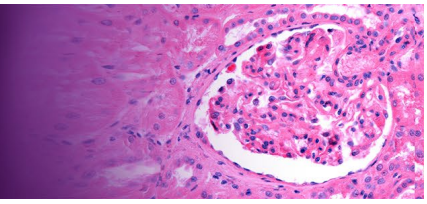
BETTER EDUCATION ON GLOMERULAR DISEASE: IMPROVING DIAGNOSIS AND TREATMENT OF C3 GLOMERULOPATHY



Editor's Note: This is a transcript of a presentation on November 9, 2022. It has been edited and condensed for clarity. To obtain CE credit **click here**.

Glomerular Disease

Carla M. Nester, MD: The global annual incidence for glomerular disease is 0.2 to 2.5 per 100,000 individuals and it comprises about 25% to 30% of end-stage renal disease (ESKD) populations. It's the third leading cause of chronic kidney disease (CKD) within the United States. Defined by intraglomerular inflammation and cellular proliferation, it is very often associated with hematuria and hypertension. The presumable cause of the disease is cell-mediated damage specific to the etiology of that particular glomerular disease, or the fact that the glomeruli are specifically a target of the immune system, the metabolic system, vascular or even malignant disorders. Decline in kidney function will be observed over time; in rare populations and rare cases, rapid deterioration may actually be the case.

Primary glomerular diseases, such as IgA nephropathy, may also have a pairing with a secondary form. IgA is often related to malignancies or gastrointestinal disorders. Focal sclerosing glomerulonephritis (FSGS) may be related to genetics. In the secondary form, it may be related to many diseases that cause initial injury to the glomerulus, which may include bacterial, viral, fungal or parasitic infections. Crescentic glomerulonephritis (GN) can be a primary form of disease, but it most often takes the form of one of the vascular diseases. For instance, a secondary form of crescentic GN would be antineutrophil cytoplasmic antibody (ANCA) disease, IgA nephropathy, lupus nephritis or even C3 glomerulopathy (C3G). Goodpasture's disease may also cause a crescentic GN.

Nephritic or membranous syndrome, particularly in adults, or minimal change disease, often in children, are primary glomerular diseases. As opposed to a secondary form, membranous or minimal change disease may be seen in the setting of nonsteroidal anti-inflammatory agents (NSAIDs) or penicillinamine.

The pathophysiology of glomerulonephritis is quite diverse. Depicted here are at least 5 of the major mechanisms. Antibody deposition may play a major role in glomerular disease, particularly deposition into the glomerulus causing inflammation. This triggers cell-mediated cytotoxicity, activating or infiltrating intrinsic kidney cells or complement.

Complement is a separate pathophysiology in the glomerular diseases; in that scenario, deposition of complement breakdown products, generation of anaphylatoxins or generation of the soluble membrane attack complex C5b-9, the terminal component of the complement system, will be observed. Each of these pathways or types of pathophysiology can contribute to glomerular disease.

How about coagulation? The activation from tissue factor results in thrombin formation frequently observed in the vascular or vasculitic diseases. Then, there are many cells involved in glomerular disease; for instance, the leukocytes. Cell recruitment and proliferation as a result of anaphylatoxin activity can lead to deposition of macrophages and lymphocytes within the interstitium and lead to disruption of the regular activity in the glomerulus. Finally, the activity of intrinsic kidney cells can participate in the pathophysiology of glomerular disease. Inflammation from the release of cytokines and chemokines are both observed in mesangial cells and related pathology, leading to abnormal kidney function in the setting of glomerular disease.

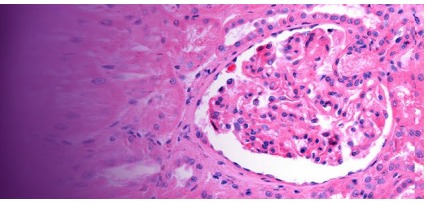
The glomerular diseases are met with many nonspecific symptoms. One of the most bothersome to patients is that of fatigue. Patients also often have headaches or dyspnea on exertion related to the degree of edema and confusion or what is often described as fuzzy headedness. There are more specific underlying presentations or specific complaints that patients may have, and it depends on what the underlying disease is. For instance, arthralgias are very common in systemic lupus or pulmonary hemorrhage may be present in Goodpasture's disease. There may be a prior history of infection as the trigger to any of the given diseases, particularly in the setting of C3G. Finally, the most specific symptoms are those of hypertension (HTN), edema, blood in the urine or hematuria (either microscopic or gross), and azotemia. Those are the symptoms that are almost always going to be present in this group of patients.

