary IgAN who are at risk of disease progression.<sup>35</sup> As of September 2024, phase 3 trials investigating the safety and efficacy of at least 11 pharmaceutical agents to treat IgAN are ongoing or have been completed.<sup>6-16</sup> In the coming months, results of many of these trials and regulatory decisions will transform the current treatment landscape for IgAN.

### TREATMENT GUIDELINES

The KDIGO 2021 guidelines for IgAN include recommendations for diagnosis, prognosis and treatment.<sup>31</sup>

**Table 1.** Key Guideline Recommendations for the Treatment of IgAN<sup>31</sup>

Management area	Recommendation
Diagnosis	Perform kidney biopsy. Consider that no validated diagnostic serum or urine biomarkers exist. Assess patients for secondary causes.
Disease stratification	Use MEST-C score with revised Oxford classification. Quantify progression risk using the International IgAN Prediction Tool. Consider that no validated diagnostic serum or urine biomarkers exist.
Treatment	Optimize supportive care: Blood pressure management Maximally tolerated dose of ACEi/ARB Lifestyle modification Mitigation of cardiovascular risk

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; IgAN, immunoglobulin A nephropathy; MEST-C, mesangial and endocapillary hypercellularity, segmental sclerosis interstitial fibrosis/tubular atrophy and crescents.

KDIGO emphasizes that kidney biopsy provides the only conclusive evidence to support a diagnosis of IgAN, as no validated diagnostic serum or urine biomarkers exist for the disease apart from estimated glomerular filtration rate (eGFR) and proteinuria (Table 1).<sup>31</sup> Patients with IgAN should be assessed for secondary causes, and their disease should be stratified according to mesangial and endocapillary hypercellularity, segmental sclerosis, interstitial fibrosis/tubular atrophy and crescents (MEST-C) score using what is known as the revised Oxford classification.<sup>31</sup> The work group highlights that the International IgAN Prediction Tool should be used to quantify risk of disease progression and inform shared decision-making with patients.<sup>31</sup>

### Guideline-Directed Treatment

With no FDA-approved treatments at the time of its writing, the 2021 KDIGO guidelines underscore strategies not based upon immunosuppression.<sup>31</sup> Aiming to slow disease progression, this *supportive care* is centered upon lifestyle modification (e.g., exercise, smoking cessation, weight loss, reduction of sodium in the diet), blood pressure control and renin-angiotensin system (RAS) inhibition.<sup>31</sup>

Cardiovascular risk should be addressed, and all patients should have their blood pressure managed, with the KDIGO work group suggesting a target systolic blood pressure of less than 120 mm Hg in most patients.<sup>31</sup> RAS inhibition should be provided to all patients with IgAN who have proteinuria exceeding 0.5 g/day

regardless of hypertension status; therapy with either an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker should be used.<sup>31</sup>

For patients who remain at high risk of progressive CKD (proteinuria >0.75–1 g/day) despite at least 90 days of optimized supportive care, the work group recommends offering participation in a clinical trial and consideration of immunosuppressive therapy, including a six-month course of glucocorticoids.<sup>31</sup> However, glucocorticoids should be given with caution or, in certain situations (e.g., diabetes, obesity, severe osteoporosis), avoided entirely, as they do not impart a proven clinical benefit in IgAN.<sup>31</sup>

### APPROVED AND INVESTIGATIONAL AGENTS IN PHASE 3 TRIALS

As of September 2024, phase 3 trials investigating the safety and efficacy of at least 11 pharmaceutical agents to treat IgAN are ongoing or have been completed (Table 2).<sup>6–16,22,37,39–44</sup> Investigated strategies include use of a targeted-release steroid, anticomplement therapies, modulators of lymphocyte activity and anti-endothelin or anti-aldosterone antagonists.

