Kidney Medicine

# Establishing the Future Direction of Clinical Outcomes in C3 Glomerulopathy: Perspectives From a Patient and a Physician

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Complement 3 glomerulopathy (C3G) is an ultra-rare glomerulonephritis caused by dysregulation of the alternative complement pathway. C3G has an estimated incidence of 1-3 cases per million people in the United States. Diagnosing C3G based solely on clinical and laboratory features is challenging because it mimics several other glomerular diseases; therefore, diagnosis requires a kidney biopsy. In the absence of disease-modifying therapies and optimal patient management strategies, C3G poses a significant physical and emotional burden on patients and caregivers. Common symptoms of glomerulonephritis include fatigue, edema, anxiety, and/or depression, which have profound effects on patients' daily lives. Approximately half of all patients progress to kidney failure within 10 years of diagnosis. Encouragingly, the treatment landscape in C3G is poised to change, with several targeted complement inhibitors in late-stage development. This perspectives article explores a patient's journey in C3G and discusses the current and future status of clinical outcomes and patient management from the viewpoints of a practicing nephrologist and a patient.

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Complement 3 glomerulopathy (C3G) is an ultra-rare complement-mediated kidney disease with an estimated incidence of 1-3 cases per million people in the United States.[1,2] It is a progressive glomerulonephritis, with up to 50% of affected adults developing kidney failure within 10 years of diagnosis.[1-3] Individuals living with C3G experience a high burden of disease, which profoundly affects their daily living and emotional well-being.[4] At present, no disease-specific treatments are available, and an optimal treatment strategy beyond supportive care has not been established.[5]

The clinical trial landscape in C3G has rapidly evolved. Several complement inhibitors are now in late-stage development, offering hope that treatments to target the underlying cause of the disease may soon become available.[6,7] This article is coauthored by a nephrologist and a patient with C3G and explores the patient's journey with this rare disease. The current and future status of clinical outcomes and patient management in C3G are discussed from both authors' perspectives. The patient and physician are both from the United States; their individual perspectives and the patient's journey and treatment outcomes may not represent those of the wider C3G community.

Lindsey is a 44-year-old patient with familial C3G. Her father suffered from kidney disease throughout his life, and at age 9, her son presented with symptoms of glomerulonephritis. Lindsey's journey to a diagnosis of C3G took 23 years. Lindsey is an advocate for the C3G community, a volunteer for the National Kidney Foundation (NKF) and NephCure, and an administrator for a social media patient support group. Her advocacy efforts are largely focused on advancing targeted therapies for C3G and improving access to equitable care.

Anuja Java is an Associate Professor of Medicine within the Division of Nephrology at Washington University School of Medicine in St. Louis and Director of Transplantation at the John Cochran Veterans Affairs Medical Center in St. Louis. She has extensive experience treating patients with glomerular diseases and has participated as a speaker at several patient summits. Her research focuses on the functional consequences of genetic variants in patients with complement-mediated kidney diseases.

## THE JOURNEY TO C3G DIAGNOSIS

### The Physician Perspective

Diagnosis of C3G represents a significant challenge because of the rarity of the disease and its heterogeneous clinical presentation. The term C3G describes a glomerular pathology characterized by predominant C3 deposition on immunofluorescence in the absence or near-absence of immunoglobulin deposits and was first adopted by expert consensus in 2013.[8] C3G occurs because of dysregulation of the alternative complement pathway. It encompasses both dense deposit disease and C3 glomerulonephritis (C3GN), which can be differentiated by electron microscopy.[8,9] Given the progressive nature of C3G,[3,10] early recognition of symptoms and prompt referral to a nephrologist are vital to enable timely management and prevention of kidney failure.