Untreated GN may progress to end-stage kidney disease (ESKD) in many of the patients. Prior to reaching end-stage, these patients often have acid-base disorders, difficulty with anemia, bone and mineral abnormalities, specifically as it relates to phosphorus and calcium metabolism, and risks for significant cardiovascular disease. At the end of the day, in order to be able to move patients past their presentation, a kidney biopsy is going to be required. It is the gold standard for diagnosis of glomerular disease.

Treatment begins with lifestyle modifications and focuses around salt restriction, so that we may be able to reduce the degree of edema. The degree of HTN frequently is related to the degree of salt intake. Weight normalization is important, meaning a good, healthy lifestyle. Weight normalization often means regular exercise. Smoking cessation may also play an important role in this setting.

Management of HTN and proteinuria are often the very next focus of the glomerular diseases. It won't surprise you that we use angiotensin converting enzyme inhibition (ACEi) or angiotensin receptor blockers (ARB) titrated specifically to a maximum tolerated dose so that we may control both the blood pressure and the urine protein.

Our target blood pressure in this setting is a systolic of less than 120 mmHg and target urine protein is less than 1 g per day. Added to these initial treatment approaches is going to be the concept of monitoring



the patient rather persistently or constantly for the risk of worsening of kidney function or the development of acute kidney injury on top of a more chronic glomerular disease, so that you can be prepared to escalate care as necessary.

Failure to achieve these lifestyle modifications or failure to respond to these initial therapies will be what ends up triggering the need to escalate care and thinking about more targeted therapeutics.

SL is a 24-year-old female who presents with the chief complaint of hematuria. Her diagnostic workup reveals an elevated blood pressure of 160/100 mmHg, and a urinalysis significant for 4+ protein and 2+ blood. Dysmorphic red blood cells are detected on microscopic exam. Other than experiencing occasional fatigue, she indicates she is generally feeling well. We will come back to this case further into this session.

C3 Glomerulopathy

Andrew S. Bomback, MD: We're now going to focus on C3 glomerulopathy, which previously was called a form of membranoproliferative GN (MPGN). We've learned a lot over the last 2 decades about how to classify the MPGN. There's a form that's due to immune complexes, which is not going to be addressed today, and there is a form that's due to hyperactivity of the alternative complement pathway, which is called C3G. That term comes from the way the biopsy looks, where on immunofluorescence, the dominant staining is for complement 3 (C3), usually without any other or very trace amounts of immunoreactants. But the C3 is the most glaring form of staining on immunofluorescence.

C3G is categorized into 2 separate forms. Most of the cases of C3G are actually termed C3 glomerulonephritis (C3GN), but a small subgroup of C3G is called dense deposit disease (DDD). That group gets its name from electron microscopy where, at ultrastructural examination of the kidney biopsy, you see very osmiophilic, very electron-dense deposits in the intramembranous portion of the glomerular basement membrane.

C3G is a very rare kidney disease. We estimate that there are about 2 to 3 cases per million in the United States and a slightly lower incidence of 0.2 to 1 case per million in Europe. The disease is characterized by dysregulation of the alternative complement pathway and you see, on immunofluorescence, intense deposition of C3 complexes in the glomeruli. We believe that the general underlying cause of intense deposition of C3 in the glomeruli comes from overactivity on the alternative complement pathway, specifically at the level of a hyperactive C3 convertase. The prevalence of C3GN is much greater than the prevalence of DDD. About 70% to 80% of all C3G will be called C3GN and roughly around 20% will be called DDD. Most of the data that has emerged from large cohorts of C3G have shown a worse prognosis in terms of a more rapid progression to ESKD in patients with the DDD as compared to C3GN. The patients with C3GN are still progressing to ESKD, but on average, are doing so at a slightly slower rate than patients with DDD.

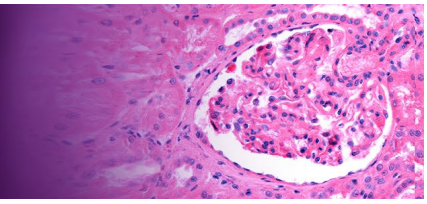
This is an overview of the complement pathways. On the left, you see the classical and lectin pathways, which are the pathways that are involved in immune complex forms of GN, and on the right, you see the alternative complement pathway, which is the pathway that is overactive in C3G. We believe that most of the cases originate at an overactivity very high up in this pathway, at the level of the C3 convertase.