#### Corticosteroid

The targeted-release formulation of budesonide (TRF-budesonide) has been developed to deliver the drug directly to the gut mucosal level and to target gut mucosal inflammation and synthesis of Gd-IgA1.<sup>6</sup> In the phase 3 NefIgArd trial (NCT03643965), the safety and efficacy of

**Table 2.** Approved and Investigational Agents in Phase 3 Trials for Treatment of IgAN<sup>6-16,22,37,39-44</sup>

Agent	Mechanism of action	Manufacturer	Phase 3 trial(s)
TRF-budesonide	Glucocorticoid	Calliditas Therapeutics AB	NCT03643965 (NeflgArd; completed) NCT04541043 (NeflgArd-OLE; ongoing)
Sparsentan	DEARA	Travere Therapeutics, Inc.	NCT03762850 (PROTECT; completed)
Iptacopan	Factor B inhibitor	Novartis	NCT04578834 (APPLAUSE-IgAN; ongoing)
Ravulizumab	Complement C5 Inhibitor	Alexion Pharmaceuticals, Inc.	NCT06291376 (ICAN; recruiting)
R07434656 (previously IONIS-FB-LRx)	Factor B inhibitor	Roche	NCT05797610 (IMAGINATION; recruiting)
Atrasentan	ET <sub>A</sub> receptor antagonist	Novartis	NCT04573478 (ALIGN; interim analysis completed)
Finerenone	Anti-aldosterone antagonist	Bayer HealthCare Pharmaceuticals, Inc.	NCT05047263 (FIND-CKD; ongoing)
Sibeprenlimab	Anti-APRIL antibody	Otsuka Pharmaceutical Co., Ltd.	NCT05248646 (VISIONARY; ongoing)
Zigakibart (BION-1301)	Anti-APRIL antibody	Novartis	NCT05852938 (BEYOND; recruiting)
Atacicept	Anti-APRIL and -BAFF antibody	Vera Therapeutics, Inc.	NCT04716231 (ORIGIN 3; recruiting)
Telitacicept	Anti-APRIL and -BAFF antibody	RemeGen Co., Ltd.	NCT05799287 (recruiting)

DEARA, dual endothelin receptor/angiotensin II type 1 receptor antagonist; IgAN, immunoglobulin A nephropathy.

oral TRF-budesonide, 16 mg/day, was compared with those of placebo over a nine-month treatment period in patients with IgAN who experienced persistent proteinuria despite optimized supportive care.<sup>6</sup> Patients were then followed for a 15-month observational period off study drug.<sup>6</sup> At two-year follow up, the results showed a treatment benefit with TRF-budesonide over placebo in terms of time-weighted average of GFR, with a GFR change of -2.47 mL/min/1.73 m<sup>2</sup> (95% CI, -3.88 to -1.02 mL/min/1.73 m<sup>2</sup>) in the TRF-budesonide group compared with -7.52 mL/min/1.73 m<sup>2</sup> (95% CI, -8.83 to -6.18 mL/min/1.73 m<sup>2</sup>) in the placebo group, indicating approximately 50% less deterioration of kidney function in the treatment group.<sup>6</sup> TRF-budesonide was granted accelerated approval by the FDA in December 2021 to reduce proteinuria in adults with IgAN and full approval in December 2023 to reduce the loss of kidney function in IgAN.<sup>34,36,39</sup>

## ANTI-ENDOTHELIN ANTAGONISTS

Among anti-endothelin agonists, both a dual endothelin receptor type A and angiotensin II receptor type 1 antagonist (DEARA) and an endothelin receptor type A (ET<sub>A</sub>R) antagonist are being studied for IgAN treatment.

## DEARA

Sparsentan is a nonimmunosuppressive, single-molecule DEARA with high selectivity for the ET<sub>A</sub>R and angiotensin II receptor type 1.<sup>7</sup> The phase 3 PROTECT study (NCT03762850) was a multinational, double-blind, randomized, active-controlled study in which the safety and efficacy of sparsentan versus irbesartan were evaluated in patients with IgAN.<sup>7</sup> The primary end point was proteinuria change at 36 weeks, with patients randomly assigned to receive a target dose of sparsentan, 400 mg, orally once daily or irbesartan, 300 mg, once daily.<sup>7</sup> At the 36-week interim analysis, treatment with sparsentan resulted in a significant reduction from baseline in proteinuria (-49.8%) versus irbesartan (-15.1%), a relative reduction of 41% (least-squares mean ratio, 0.59; 95% CI, 0.51-0.69; p-value<0.0001), which was maintained through 110 weeks of follow-up.<sup>7,45</sup> In September 2024, the FDA granted full approval to sparsentan to slow kidney function decline in adults with primary IgAN who are at risk of disease progression.<sup>35</sup>