The spectrum of clinical presentation in C3G is vast. It is diagnosed in both children and adults, with some studies reporting a lower mean age at diagnosis for dense deposit

disease.[3,10] Commonly, patients present with the nonspecific symptoms of hematuria and proteinuria and with preserved kidney function; however, patients may also present with nephrotic syndrome and/or a rapidly progressive glomerulonephritis.[2,3,10] There are currently no validated serological or urinary biomarkers to aid in C3G diagnosis,[11] although many patients have low serum C3.[12,13]

Definitive diagnosis relies on a kidney biopsy, with C3G defined as predominant glomerular C3 deposition at least 2 orders of magnitude greater than any other immune reactant as seen by immunofluorescence.[5,8] This definition remains a challenge, as subjectivity influences the grading of staining intensity and C3G "mimics," such as post-infectious glomerulonephritis (PIGN) or immune complex-mediated glomerulonephritis, pose a significant diagnostic dilemma.[1,14]

A diagnostic pathway for C3G is presented in Figure 1. Clinicians should investigate for both genetic (~13% of patients) and acquired (attributed to autoantibodies such as nephritic factors; ~45% of patients) causes.[2,3,15-18] It is noteworthy to mention that patients may carry genetic variants of unknown significance (VUS).[19] The presence of such rare variants is particularly challenging for clinical management; therefore, laboratories specializing in structural and functional analyses of VUS should be contacted to assist in defining the significance of the variant. Adult patients should undergo testing for monoclonal gammopathy, which is more common in those 50 years of age or older.[5] It is speculated that monoclonal immunoglobulins can function like autoantibodies and impair complement regulation.[16] Identification of these patients has therapeutic implications since treatment of the monoclonal gammopathy can result in remission and stabilization of kidney function.[20] Proteolytic digestion on paraffin-embedded biopsy tissue may be needed to unmask monoclonal immunoglobulin deposits.[5,21] C3G may also occur following an infectious episode; a patient's clinical course and laboratory findings over time should ultimately differentiate between PIGN and C3G.[9] Persistent clinical abnormalities, hypocomplementemia, hematuria, proteinuria, or declining kidney function should lead to further investigation for C3G.

The Division of Nephrology, Washington University School of Medicine, encounters ~1-2 new cases of C3G per year; this includes patients who have been diagnosed with C3G in their native kidney, as well as those who have recurred after a kidney transplantation. Some have lost a prior allograft to recurrent C3G because the disease was either not diagnosed in the native kidney or not treated after transplantation because of the absence of effective treatments. Other patients have stable kidney function with minimal proteinuria at diagnosis. Patients are referred to Washington University School of Medicine to assist with specialized complement testing, interpretation of genetic