Now, why are we seeing this overactivity? That is the first question we start to ask of our patients when we work them up once they've been given a diagnosis of C3G. Some patients have overactivity due to genetic variants that they've inherited. Some patients have overactivity due to abnormalities in the form of autoantibodies that they acquired in their lifetime. Some patients have overactivity, especially adult patients generally 50 years of age and older, who have monoclonal gammopathies that are interfering with regulation of the alternative pathway. Some patients we never actually uncover a reason why their complement pathway is overactive, despite clear evidence in their biopsy.

One aspect that has emerged is that there are clear signals infection can trigger the onset of disease. This doesn't necessarily mean that infection is the cause of the disease, but infection may be the second hit required to bring out the disease in a patient who has a susceptibility to C3G. It is not uncommon when you see a new C3G patient to find out that their presentation began with the form of an infection which may have elicited some of that evidence of overactivity of the alternative complement pathway.

The prognosis for C3G unfortunately is not good. We hope with new treatments being evaluated, and those that will hopefully emerge to help with this disease, that the prognosis will change. Progression to ESKD is expected, on average, within 10 years of diagnosis. The progression is slightly different depending on whether you've been diagnosed in childhood vs adulthood. Unfortunately, when these patients do progress to ESKD and eventually kidney transplantation, the vast majority of patients will see recurrence of the C3G in their transplanted kidney. Recurrence is associated with loss of the transplant. It is extremely important, as we look at this prognosis, that we develop available therapies to stop the natural history of disease.

To that end, the National Kidney Foundation in 2017 brought in a group of patients who are living with C3G, as well as their caregivers, to do "The Voice of the Patient." This was an important meeting because we wanted to hear what patients were experiencing with this disease, what they knew about their prognosis, and to hear their thoughts about participating in clinical trials and new therapies. Some of the key themes that emerged from this session were that the symptoms of C3G were negatively affecting their daily quality of life, affecting their ability to go to school, if they were children, or go to



work, if they were adults. There was tremendous insecurity about their health and also about what therapies could be available to them. They had plenty of experience with some of the current treatment options and they did seem to know that kidney transplantation was the inevitable end for them once they reach ESKD. But they also were well aware that the disease would come back in their kidney transplants. One of the biggest messages we got from the patients and their caregivers at this meeting was that there was a tremendous willingness to participate in clinical trials and a real enthusiasm for getting early access to new therapies that were under investigation.

Direct quotes from the patients about their disease and treatment options: "It's horrible all around; you know it's going to get worse." One patient talking about eculizumab, a complement-targeting therapy that I'll discuss later, talked about the great results that were seen in some trials, but seeing the kidney function go back to the pretrial levels at the end of the trial was very difficult.

What patients were telling us was they needed to avoid a lifetime of dependence on dialysis or a series of failed transplants. They were very much voicing their need for timely and effective treatments to preserve their kidneys where they were. Really, what they wanted was some degree of stability. What's frustrating if you're a newly diagnosed C3G patient is that there is no standard of care. We're hoping that with the development of new therapies we can actually give them some effective and safe standard of care.

Diagnosis of C3G

Carla M. Nester, MD: According to many of the old nomenclature or older publications, we always start with MPGN when we're discussing how to separate out whether a patient may have C3G or not. But I will mention here that some of the newer literature would suggest that some of these patients may actually just have proliferative GN, so not yet have terribly abnormal basement membranes which moves them into the MPGN category. Nonetheless, it is the standard for us right now to think of these in terms of MPGN. The biopsy is the gold standard for diagnosing C3G. We start with this biopsy to help us figure out whether these patients actually have C3G or one of the other patterns of disease.

If there is immunoglobulin present, and there may or may not be C3 present, then we are moving into probably assigning these patients the diagnosis of either a monoclonal gammopathy, postinfectious, peri-infectious or concurrent infection picture, or autoimmune disease. For instance, like lupus, those patients are often having both immunoglobulin and C3. Very rarely in adults, not quite as rare in children, is this idea of immune complex MPGN or idiopathic form of the disease. Again, this is if it includes both immunoglobulin and C3.

If you move to the possibility that there is complement present only, or the complement deposition is predominant, then that's when we move into the setting of having a patient presumably with C3G. To be complete, let's think about if we have no immunoglobulin and no complement deposition, you will find yourself very likely with a diagnosis of antiphospholipid antibody syndrome, hemolytic uremic syndrome (HUS), or even a more generic thrombotic microangiopathy that may be, for instance, in a posttransplant setting. To categorize a patient with C3G, you first have to have the biopsy and then you sort through whether they have immunoglobulin present. If immunoglobulin is present, they must have at least that 2 orders of magnitude of C3 over that immunoglobulin to make the diagnosis.