## ET<sub>A</sub>R ANTAGONIST

Atrasentan (Novartis), an oral ET<sub>A</sub>R antagonist, is being evaluated in the phase 3 ALIGN study (NCT04573478) in

patients with IgAN.<sup>11,46</sup> The global, randomized, multicenter, double-blind, placebo-controlled trial enrolled approximately 320 patients to evaluate the efficacy and safety of atrasentan versus placebo in patients with IgAN.<sup>11</sup> Participants are being randomly assigned to receive once-daily atrasentan, 0.75 mg, or placebo orally for 2.5 years as they continue to receive a maximally tolerated dose of a RAS inhibitor.<sup>11,46</sup> The primary end point is change in proteinuria from baseline to 136 weeks, and topline results are expected in the first quarter of 2026.<sup>46</sup> In October 2023, Novartis announced that the study met its primary end point at the 36-week interim analysis and plans to review those results with the FDA to allow for a potential regulatory submission for accelerated approval.<sup>46</sup>

### *Anti-Aldosterone Antagonist*

Finerenone (Kerendia; Bayer HealthCare Pharmaceuticals, Inc.) is a nonsteroidal, selective mineralocorticoid receptor antagonist that reduces the risks of CKD progression and cardiovascular events in patients with CKD and type 2 diabetes.<sup>47</sup> The large, randomized, double-blind, placebo-controlled, phase 3 FIND-CKD trial (NCT05047263) is currently underway to evaluate the effect of finerenone in the nondiabetic CKD patient population including individuals with IgAN.<sup>12</sup> An estimated 1,584 participants will be randomly assigned to take finerenone, 10 mg or 20 mg, orally once daily or placebo for 50 months.<sup>12</sup> Mean rate of change in eGFR from baseline to month 32 will be measured as the primary outcome.<sup>12</sup>

### *Anticomplement Therapies*

The complement system is another target for IgAN therapy. Agents targeting the alternative pathway and complement pathway are being investigated.

### ALTERNATIVE PATHWAY INHIBITION FACTOR B INHIBITORS

Iptacopan is a proximal complement inhibitor that specifically binds to factor B and inhibits the alternative complement pathway, a potential target for IgAN pathophysiology.<sup>43</sup> The ongoing phase 3 APPLAUSE-IgAN trial (NCT04578834) evaluates the efficacy and safety of iptacopan in managing IgAN.<sup>8,43</sup> Patients with IgAN have been randomly assigned to iptacopan, 200 mg, or placebo

twice daily orally during a 24-month treatment period; the primary objectives are to establish the superiority of iptacopan over placebo in reducing proteinuria at 9 months and to demonstrate a slowing of the rate of eGFR decline over 24 months.<sup>8,43</sup> In October 2023, Novartis announced positive results from the prespecified interim analysis, indicating that iptacopan demonstrated superiority versus placebo in proteinuria reduction at nine months.<sup>48</sup> In August 2024, the FDA granted accelerated approval to iptacopan for reduction of proteinuria in adults with primary IgAN at risk of rapid disease progression.<sup>37,38</sup> Study completion is expected in 2025.<sup>38</sup>

RO7434656 (IONIS FB-LRx; Roche) is another factor B complement inhibitor and is being studied in the phase 3 IMAGINATION trial (NCT05797610).<sup>10,22</sup> The trial currently is in the recruiting phase. In all, 428 eligible study participants will be enrolled and randomly assigned 1:1 to receive RO7434656 or placebo subcutaneously (SC) on days 1, 15 and 29 and every four weeks thereafter for 105 weeks.<sup>10</sup> The primary end point is change from baseline in 24-hour urine protein-to-creatinine ratio (UPCR) at 37 weeks.<sup>10</sup>

### COMPLEMENT C5 INHIBITOR

Ravulizumab (Ultomiris; Alexion Pharmaceuticals) is a humanized monoclonal antibody that inhibits complement C5; it is approved in the U.S. for the treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, anti-acetylcholine receptor antibody-positive generalized myasthenia gravis, and AQP4 antibody-positive neuromyelitis optica spectrum disorder.<sup>49</sup> Investigators are currently recruiting for the phase 3 ICAN study (NCT06291376), a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ravulizumab in patients with IgAN.<sup>9</sup> Approximately 450 patients will be enrolled and randomly assigned to receive a weight-based intravenous infusion of either ravulizumab or placebo on days 1 and 15 and then every eight weeks thereafter. An interim analysis is planned for week 34 to evaluate change in proteinuria; the final analysis will be conducted at week 106 to evaluate eGFR.<sup>9</sup>

### *Lymphocyte Activity Modulators*

In the treatment of IgAN, the modulation of lymphocyte

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activity is also being evaluated. Strategies include anti-proliferation-inducing ligand (APRIL) antibodies and dual anti-cytokine B-cell activating factor (BAFF) and APRIL antibodies.

