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Rheumatologic and Immunologic Disease
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From the editor

In this supplement, I have invited 2 experienced clinical nephrologists and medical educators to present overviews of C3 glomerulopathy (C3G) and IgA nephropathy. These 2 disorders are strikingly different in their prevalence. IgA nephropathy is the most common primary glomerulonephritis worldwide, while C3G is rare. They share several characteristics. Both require renal biopsy for definitive diagnosis and both have a variable long-term course, although untreated C3G has a generally poorer prognosis. Progression of both can be slowed by manipulation of renal hemodynamics and, to an often unsatisfying degree, by utilizing broadsword immunosuppression with corticosteroids and other agents including mycophenolate mofetil.

The fascinating observation that further unifies these disorders, as discussed by Mehdi and Taliercio, is that they share as a pathophysiologic mechanism the localized activation of complement via its "alternative pathway." The activation triggers differ in the 2 disorders, but the rapidly growing understanding of this pathway has already led to the implementation of specific therapeutics in clinical trials.

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C3 glomerulopathy

ABSTRACT

C3 glomerulopathy (C3G) is a rare kidney disease that causes kidney dysfunction as a result of dysregulation of the complement system alternate pathway (AP). C3G encompasses 2 separate disorders, C3 glomerulonephritis and dense deposit disease. The presentation and natural history is variable and kidney biopsy is needed to confirm the diagnosis. The overall prognosis is poor with high recurrence rates after transplant. A better understanding of C3G is needed as is high-quality evidence to guide therapy, which currently includes mycophenolate mofetil and steroids for moderate to severe disease, and terminal complement blockade with anti-C5 therapy in unresponsive cases.

KEY POINTS

- C3G affects children and adults and is caused by dysregulation of the complement AP.
- Patients typically present with proteinuria and hematuria, ranging from asymptomatic urinary abnormalities to classic acute glomerulonephritis with kidney dysfunction and hypertension.
- Children and young adults usually present with urinary abnormalities following an upper respiratory tract infection.
- Progression to end-stage kidney disease occurs in up to 50% of patients in 10 years.

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INTRODUCTION

C3 glomerulopathy (C3G) is a group of rare diseases that cause kidney malfunction encompassing 2 entities that likely represent a continuum: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD). These disorders are mediated by dysregulation of the complement system alternate pathway (AP) affecting children and adults. The term C3 glomerulopathy was adopted in 2013.[1] DDD has historically been known as membranoproliferative glomerulonephritis type II, but is now reclassified as complement-mediated membranoproliferative glomerulonephritis.

C3G has a variable clinical presentation. The prognosis is quite poor, with approximately 50% of adults progressing to end-stage kidney disease within 10 years of diagnosis.[1] C3G is notorious for recurrence after transplantation, with poor allograft survival rates. Better understanding of this disorder has recently been attained, paving the way for new therapeutic options.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

The incidence of C3G in the United States is estimated to be between 0.5 and 3 cases per 1 million, with a point prevalence ranging from 14 to 40 cases per 1 million.[1] DDD appears to be less common than C3GN and is usually diagnosed in childhood or early adulthood.[2,3] Patients usually present with proteinuria and hematuria ranging from asymptomatic urinary findings to the classic acute glomerulonephritis with kidney dysfunction and hypertension. Proteinuria can be subnephrotic or nephrotic, and kidney dysfunction can be acute with rapidly progressive glomerulonephritis or subacute. Children and young adults, unlike older adults, usually present with urinary abnormalities following an upper respiratory tract infection. The prognosis for patients with C3G is generally poor, worse for DDD than C3GN, with progression to end-stage kidney disease in up to 50% of patients in 10 years.[2]

Extrarenal manifestations include retinal drusen,[4] similar to those seen in age-related macular degeneration. Acquired partial lipodystrophy may be present,

mostly with DDD, in what is called the Dunnigan-Kobberling syndrome.[5] These patients present with fat loss in the upper part of the body sometimes years before C3G is diagnosed. As is the case with C3G, dysregulated complement activation in the retina and adipose tissue are thought to be the mediator of these extrarenal pathologies.