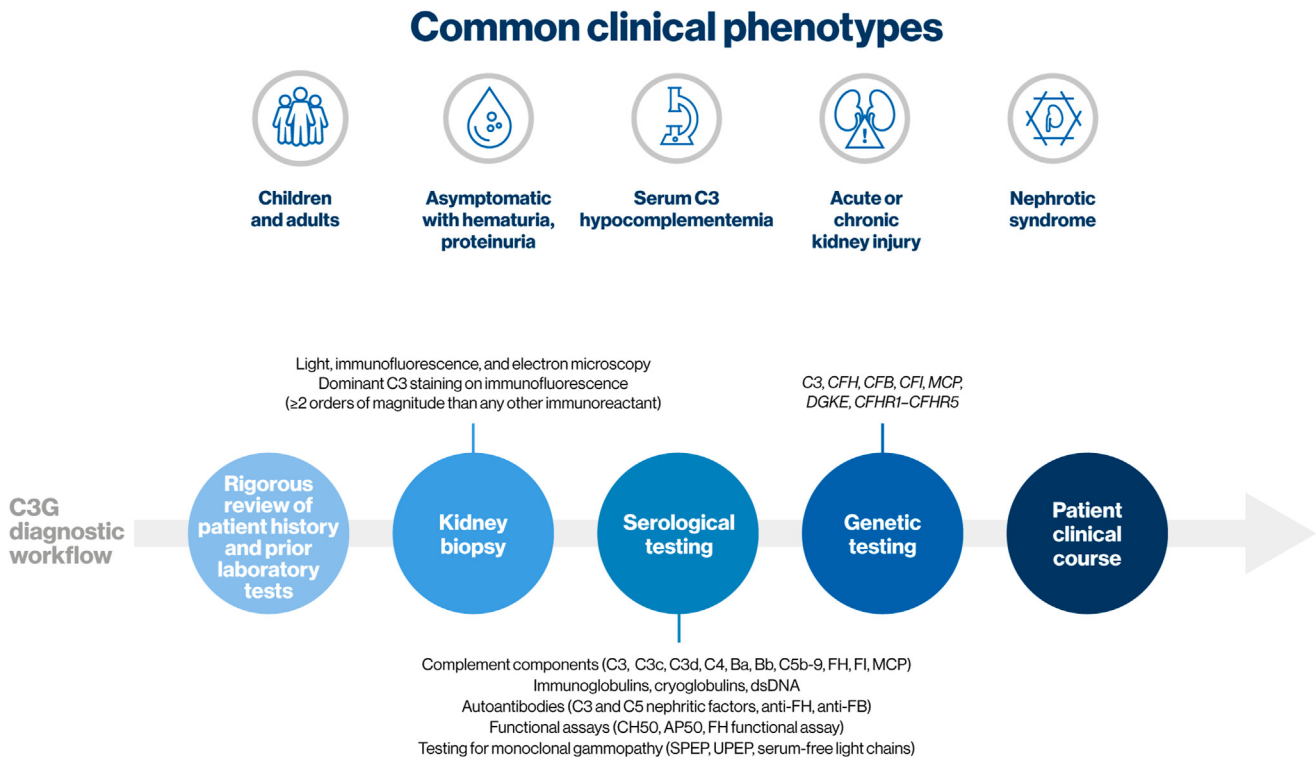


**Figure 1.** The diagnostic workflow in C3G. Abbreviations: AP50, alternative pathway activation 50%; C3G, complement 3 glomerulopathy; CH50, complement hemolytic activity 50%; dsDNA, double-stranded deoxyribonucleic acid; FB, factor B; FH, factor H; FI, factor I; MCP, membrane complement protein; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

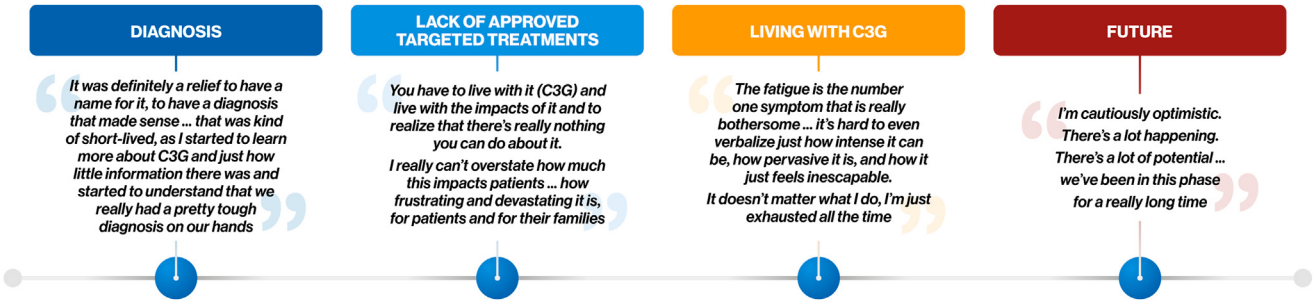


**Figure 2.** A patient's perspective on the C3G journey. Abbreviation: C3G, C3 glomerulopathy.

and complement test results, and to facilitate treatment decisions. The age range of our current cohort of patients is 24-83 years. A subset of these patients developed disease in adolescence and transitioned care to adult nephrology after being followed by their pediatrician for several years.