### *APRIL Antibodies*

Sibeprenlimab (VIS649; Otsuka Pharmaceutical) is an investigational humanized immunoglobulin G2 monoclonal antibody that reduces the production of Gd-IgA1 by binding to APRIL.<sup>50</sup> In the ongoing phase 3 VISIONARY study (NCT05248646), the effects of sibeprenlimab, 400 mg, given SC every four weeks versus placebo on proteinuria and eGFR are being evaluated in 530 enrolled participants with IgAN.<sup>13</sup> The primary outcome measure is 24-hour UPCR at nine months, with study completion estimated in 2026.<sup>13</sup>

Zigakibart (BION-1301; Novartis) is another novel humanized anti-APRIL monoclonal antibody that is in phase 3 development to manage IgAN.<sup>14,51</sup> The BEYOND study (NCT05852938) is a global, randomized, double-blind, placebo-controlled trial in which investigators will randomly assign approximately 272 patients with biopsy-proven IgAN to receive zigakibart, 600 mg, or a matched placebo SC every two weeks for 104 weeks. The primary end point is the change in proteinuria at 40 weeks.<sup>14</sup>

### *Dual Anti-Cytokine BAFF and APRIL Antibodies*

Atacicept (Vera Therapeutics) is an investigational dual inhibitor of BAFF and APRIL.<sup>41,44</sup> Its safety and efficacy in IgAN treatment is being evaluated in the ORIGIN 3 phase 3 clinical trial (NCT04716231), a multinational, randomized, double-blind, placebo-controlled study that is currently recruiting.<sup>15</sup> An estimated 376 study participants will be randomly assigned 1:1 to receive atacicept, 150 mg, once weekly by SC injection or placebo SC injections once weekly for 104 weeks, followed by a 52-week open-label extension.<sup>15</sup> The primary end point is the change in proteinuria at week 36.<sup>15</sup>

Another dual BAFF-APRIL inhibitor is telitacicept (RemeGen Co.), which is also being investigated for efficacy and safety in IgAN.<sup>16</sup> Investigators involved with a phase 3 trial (NCT05799287) currently are recruiting patients in China.<sup>16</sup> An estimated 308 patients will be randomly assigned 1:1 either to telitacicept, 240 mg, SC given

once weekly (phase A) for 39 doses and then every two weeks (phase B) for 32 doses or to placebo.<sup>16</sup> The primary end points are the change in proteinuria from baseline at week 39 and the annualized eGFR slope at week 104.<sup>16</sup>

### ADDITIONAL STRATEGIES

A phase 3 clinical trial (NCT02682407) for narsoplimab (OMS721; Omeros), a humanized monoclonal antibody targeting the MASP-2 pathway, was terminated for insufficient antiproteinuric effect compared with placebo.<sup>52,53</sup> The phase 3 BRILLIANT-SC trial (NCT02052219) evaluating blisibimod (Anthera), a BAFF antagonist, was withdrawn in 2021.<sup>54,55</sup>

Originally implemented for the treatment of type 2 diabetes, use of SGLT2 inhibitors has demonstrated significant improvements in cardiovascular and renal outcomes for both diabetic and nondiabetic CKD patients, including those with IgAN.<sup>22</sup> A meta-analysis of 13 randomized controlled trials pooled the effects of SGLT2 inhibitors, demonstrating that SGLT2 inhibitors reduced the relative risk of kidney disease progression in patients with IgAN by 49% (95% CI, 0.32%-0.74%).<sup>56</sup> In studies involving large patient populations with IgAN, SGLT2 inhibitors are being investigated for use in kidney disease; these studies include the DAPA-CKD (NCT03036150) and EMPA-KIDNEY (NCT03594110) trials.<sup>57,58</sup>

Additional strategies being investigated in phase 2 trials include MASP-2 inhibition, neutralization of the CD40 ligand, inhibition of factor D, suppression of both the alternative and terminal pathways of the complement system and neutralization of both APRIL and BlyS/BAFF.<sup>22,59-63</sup>