SEROLOGIC WORKUP AND DIAGNOSIS

The presentation of C3G is quite variable, with considerable overlap with other glomerular pathologies. It remains a histopathologic diagnosis hinging on immunofluorescence and electron microscopy for subcategorization.[1] Serologic workup reveals low C3 levels in around two-thirds of patients with C3G (75% of DDD; 50% of C3GN). Adults are less likely to present with low C3.

Kidney biopsy reveals granular to semilinear deposits that are C3 dominant, at least 2 orders of magnitude greater intensity than other immunoreactants. Subclassification of C3G to C3GN or DDD requires electron microscopy, which in DDD would highlight "sausage-shaped," intensely electron-dense, osmiophilic deposits within the lamina densa of the glomerular basement membrane. Electron microscopy in C3GN shows lower intensity (or less intense) electron-dense, hump-like deposits in the mesangium, subendothelial, and sometimes subepithelial spaces. Mass spectroscopy of these deposits can reveal components of the AP.[1,3] It is noteworthy that classic subepithelial humps identical to those seen in post-streptococcal glomerulonephritis can be seen in both DDD and C3GN, making pathologic distinction between these entities impossible.

While immunofluorescence and electron microscopy are diagnostic of C3G, light microscopy findings are highly variable, showing mesangial hypercellularity, membranoproliferative, endocapillary proliferative, sclerosing, or more rarely, exudative and crescentic patterns.[1,3] Patterns seen on light microscopy can suggest disease severity, predict prognosis, and provide guidance in terms of the need for immunomodulatory therapy.

When dealing with a C3-dominant kidney process, an infection-related glomerulonephritis must be excluded. While most cases of infection-related glomerulonephritis are immune complex-mediated, showing immunoglobulin (Ig) M, IgG, or IgA positivity in addition to C3, some cases can be C3 dominant. In such cases, it is indistinguishable from C3G pathologically, and an infectious process should be excluded. Persistent or worsening kidney dysfunction after resolution of an infectious process with persistent low C3 should raise the suspicion for C3G, with consideration for repeat kidney biopsy after 12 weeks to exclude C3G.

PATHOGENESIS AND EVALUATION

C3G is driven by dysregulation and excessive activation of the AP resulting in deposition of complement components in the glomerulus.

The AP is constitutively active with a low-level spontaneous hydrolysis of C3. This leads to the formation of C3 convertase (C3bBb), which then leads to robust amplification of the complement response, cleaving more C3 and ultimately generating the C5 convertase (C3BbC3b). These convertases cleave C5 into C5a, a powerful anaphylatoxin, and C5b, which initiates assembly of C5b-9, the membrane attack complex. Activation of the AP is tightly controlled via regulators of complement activation, mainly factor H, which facilitates the decay of the active C3 and C5 convertases. Other regulators of complement activation include factor I- and factor H-related protein as well as membrane cofactor protein, complement receptor 1, and decay-accelerating factor.[1]

AP dysregulation results from genetic or acquired factors. Genetic factors are involved in around 25% of patients with C3G, mainly in C3 and factor B proteins,[6] rendering the active convertases resistant to hydrolysis. More commonly, AP dysregulation results from autoantibodies to various complement proteins. The most common autoantibody is C3 nephritic factor, which stabilizes C3 convertase. Autoantibodies are present in up to 80% of patients with DDD and 50% of patients C3GN.[7] C5 nephritic factors are also common, stabilizing the C5 convertase with ongoing AP activation.

Patients diagnosed with C3G should have a complete evaluation for complement abnormalities, including levels of factors H, B, and I, membrane cofactor protein, and soluble membrane attack complex. Complement-directed antibodies should be checked, in addition to a complete genetic evaluation of the AP components. Some specialized laboratories offer panels, such as Cincinnati Children's Hospital Medical Center and Mayo Clinic. Identifying the driving pathology can have important clinical and therapeutic implications.