### The Patient Perspective

*My diagnostic process was very long, drawn out, and complicated. My symptoms were first noticed at around age 11. As a child, I had respiratory issues and experienced joint pain and swelling. My mother noticed a pattern of proteinuria and hematuria in my laboratories. My kidney function was evaluated as my father had undergone multiple kidney transplants, and my grandfather had died of kidney failure. They diagnosed chronic hematuria, and I was monitored every few years by a nephrologist, and my kidney function stayed stable. At age 23, my symptoms escalated during pregnancy. I experienced significant fatigue, my blood pressure was unstable, and I had swelling and increased hematuria and proteinuria. After pregnancy, I stabilized again.*

*About 2 years after my son was born, I started having autoimmune-type symptoms, which led to a diagnosis of systemic lupus erythematosus (SLE). At the time, I had a very high anti-nuclear antibody (ANA) titer, but I haven't had a positive ANA result since. Over the next 2 years, I received treatments for SLE, with little response. This prompted my nephrologist to conduct a kidney biopsy. The initial diagnosis was PIGN, as at that time C3G wasn't really known. Although we knew that it didn't make sense given my family history, we really didn't have a better diagnosis to go with. There was no indication of SLE on the biopsy.*

*At age 34, my kidney biopsy was reevaluated: my kidney function had started to decline, and my son was found to have hematuria and proteinuria. It was then that I received a diagnosis of C3G, which had been defined only a year before (in 2013).*[8] *Initially, I felt relief to have a diagnosis that made sense. We knew I had a low C3 level since my first work-up, but that was short-lived as I started to learn more about just how little information there was (Fig 2). Genetic testing revealed a VUS in the C3 gene (Asp797Val), later characterized by Dr Java and colleagues as a defective variant and confirmed as the familial cause of the disease (unpublished data). VUS designation is a major hurdle in the diagnosis of C3G, particularly for patients who may not yet have severe enough kidney symptoms to merit a biopsy. Diagnosis, monitoring, and ongoing care are almost impossible for those patients to obtain before significant damage occurs—which is really problematic when therapies are starting to become available that could potentially prevent that damage.*

A 2018 NKF Voice of the Patient report detailing an externally led, patient-focused drug development meeting affirmed patients' challenges in obtaining a C3G diagnosis.[4] Meeting participants, including 59 patients and caregivers, described how patients with C3G are often misdiagnosed from childhood, resulting in their kidney symptoms not being treated for many years. Patients expressed frustration at the lack of awareness of the symptoms and etiology of C3G among some health care professionals.[4] The report echoed Lindsey's description of the emotional impact of C3G diagnosis, highlighting how patients experience a sense of anxiety and desperation in receiving a diagnosis for which no disease-modifying treatments are available.

## THE ROLE OF KIDNEY BIOPSY

### The Physician Perspective

C3G is a histopathological diagnosis that requires a kidney biopsy.[5] A kidney biopsy is often needed to establish a diagnosis, guide therapy, and ascertain the degree of active and chronic changes in most kidney diseases.[5,22] Although an invasive procedure, numerous studies have shown kidney biopsy to be safe with a low incidence of major complications.[23-25] Nonetheless, bleeding is the most common clinically relevant complication, and patients may report pain postbiopsy.[26,27] Before biopsy, patients with suspected glomerulonephritis should be assessed for contraindications such as thrombocytopenia, coagulopathy, severe and uncontrolled hypertension, or active urinary tract infection.[26,28] The length of the observation period postbiopsy should consider the individual patient's level of risk and length of travel to the hospital.[26] All patients should provide informed consent.

At Washington University School of Medicine, patients are provided with information on pre- and postbiopsy considerations, including a detailed explanation of the procedure conducted by experienced professionals under ultrasound guidance with local anesthesia. The physician or pharmacist conducts a medication review and ensures that any anticoagulants are held for at least 1 week before biopsy. Laboratory testing at admission includes a complete blood count, kidney function panel, and coagulation profile to determine a patient's risk of complications.

In light of advances in complement inhibitor development, repeat biopsies are often an important tool, particularly in clinical trials, to monitor treatment responses and disease activity. Therefore, the procedure's risk–benefit ratio needs to be carefully considered and explained to the patient. Patient collaboration during the procedure is crucial, given the motion of the kidneys during respiration. Therefore, the use of anxiolytic drugs can be considered in apprehensive patients.[29] Provision of organized recovery areas may further improve patient experiences.