### Managed Care Considerations

Managing IgAN requires comprehensive strategies to increase disease awareness, address its underdiagnosis and improve patient outcomes (Table 3).<sup>3,64-70</sup> If left undiagnosed and untreated, IgAN carries a significant mortality risk; further, it is closely linked to the development of ESRD.<sup>19</sup> Early diagnosis and treatment intervention may delay disease progression, reduce overall healthcare use and extend the lifespan of patients.<sup>23-25</sup> Care management programs that focus on the early detection and treatment of IgAN may reduce healthcare expenditures on renal replacement therapies and improve patient outcomes by slowing disease progression.<sup>64</sup>



**Table 3.** Strategies for Addressing Barriers to IgAN Treatment<sup>3,64-70</sup>

Barriers	Strategies for addressing barriers
Underdiagnosis	Screening tools such as urinalysis and novel biomarkers
Lack of awareness	Provider and patient education on disease prevalence
Early access to supportive care	Stratification of patients based on risk to allow for early medical interventions
Healthcare disparities related to socioeconomic status, sex, age and race/ethnicity	Community-based programs for screening and kidney-focused care plans
Polypharmacy	Pharmacy-based programs supporting medication management
Access to novel therapies	Timely formulary addition of newly approved treatments

IgAN, immunoglobulin A nephropathy.

Community-based screening programs that are integrated into population health interventions can help with early identification of high-risk patients and allow for timely medical interventions to delay CKD progression.<sup>64,65</sup> A screening tool as simple as urinalysis may be used to detect urinary markers suggestive of glomerular injury. For instance, the National Kidney Foundation Kidney Early Evaluation Program uses dipstick urinalysis for hematuria; this method has been shown to reduce costs for mass screenings.<sup>66,67</sup> The use of novel biomarkers (e.g., Gd-IgA1, Gd-IgA1 antibodies and Gd-IgA1 immune complexes) is being evaluated to possibly enhance clinical screening for IgAN.<sup>68,69</sup>

Early risk stratification and intervention including timely access to antihypertensives and supportive care for patients with CKD has demonstrated cost savings and improved patient outcomes in renal disease. While not limited to IgAN, a pilot patient-centered medical home program was implemented by CareFirst Blue Cross Blue Shield of Maryland from 2015 to 2017 to identify high-risk patients and enroll them in kidney-related care plans that provided kidney testing, patient education on lifestyle modifications, disease awareness, nephrologist referral and medication management.<sup>65</sup> The program demonstrated a per-member, per-month cost savings in the first year due to reduced hospital admissions for patients having stage 3 or 5 CKD; authors anticipated future improvements in rates of patients progressing to dialysis over a longer period of time.<sup>65</sup>

Managed care professionals can play a crucial role in medication management of kidney disease.

Polypharmacy is common among CKD and dialysis patients, who may use up to 10 to 12 medications on average; these patients are at increased risk for medication-related side effects and drug interactions.<sup>70</sup> In addition to optimizing pharmacotherapy, managed care professionals can support patient education initiatives to promote lifestyle modifications.<sup>3</sup> Provider knowledge of the safety and efficacy of available treatments is critical to the successful management of renal disease. Timely incorporation of novel therapeutics ensures early patient access to treatment and promotes improved patient outcomes.<sup>3</sup>

## Conclusions

IgAN is the most common cause of primary glomerular disease. It is associated with significant morbidity and mortality with increased risk of progression to ESRD in patients who are left untreated. Significant advances in understanding IgAN as an immune-mediated disease have led to the development of targeted therapies currently being evaluated in clinical trials, potentially expanding therapeutic options for treating IgAN. Armed with the knowledge of investigational therapies and pipeline drugs, managed care professionals can reduce overall healthcare expenditures by addressing gaps in treatment diagnosis, implementing early disease management and improving patient outcomes in the setting of IgAN.

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# Looking to the Future of IgA Nephropathy Treatment

A Q&A with Jonathan Barratt, Ph.D., FRCP

**MHE:** What do you see as the most significant unmet needs in the diagnosis and management of immunoglobulin A nephropathy (IgAN)?

**Barratt:** The development of noninvasive diagnostic tools and early detection methods constitute the most significant needs. Currently, diagnosis relies on kidney biopsies, which are invasive and uncomfortable for patients. There is a critical need for blood or urine biomarkers that can identify IgAN and provide prognostic information about the risk of progressive kidney disease.