A monoclonal gammopathy should be tested for in all adults with C3G. Although the paraprotein may not be evident on the kidney biopsy, it may target regulatory elements of the AP leading to complement

activation and C3G. Treatment should be directed toward eliminating the hematologic clone.[8]

TREATMENT

Nonimmunomodulatory therapy

There currently is no uniform therapy for C3G, but several compounds in clinical trials are showing promise. Currently, patients with relatively mild disease (preserved kidney function and proteinuria less than 1.5 g per 24 hours) should be managed with nonimmunomodulatory therapy. Unless a contraindication exists, all patients with C3G should receive antiproteinuric therapy by inhibiting the renin-angiotensin system. This is consistent with the 2021 Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[9] Interestingly, renin has been shown to facilitate the enzymatic cleavage of C3 to activate the AP. Aliskirin, a renin inhibitor, was shown to modulate that effect[10] and is now being investigated compared with enalapril in an ongoing clinical trial. Other conservative measures include dietary sodium and animal protein restriction, blood pressure management, and cholesterol management. Sodium-glucose cotransporter inhibitors have become a pillar of conservative anti-proteinuric therapy in patients with glomerular diseases. Although data are wanting in C3G, unless a contraindication exists, these agents should be utilized.

Nonspecific immunomodulatory therapy

Patients with moderate to severe disease should be considered for treatment with immunomodulatory therapy. The KDIGO guidelines suggest initial therapy with mycophenolate mofetil (MMF) plus glucocorticoids in these patients.[9] This is based on observational studies showing higher rates of remission in patients treated with MMF plus steroids than with other forms of immunosuppression. Remission rates with MMF ranged between 36% and 65%, with around one-third of patients relapsing after therapy discontinuation.[11,12] Patients who had positive C3 nephritic factors appeared to respond better to MMF therapy. Given the lack of high-grade evidence to guide therapy, we encourage patients to enroll in clinical trials.

Plasma exchange or infusion is another immunomodulatory therapy used in patients with C3G. Robust data are lacking, with supporting evidence coming from case reports. Positive outcomes were reported only in patients with factor H abnormalities (genetic variant or an acquired deficiency).[13] It is the infusion of healthy factor H, as opposed to antibody removal, that is thought to be helping these patients. The use of plasma exchange is reserved for severe cases (with factor H pathology) not responding to initial treatment. No data exist to guide the duration of therapy. If patients respond, therapy could be chronic.

Specific anticomplement therapy

The KDIGO guidelines suggest terminal complement blockade with eculizumab (anti-C5 monoclonal antibody) in patients who fail to respond to MMF.[9] Failure to respond is indicated by worsening kidney function or proteinuria or both. Data for this strategy are not robust, with less than 50% of patients responding to eculizumab.[14] Le Quintrec et al found that patients presenting with lower glomerular filtration rate, more rapidly progressive disease, and more extracapillary proliferation were more likely to respond. This modest efficacy has been hypothesized to be related to the fact that eculizumab fails to impact upstream C3 dysregulation[1] Multiple agents targeting upstream elements of the AP are currently in advanced clinical trials with encouraging preliminary data. These include a factor B inhibitor (iptacopan),[15] factor D inhibitor (danicopan),[16] and a C3 inhibitor (pegcetacoplan). An oral C5a receptor 1 inhibitor (avacopan) is also in clinical trials. Currently, patients not responding to initial therapy or having severe disease are recommended anti-C5 therapy, but we favor enrolling these patients in available clinical trials. Meningococcal vaccination is imperative for patients treated with anti-C5 therapy, ideally 2 weeks before the first dose. Fatal meningococcal infections have been reported.[17] We also suggest long-term daily antimicrobial prophylaxis.