### The Patient Perspective

*Unfortunately, my initial kidney biopsy did not go smoothly. It was not a good experience, and I think I was unprepared for that. After discharge from the hospital, I was in significant pain and developed a fever, and I was treated for a presumed infection. It was a long time before I would even consider another biopsy. I know of other patients who have had similar experiences, but my own lack of experience made it very difficult to advocate for myself. I also wasn't well prepared for the possible complications and didn't understand which symptoms were concerning.*

*The need to undergo repeat biopsies in clinical trials is a topic of specific concern for the C3G community. Patients want to participate in trials due to a desperate need for new treatments, but that may require submitting to several more biopsies than would otherwise be needed. The risks of the procedure, the burden of recovery, etc., weigh heavily on patients with C3G. I believe that, sometimes, there is a disconnect between physicians and patients. For physicians, a kidney biopsy is seen as routine. But for patients, the procedure presents risks and a recovery period that are not at all routine and are disruptive to our lives.*

In agreement, a postmeeting survey summarized within the NKF Voice of the Patient report documented that patients' enthusiasm toward clinical trial participation reduces as the number of biopsies within a trial increases.[4] Patients indicated they would "likely" or "definitely" enter a clinical trial if the option to take antianxiety medication before a kidney biopsy was an option.[4] Further, although limited, the literature confirms a need for patient-focused education before, during, and after the procedure.[30,31]

## CLINICAL OUTCOMES IN C3G: MEASURING THE SEEN AND UNSEEN

### The Physician Perspective

Routine monitoring of kidney function in patients with C3G is critical to assess disease progression and monitor treatment responses. During follow-up, proteinuria, hematuria, serum creatinine, and estimated glomerular filtration rate should be assessed, along with serological markers of complement activity (C3, C4, C3c, and sC5b-9) and complement functional assays (complement hemolytic activity 50% [CH50], and alternative pathway activation 50% [AP50]), when available (Fig 3).[32]

Traditionally, clinical trial endpoints relating to a delay in progression to kidney failure have been used for the registration of novel therapies for glomerular diseases.[33]

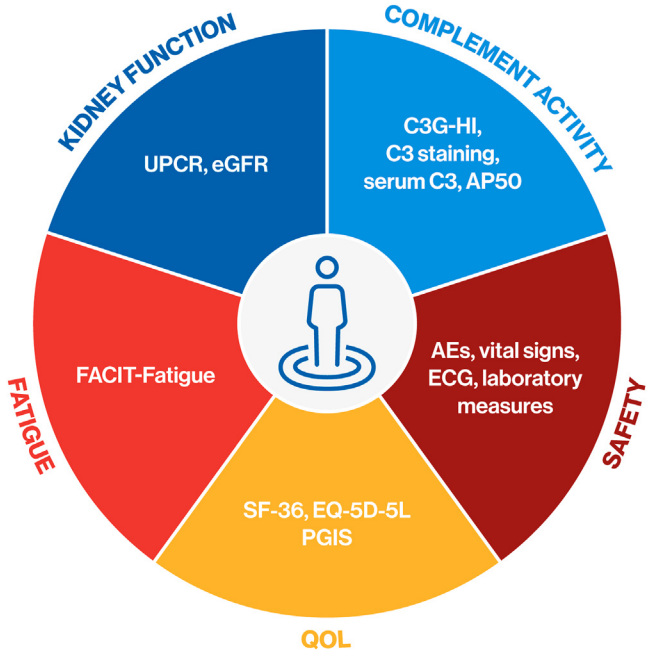


**Figure 3.** Key measurements and clinical outcomes in C3G. Abbreviations: AE, adverse event; AP50, alternative pathway activation 50%; C3, complement component 3; C3G, complement 3 glomerulopathy; C3G-HI, C3G-Histologic Index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol-5 Dimension-5 Level; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue Scale; PGIS, Patient Global Impression of Severity; QOL, quality of life; SF-36, 36-Item Short Form Health Survey; UPCR, urine protein:-creatinine ratio.