Patients with IgAN often present late because the disease is asymptomatic and not routinely screened for. Ideally, a public health-level screening process could identify individuals at risk, allowing for earlier intervention and closer monitoring.

Data from UK Biobank suggest that the majority of IgAN cases remain undiagnosed,<sup>1</sup> a situation likely mirrored in the U.S. Therefore, there is a substantial unmet need for better diagnostic methods to reduce reliance on invasive kidney biopsies and improve patient outcomes through earlier detection and management.

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**MHE:** What are the long-term outcomes of these patients with IgAN, and how often do patients progress to end-stage renal disease?

**Barratt:** Long-term outcomes are often poor, particularly because many patients are diagnosed late in the course of their disease. By the time diagnosis occurs, patients typically have already lost at least half of their functioning nephrons, making treatment challenging. Population-level data from the U.K., Europe and the U.S. highlight that a significant number of these patients will likely develop kidney failure during their lifetime with current treatments.<sup>2</sup>



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Moreover, among patients with IgAN, the U.S. has a higher proportion of patients being diagnosed in late-stage chronic kidney disease (CKD) than that seen in European countries. Specific populations, such as Asian American and Hispanic patients, exhibit a higher risk of having this disease.<sup>2</sup>

Understanding these population-specific nuances is crucial for improving management and outcomes for all patients with IgAN.

**MHE: How does IgAN impact the quality of life of patients?**

**Barratt:** IgAN significantly impacts patients' quality of life, both physically and psychosocially. At the recent IgAN Foundation's annual patient meeting in Austin, Texas, patients shared their experiences of dealing with this disease. A major issue is the lack of accessible, high-quality information about IgAN and the limited expertise among nephrologists, leading to unanswered questions and increased patient anxiety.

Physically, the symptom burden is high and poorly understood. Despite medical textbooks often describing IgAN as being asymptomatic, patients report significant symptoms that many general nephrologists are not well versed in managing.

Psychosocially, the impact is profound, especially since this disease primarily affects young adults. These individuals, often at the start of their careers, planning families and making major life decisions, are suddenly faced with a chronic illness that has no cure and the possibility of ending up on dialysis or needing a kidney transplant. This diagnosis can drastically alter their life plans and aspirations, causing significant mental health challenges.

Furthermore, the disease affects not only the patients but also their families and friends. The emotional and practical support needed places a considerable burden on partners, parents, siblings and extended families, deeply affecting their lives as well.

**MHE: What evidence-based treatments are currently available for managing IgAN?**

**Barratt:** Evidence-based treatments are evolving rapidly. According to the latest KDIGO (Kidney Disease:

Improving Global Outcomes) guidelines, management includes lifestyle modifications such as maintaining an ideal weight, regular exercise, dietary sodium restriction and smoking cessation.<sup>3</sup> Pharmacologically, patients should be on renin-angiotensin system (RAS) inhibitors like ARBs (angiotensin II receptor blockers) to control high blood pressure and reduce proteinuria.

For patients at high risk of progressive kidney function loss, indicated by residual proteinuria above 1 gram per day, the guidelines recommend considering enrollment in clinical trials. Systemic corticosteroids, such as prednisone or methylprednisolone, are an option, although they come with significant toxicity and uncertain long-term efficacy.

Since the publication of the 2021 guidelines, the treatment landscape has significantly advanced. A delayed-release formulation of budesonide, which targets the formation of IgA immune complexes, is now available in the U.S., Europe, China and other regions. Additionally, SGLT2 (sodium-glucose cotransporter-2) inhibitors have been shown to slow kidney function decline and protect against cardiovascular disease.<sup>4</sup> Sparsentan, a dual endothelin angiotensin receptor antagonist, has demonstrated efficacy in slowing kidney function loss beyond what RAS inhibitors alone can achieve.<sup>5</sup>

Looking ahead, we anticipate the approval of two new therapies by the end of this year, with additional treatments expected every 12 to 18 months over the next several years. This expanding arsenal of treatments promises to improve outcomes for patients with IgAN by addressing both the specific pathology of the disease and the general pathways of kidney function loss.