CONCLUSION

C3G is a rare kidney disease resulting from dysregulated AP. Presentation is quite variable and kidney biopsy is necessary to confirm the diagnosis. Natural history varies, with an overall poor prognosis and high rates of recurrence after transplant. High-quality evidence is lacking, but therapy with MMF and steroids is currently recommended for moderate to severe disease. Terminal complement blockade with anti-C5 therapy is reserved for unresponsive cases, with modest efficacy. Multiple trials of proximal complement blockade are ongoing. It is highly likely that C3G is more than a single disease entity. As we better stratify and understand our patients based on complement activity and underlying genetic predispositions, and as new drugs become available, we hope to be able to provide better personalized care for our patients.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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IgA nephropathy

ABSTRACT

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis in the world. The etiology is unknown but a dysregulated T-cell immune response to viral, bacterial, and food antigens activating mucosal plasma cells to produce polymeric IgA has been proposed. No serological test exists to diagnosis IgAN. A definitive diagnosis requires kidney biopsy which is not always necessary. Kidney failure occurs in 20% to 40% of patients within 10 to 20 years.

KEY POINTS

The classic presentation of IgAN includes gross hematuria after an upper respiratory infection.

Lifestyle modification and maximal renin-angiotensin system blockade, especially if proteinuria is present, is recommended for all patients.

Prognostication tools are available to assess for progression to kidney failure and to balance the risk and benefits of non-immunosuppressive and immunosuppressive therapies.

New therapies are emerging though long-term data evaluating estimated glomerular filtration rate preservation are needed.

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INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis in the world, with an overall incidence of 2.5 per 100,000 per year.[1] It was first identified in 1968 by French nephrologist Dr. Jacques Berger and therefore was historically referred to as Berger disease.[2] IgAN was initially considered a benign self-limited disease, but epidemiological studies suggest that 20% to 40% of patients will develop kidney failure within 10 to 20 years of diagnosis.[3–8] IgAN has a wide spectrum of clinical manifestations and outcomes, attributable to practice patterns relating to obtaining screening urinalysis and kidney biopsy, environmental and genetic factors, and treatment. There are therapeutic agents under investigation that show promise.

EPIDEMIOLOGY AND PATHOGENESIS

Individuals of European and East Asian ancestry are at higher risk for IgAN. Onset is typically during the second and third decades with a 2:1 male-to-female predominance in the United States.[9] IgAN is considered to be sporadic, although genome-wide analysis studies have identified non-Mendelian polymorphisms in the major histocompatibility complex (MHC) and non-MHC risk alleles.[10] The etiology of IgAN is unknown, but has been attributed to a dysregulated T-cell immune response to viral, bacterial, and food antigens activating mucosal plasma cells to produce polymeric IgA.[11]

IgA1 is structurally different from IgA2, in that it contains a disulfide hinge region on the heavy chain and contains an oxygen-linked glycosylation of serine and threonine.[12] This hinge region has a high affinity toward type IV collagen, the main component of the glomerulus. Production of galactosylated deficient IgA1 (Gd-IgA1) and formation of an IgG anti–Gd-IgA1 results in antigen-antibody complexes. Complexes deposit in the mesangium and activate the alternative and lectin complement pathways depositing C3.

CLINICAL MANIFESTATIONS

Clinical manifestations of IgAN range from asymptomatic microscopic hematuria to rapid progressive glomerulonephritis. Classicly patients present with gross hematuria following an upper respiratory tract infection. Others present with microscopic glomerular hematuria, non-nephrotic range proteinuria, and decreased kidney function. Less commonly, patients present with rapid progressive glomerulonephritis manifesting with acute kidney injury and hypertension, with or without nephrotic syndrome.

LABORATORY AND HISTOLOGIC FEATURES

Unfortunately, there is no serologic test to diagnosis IgAN, including serum levels of Gd-IgA1 or IgG anti–Gd-IgA1 antibodies. Screening serologies are negative and complement levels will be normal. A definitive diagnosis requires kidney biopsy, which may not be necessary in all cases. Histologic findings range from mild mesangial expansion to diffuse proliferation with crescents. Immunofluorescence microscopy will have dominant or codominant IgA mesangial staining with lesser degrees of IgG and IgM. C3 is often co-localized, suggesting activation of the alternative complement pathway. Mesangial and occasional subendothelial deposits of IgA will be seen by electron microscopy.