However, recent trials of targeted agents in C3G and other complement-mediated kidney diseases have adopted surrogate endpoints such as proteinuria reduction.[6,34,35] Patients with glomerular disease, including those with C3G, are largely affected by symptoms such as fatigue and edema, and may experience anxiety, depression, and social isolation.[4,36] As such, endpoints relating solely to measures of kidney function may not fully capture meaningful effects of novel treatments on this high symptom burden.

The value of patient-reported outcomes is gradually becoming recognized in both research and clinical practice.[36,37] Importantly, patient-reported outcome tools such as the Functional Assessment of Chronic Illness Therapy – Fatigue Scale, 36-Item Short Form Health Survey, EuroQol-5 Dimension-5 Level, and Patient Global Impression of Severity are used in ongoing clinical trials in C3G.[6,38] Incorporation of these tools enables clinicians and researchers to capture patients' perspectives on the impact of therapies on their health in a quantitative way that ultimately might result in improved patient management.

### The Patient Perspective

*My most profound symptoms of C3G are fatigue, swelling, and joint pain, which vary according to how active my disease is. For me, fatigue is the*

*number one symptom. It makes it hard to function in normal life when I'm exhausted all of the time; I get overwhelmed and overburdened (Fig 2). It was particularly intense during pregnancy. I would get up, go to work, and I would come home, lay down, and go to sleep. Sometimes, I would wake up long enough to eat something, and then I would go to bed and sleep the rest of the night. Even outside of pregnancy, this disease creates a level of deep fatigue that I cannot overcome, on top of the usual fatigue that I might otherwise experience with declining kidney function. It is debilitating.*

*The swelling is problematic as well. I'm fortunate compared with many patients with C3G in that mine is not often severe. But it can be difficult. Clothes or shoes may not fit, and, as a schoolteacher, I have to walk a lot, which can be painful.*

*In terms of understanding how C3G is monitored in the clinic, I think, often, there may be a disconnect between what a physician explains and what a patient understands. Many patients may need repeated exposure to information before they are able to remember it. That's even more true when speaking of a very complex disease like C3G. Similarly, there are some online resources available, but that doesn't mean the patient is capable of locating and digesting the information in a meaningful way. The resources that do exist are typically complex and generally not written for patients, making it very difficult to create a deep understanding of the disease.*

The NKF Voice of the Patient report confirmed that more than half of patients or caregivers surveyed described their daily life as being "moderately" or "significantly" affected by C3G. The symptoms reported to most negatively affect patients' daily lives were fatigue, edema, and anxiety and/or depression.[4]

## OVERCOMING CHALLENGES IN C3G: AN EVOLVING TREATMENT LANDSCAPE

### The Physician Perspective

The absence of targeted treatments for C3G poses a significant challenge to physicians, with approximately half of patients progressing to kidney failure within 10 years of diagnosis.[1-3] Current management aims to minimize proteinuria and suppress kidney inflammation; in addition to supportive care with renin-angiotensin system blockade and lipid-lowering therapies, immunosuppression with mycophenolate mofetil (MMF) plus glucocorticoids is recommended as first-line therapy in those with moderate-to-severe disease.[5,39] In patients with progressive disease who fail to respond, Kidney Disease Improving Global Outcomes guidelines recommend consideration of an anti-C5 antibody, but note that the benefits of terminal complement blockade in C3G remain to be established.[5,40,41] Patients who fail to respond to treatment should be considered for clinical trial enrollment.[5] Although kidney transplantation remains an option, C3G has a high risk of recurrence which can lead to allograft loss.[42,43]

Encouragingly, the treatment landscape in C3G is evolving.[6,7] Several complement inhibitors have entered late-stage clinical trials (Table 1),[6,7,44-52] and these therapies are anticipated to become available soon. Nonetheless, with a rare disease, clinical trial enrollment is challenging. The NKF Voice of the Patient report documented that although 60% of meeting participants expressed interest in clinical trial involvement, only 18% had participated in one.[4] Of remaining respondents, 15% had not considered clinical trial participation, and 9% had attempted to participate in a clinical trial but were ineligible.