**MHE: What is your approach to managing a patient with IgAN? How do you go about individualizing a treatment regimen for a patient?**

**Barratt:** When managing a patient with IgAN, my primary goal is to stop the formation of IgA immune complexes and prevent them from depositing in the glomeruli, which causes kidney damage. The first drug I reach for is delayed-release formulation budesonide, as it has been shown to effectively address this issue.<sup>6</sup> If the initial kidney biopsy reveals significant inflammation, I may consider a short course (two to four weeks) of systemic

When managing a patient with IgAN, my primary goal is **to stop the formation of IgA immune complexes and prevent them from depositing in the glomeruli, which causes kidney damage.**”

JONATHAN BARRATT, PH.D., FRCP

glucocorticoids to control it, although this is rare in my practice with European ancestry patients.

Simultaneously, I assess the extent of chronic damage and nephron loss. Given that many patients in the U.K. present late, most will need additional treatments to protect the remaining nephrons. This typically includes a RAS inhibitor, an SGLT2 inhibitor, and potentially a dual endothelin angiotensin receptor antagonist like sparsentan.

Prescription practices in the U.K. are guided by specific levels of proteinuria and GFR (glomerular filtration rate), and access to drugs like delayed-release budesonide is currently limited by its approval only for patients with high levels of proteinuria (more than 1.5 g of urine per 1 g creatinine), but this is expected to change. For patients with diabetes, an SGLT2 inhibitor is essential. For others, the choice depends on the degree of kidney function already lost. At the moment, sparsentan is not approved in the U.K.

In summary, my approach involves a combination of targeting the production of pathogenic IgA with delayed-release budesonide, managing any inflammation with systemic glucocorticoids and protecting kidney function with RAS inhibitors, SGLT2 inhibitors and potentially sparsentan, when approved in the U.K., tailored to the individual patient's condition and response to treatment.

**MHE:** How do you monitor disease progression and ensure treatment effectiveness in managing IgAN?

**Barratt:** During follow-up, I monitor disease progression and treatment effectiveness using serum creatinine, eGFR (estimated glomerular filtration rate) and the urine protein-to-creatinine ratio. Blood pressure is also meticulously managed. During the active phase of treatment, I monitor these markers every four to eight weeks, and every three to four months over the long term. While some nephrologists consider hematuria as an indicator, I primarily focus on proteinuria and changes in GFR to guide my clinical decisions.

**MHE:** Given this approach, have you encountered patients who are unresponsive to standard-of-treatment regimens? What are the next steps if patients are not responding to initial treatments?

**Barratt:** Previously, we had limited options and continued with existing treatments. However, with the emergence of new drugs, we now have more choices for patients who are unresponsive to standard regimens. Currently, we use delayed-release budesonide to reduce pathogenic IgA. In the next 18 months, we expect two additional drugs, ataccept and sibeprenlimab, targeting BAFF and APRIL signaling, that are also capable of reducing pathogenic IgA levels.

For glomerular inflammation, systemic glucocorticoids are our primary option, but iptacopan, an alternative pathway complement inhibitor, has just been approved for use in IgAN in the U.S. and will be available in Europe in the future.

In terms of general treatments, we have RAS inhibitors, SGLT2 inhibitors and a dual endothelin angiotensin receptor antagonist. We anticipate the availability of atrasentan, an endothelin receptor antagonist that can be combined with any RAS inhibitor, and potentially the mineralocorticoid receptor antagonist finerenone. Additionally, GLP-1 receptor agonists, particularly relevant for patients with IgAN and diabetes or who are significantly overweight, could be considered.

With these diverse tools, we can tailor treatments based on the patient's phenotype to better protect their kidneys and slow the rate of kidney function loss.

**MHE: What are the greatest challenges in treating patients with IgAN?**

**Barratt:** IgAN affects young people and often requires lifelong medication. This is the greatest challenge. The goal is to switch off the disease permanently, so patients aren't dependent on immunosuppressive drugs indefinitely, as this brings risks such as increased susceptibility to infections and possibly reduced vaccine responses.

Currently, we don't know how long treatment should last. Most trials involve continuous treatment for two years with an open-label extension, but they don't address long-term outcomes after stopping the medication. The key question for nephrologists is: When can we safely stop treatment? Unfortunately, we don't yet have an answer, and it will take years of study to determine.

**MHE: How do we manage the costs of providing expensive lifelong treatment for a rare disease like IgAN?**

**Barratt:** This is a significant concern. With the advent of new treatments, we must consider the right combinations and dosages to optimize efficacy while also considering healthcare costs. Previously, we had no treatments; now, we can explore combinations targeting different aspects of the disease, assuming they are affordable.