PROGNOSTICATION OF KIDNEY DISEASE PROGRESSION

Clinicians have used various clinical surrogates to prognosticate patients' progression to kidney failure. Risk factors include proteinuria greater than 0.5 to 1 g/day, hypertension, reduced glomerular filtration rate, and persistent microscopic hematuria. Many of these surrogates impact a clinician's decision whether to biopsy a patient with suspected IgAN. The International IgA Nephropathy Network and the Renal Pathology Society developed the Oxford MEST-C pathologic scoring system, which should accompany all kidney biopsy reports to help predict kidney outcomes in patients with IgAN.[13] The score is based on the presence or absence of the following 5 histologic features:

- Mesangial IgA deposits
- Endocapillary hypercellularity
- Segmental glomerulosclerosis
- Tubular atrophy/interstitial fibrosis
- Crescents.

Kidney biopsies that reveal chronic lesions (higher S and T scores) are probably less likely to be amendable to immunosuppressive therapy. The International IgA Nephropathy Prediction Tool (https://ukkidney.org/resource/international-iga-nephropathy-prediction-tool), an online calculator derived from a cohort of 2,781 patients with IgAN confirmed by kidney biopsy, may be used to impute clinical data and MEST-C scores to predict the risk of a 50% decline in estimated glomerular filtration rate (eGFR).[14]

DIFFERENTIAL DIAGNOSIS

Mesangial IgA deposition has been identified in up to 16% of renal allograft donors.[15] IgA is primarily catabolized by hepatocytes, and chronic liver disease may lead to increased circulating IgA1 and increased nonpathogenic mesangial deposition. *Staphylococcus aureus* infection-associated glomerulonephritis is a well-described entity that may have similar clinical characteristics, including multisystem small-vessel vasculitis manifestations and kidney biopsy pathology.[16] Assessing for occult infection is critical when considering immunosuppressive therapy for patients with presumed primary IgAN. IgA vasculitis (formerly referred to as Henoch-Schönlein purpura) is a systemic small-vessel vasculitis associated with leukocytoclastic vasculitis of the skin, abdominal pain, and arthralgias. Although kidney biopsy would reveal the same histologic finding of IgAN, many experts believe that the epidemiology, prognosis, and treatment are different.

NONIMMUNOSUPPRESSION MANAGEMENT

Conservative strategies that may reduce disease progression include sodium intake of less than 2 g/day, weight management, smoking cessation, regular activity, and avoidance of nonsteroidal anti-inflammatory medications. Clinicians should target blood pressure less than 130/80 mm Hg and proteinuria to less than 1 g/day or lower if possible, using maximal renin-angiotensin system (RAS) blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Fish oil greater than 3 g/day has been touted as beneficial with little known downside, but results are conflicting, so it should not be used in place of proven therapies.[17]

Sodium-glucose cotransporter 2 inhibitors have recently been approved by the US Food and Drug Administration (FDA) for patients with or without diabetes and with an eGFR greater than or equal to 25 mL/min/1.73 m^2 of body surface area after showing reductions in chronic kidney disease (CKD) progres-

sion in the DAPA-CDK (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) study.[18] The study randomized 270 patients with IgA nephropathy. Subgroup analysis demonstrated that dapagliflozin decreased the risk of CKD progression by 1.2 mL/min/1.73 m^2 per year and reduced the urine albumin-creatinine ratio by 26%. These benefits were confirmed in a meta-analysis of 817 patients with IgAN enrolled from the EMPA-Kidney (Study of Heart and Kidney Protection With Empagliflozin) trial, which demonstrated a 44% relative risk reduction in kidney disease progression.[19]

On February 17, 2023, the FDA granted accelerated approval for sparsentan, a single-molecule dual endothelin-1 angiotensin receptor II antagonist, for reduction in proteinuria in patients with IgAN at high risk of progression based on the phase 3 Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy (PROTECT).[20] Entry criteria required patients to have a urine protein-to-creatinine ratio greater than 1.5 g/g. Sparsentan reduced proteinuria by 45% compared with 15% in the irbesartan group. Prescribers are required to meet FDA Risk Evaluation and Mitigation Strategy requirements, and the drug's approval may be contingent on the demonstration of slowing CKD progression.