### The Patient Perspective

*I really can't overstate the impact of having nothing (no treatments) targeted for your disease. It's a big burden to carry, and I think it really contributes to feeling hopeless; it takes a big emotional toll (Fig 2). In terms of treatment outcomes, preserving kidney function is most important to me; it's the number one goal. As far as impacts on daily living, I think being able to control fatigue and edema are probably the most meaningful (outcomes) for me.*

*It is important to realize that my experience with C3G is often not typical. Having hereditary C3G has an impact on how my disease presents, progresses, and is treated. Early on, my symptoms were mild enough that I didn't need to be treated, and my doctors were cautious with prednisone, which I'm grateful for. I was treated with hydroxychloroquine and non-steroidal anti-inflammatory drugs for SLE, which were aimed at my inflammatory-type symptoms. We've tried various other things to control these symptoms, such as MMF, but I was not on that for very long. A few years following my C3G diagnosis, I started on eculizumab treatment.*

*I'm cautiously optimistic about the future treatment landscape in C3G; there's a lot happening (Fig 2). I'm still hopeful, but I try not to be overly hopeful. In terms of an "ideal treatment," if I'm asking for the moon: one we can access and that is affordable, an oral form would be a*

**Table 1.** Targeted Therapies in Clinical Development for C3G

| Investigational Therapy | Administration | Mechanism of Action | Phase (NCT Number) |
|---|---|---|---|
| Iptacopan (LNP023)[6,44] | Oral | Factor B inhibitor | Phase 3 (NCT04817618) |
| Pegcetacoplan (APL-2)[45] | SC infusion | C3 inhibitor | Phase 3 (NCT05067127) |
| Avacopan (CCX168)[7,46] | Oral | C5a receptor antagonist | Phase 2 (NCT03301467) |
| Narsoplimab (OMS721)[47] | IV injection | Anti-MASP-2 antibody | Phase 2 (NCT02682407) |
| KP104[48,51] | SC injection | Bi-functional biologic targeting C5 and factor H | Phase 2 (NCT05517980) |
| ARO-C3[49,52] | SC injection | RNA interference | Phase 1/2a (NCT05083364) |
| NM8074[50,52] | IV infusion | Anti-Bb monoclonal antibody | Phase 1/2 (NCT05647811) |

Abbreviations: C3G, C3 glomerulopathy; IV, intravenous; MASP-2, mannan-binding lectin-associated serine protease-2; SC, subcutaneous.

*great option, as few side effects as possible, and being able to control fatigue and inflammation. There's always concern for safety when you're talking about a new drug. I do think that the more experienced you become as a C3G patient, your tolerance of that risk becomes more because you start to understand that there really aren't other options. Somebody has to do this if we're ever going to have treatments, and for this generation of C3G patients, it's us; we have to do it.*

*In terms of unmet need, I really think children with C3G have the toughest deal. They don't get to make their own decisions and they should be included in their care and their decision-making to some extent. There's a lack of educational resources and inclusion in clinical trials. Safety and long-term consequences are of great concern, but I think the mindset has to shift when it's a matter of a rare disease with no treatment. When you are the parent of a child who is sick and suffering, and there are no treatments available, your view of the risk-to-reward ratio changes.*

## CONCLUSIONS

C3G is an ultra-rare and progressive complement-mediated kidney disease that poses a significant physical and emotional burden on patients and caregivers. Although the lack of targeted therapies and optimal patient management strategies are unmet needs and a source of frustration for both physicians and patients, targeted complement inhibitors in late-stage development for C3G offer hope that disease-modifying treatments may soon become available.

## ARTICLE INFORMATION

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