For this, we need reliable biomarkers to guide our decisions. Current clinical trials are collecting vast biorepositories of blood and serum, offering an opportunity to develop partner diagnostics. These diagnostics can help us determine early on if a patient is responding to an expensive drug. If they are, we continue; if not, we quickly switch to an alternative.

Collaborating with pharmaceutical companies to develop these biomarker panels is crucial for efficiently managing treatment and ensuring cost-effectiveness.

**MHE: You've mentioned upcoming advancements in IgAN. In your opinion, what are the most promising developments we should look forward to?**

**Barratt:** Delayed-release budesonide is the first drug to reduce pathogenic IgA, marking a significant advancement. Additionally, drugs targeting BAFF and/or APRIL signaling, crucial cytokines in the production of

pathogenic IgA, show promise. Among the five drugs in this category being evaluated, atacicept currently stands out with 18-month follow-up data showing it nearly halts kidney function loss in high-risk patients,<sup>7</sup> bringing loss of kidney function back to the level of physiological aging – a potential game-changer.

Complement inhibitors also offer a new approach to blocking inflammation without the toxicity of systemic steroids. These inhibitors may also help slow kidney function loss beyond glomerular inflammation, impacting tubular interstitial inflammation and fibrosis.

Moreover, endothelin receptor antagonism could inhibit glomerular inflammation and protect mesangial cells from IgA immune complexes.

The potential combination of these different drug classes is exciting as it could allow for shorter treatment durations or lower doses, minimizing side effects. These advancements are going to significantly improve the management of IgAN.

**MHE: Where do you see the field going in the next five years?**

**Barratt:** In the coming years, our focus should be on ensuring access to affordable drugs. With the current and upcoming treatments, we realistically could prevent kidney failure in most patients with IgAN. The key is early diagnosis, allowing us to save more nephrons.

We need to diagnose the disease earlier, perform kidney biopsies sooner and intervene before patients reach advanced stages. This approach represents a significant shift, aiming to diagnose more people and treat them earlier. If we can secure access to these likely expensive drugs, we could potentially prevent kidney failure in any patient diagnosed with IgAN.

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# THE FIRST STEP IN MASTERING MANAGED CARE DECISIONS: EXPERTISE

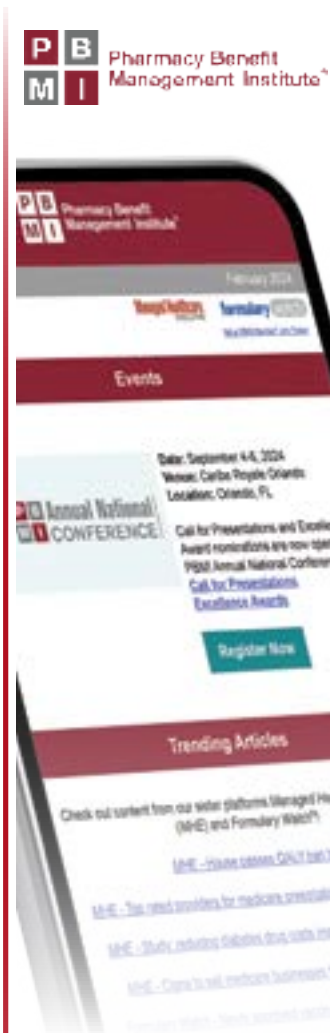
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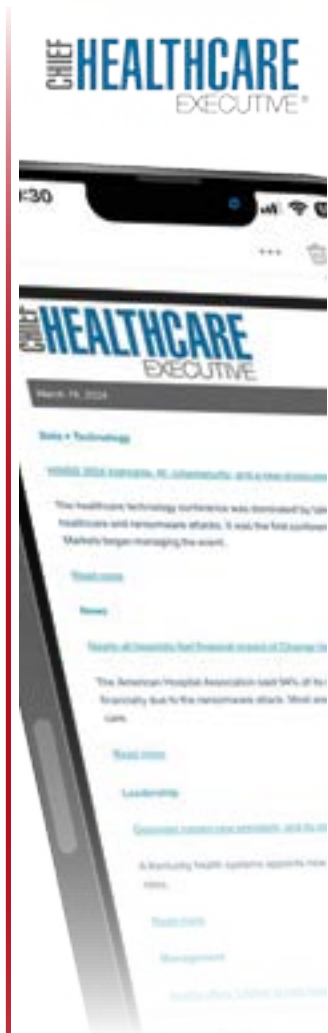
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