IMMUNOSUPPRESSION

A trial of oral glucocorticoid may be indicated if greater than 1 g of proteinuria persists for 3 or more months after maximal non-immunosuppressive therapy has been tried or the patient is already at high risk of kidney disease. Glucocorticoid therapy and other immunosuppressive medications have been studied yielding conflicting results. The STOP-IgAN (Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy) trial enrolled 337 patients with IgAN to supportive care (n = 80) or cyclophosphamide 1.5 mg/kg/day for 3 months, followed by azathioprine 1.5 mg/kg/day for 36 months, plus oral prednisolone 40 mg/day with taper (n = 82).[21] Patients with CKD stage 1 to 3 and proteinuria less than 3.5 g/day treated with immunosuppression had no difference in eGFR decline and were at higher risk for severe infections.

The TESTING (Therapeutic Effects of Steroids in IgA Nephropathy Global) trial randomized 503 patients to oral methylprednisolone initially 0.6 to 0.8 mg/kg/day (maximum 48 mg/day), weaning by 8 mg/day/month vs placebo and showed a reduction of kidney composite outcomes including kidney failure or death due to kidney disease.[22] Unfortunately, the incidence of serious adverse events was increased in the high-dose methylprednisolone group.

Gut-associated lymphoid tissue and Peyer patches located in the ileum are a source of Gd-IgA1 antibody production. A targeted-release formulation of oral budesonide, postulated to release drug in the ileum, has been granted FDA approval under the accelerated approval program for patients with IgAN who are at high risk for progression (urine protein-to-creatinine ratio greater than or equal to 0.8 g/g or proteinuria greater than or equal to 1 g per 24 hrs). The NeflgArd Part A trial randomized 199 patients with IgAN on maximal RAS blockade and targeted-release formulation budesonide 16 mg/day or placebo for 9 months and demonstrated a 27% reduction in proteinuria and eGFR preservation difference of 3.87 mL/min/1.73 m^2 compared with placebo.[23] As expected, there were more side effects in the treatment arm, and despite a targeted-release steroid, patients experienced systemic glucocorticoid-related adverse effects. As a precondition of the accelerated approval program, part B of the trial will need to confirm preservation of kidney function assessing a GFR-based end point over 2 years, with final results expected in 2023 (NCT03643965).

A randomized trial of mycophenolate mofetil in 170 patients with IgAN at high risk of kidney function decline reported primary composite outcome events occurred in 6 patients (7.1%) in the mycophenolate mofetil group compared with 18 patients (21.2%) in the standard-of-care group.[24] Patients who discontinued mycophenolate mofetil in post-trial follow-up had eGFR loss of 6.1 mL/min/1.73 m^2 compared with an eGFR loss of 2.9 mL/min/1.73 m^2 in the standard-of-care group. There was no difference in serious adverse events. In small trials, calcineurin inhibitors, rituximab, cyclophosphamide, and hydroxychloroquine provided no clear benefit.

The alternate and lectin pathways are hypothesized to be involved in the pathogenesis of IgAN as evidence of C3 deposition. Avacopan, an oral C5a receptor inhibitor, has demonstrated encouraging results in reducing proteinuria in a small phase 2 pilot study of 15 patients with high-risk IgAN on maximal RAS inhibition.[25] In a phase 2 study of iptacopan, a factor B inhibitor, 112 patients with IgAN were randomized to placebo or various doses of iptacopan. Investigators reported a 23% reduction in proteinuria in patients taking high-dose iptacopan compared with placebo at 90 days.[26] We anxiously await the phase 3 trials results (NCT04578834).

CONCLUSION

IgAN has a wide spectrum of clinical presentations and 20% to 40% of patients will develop kidney failure within 10 to 20 years of diagnosis. All patients should be treated with lifestyle modification and maximal RAS blockade, especially if proteinuria is present. Prognostication tools are available to balance the risk and benefits of non-immunosuppressive and immunosuppressive therapies. New therapies have been granted FDA accelerated approval, but long-term data regarding preservation of eGFR are still needed. Finally, IgAN is receiving the attention it deserves, and the nephrology community should remain optimistic about novel treatment options for our patients.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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