When thinking about the diagnosis of C3G, it's important to remember that C3G is not specific to any 1 age range and, in fact, it may present at any time. The average age at the time of diagnosis is late teenage or early adulthood. This tends to be a disease of younger individuals. In fact, it is unusual or less common that a patient presents over the age of 50 years and, if they do, we should remember to consider this idea of an underlying monoclonal protein. Regardless of at which age a patient presents, it is a disease of the alternative pathway. Either the patient has a more primary form of alternative pathway disruption, or, in the case of that patient who is over the age of 50 years, we think about the monoclonal potentially dysregulating the alternative pathway.

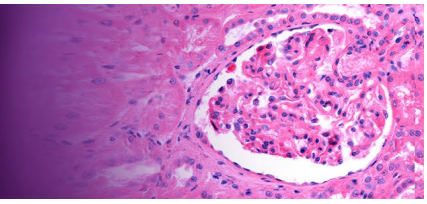
It's very important to remember that these patients frequently have a delay in their diagnosis primarily because it's an ultrarare disease. It's not the first disease that comes to the top of our diagnostic list and, unfortunately, the particular C3G biopsy that is diagnostic may also have some mimics of other diseases that share very similar patterns.

There's a spectrum of C3G symptoms that are very much dependent on the duration or severity of the disease. Very commonly, hematuria is present. Proteinuria is invariably or very frequently present and it may be nephrotic or subnephrotic range, but in a chronic fashion. These patients often have high blood pressure, and they very frequently have edema. However, all patients will not have all of these symptoms. The heterogeneity of presentations can be significant.

With respect to how chronic the disease is, these patients sometimes can end up with an eye disease known as Drusen, which is complement deposition in the eyes, or lipodystrophy, which refers to an abnormality of the fat content secondary to complement dysregulation.

Finally, nonspecific symptoms are very frequent in these patients. For instance, this idea of fatigue, confusion or fuzzy headedness is very frequently reported. Frequently reported is a prior history of infection in this group of patients. Neither of these nonspecific findings are going to point you to C3G. This is a biopsy-based diagnosis; however, they may be something that you will have to manage clinically.

If you think about the symptoms and try to separate C3G into its DDD form and C3GN form, you'll find that they're not terribly different.



The male to female ratio is very similar. The age, frequently a young population, doesn't seem to be a big difference between DDD and C3GN patients. Neither does the presence of gross hematuria or proteinuria. It has been stated that renal impairment can be different across groups; for instance, that DDD patients may have more significant renal impairment. That has not been routinely proven across cohorts.

Trigger events are very frequent in both categories. It is important to note that there are some patients, whether they are DDD or C3GN, do not have obvious complement abnormality, such as a low C3 in the circulation at the time of diagnosis. One of the few places that there may be a significant difference is in the area of a plasma C5b-9 or soluble membrane attack level. It has been reported in multiple cohorts that C3GN patients tend to have a slightly higher C5b-9. However, when you look at the statistics across all of the groups, it is not enough for you to be able to use this as a clear diagnostic tool.

At the end of the day, diagnosing C3G continues to be met with many challenges, not the least of which is that we unconsciously omit it from our thought process because it's such a rare disease. Even if we think about it, there's limited information for many clinicians that would make it easy for us to consider C3G at the top of our list. Once we begin thinking about C3G and our treatments, there really have been very few opportunities to study in large cohorts of patients. In fact, most of what we use currently has been extrapolated from the other glomerulonephritides and what's been successful in that setting may not always be in the setting of C3G.

One of the largest challenges to C3G treatment is this idea of not having prescribable, targeted therapeutics. And when I say targeted, I mean targeted towards what we believe is the underlying mechanism for this disease. A challenge for diagnosis is access to centers who actually specialize in the diagnosis of C3G. If a center is more specialized in this area, it is more accustomed to this potential diagnosis. It will come quicker that this might be the diagnosis and testing may be done earlier in that setting.

Recommended testing may not be available at all centers. Specific biomarkers or genetic testing required to diagnose, for instance, the familial form of C3G, may simply not be available to a given clinician at a center. For patients, that leads to the challenge of having to get themself to a center. Maybe they cannot get to the center and they have to deal with tertiary consults or shipping specimens around. You can see that there are a number of challenges with the diagnosis of C3G.

If you have an initial presentation of GN and have not thought of C3G, you're probably going to be headed for the biopsy. The pre-workup for a biopsy is perhaps a little bit different across centers, but many will begin with a basic metabolic panel, a complete blood count, and a serum complement level. The complement levels, C3 and C4, have been able to help push us towards 1 group of glomerular diseases if they're low and another group of glomerular diseases if they're in the normal range. In addition, you're likely to collect a urine protein to creatinine ratio. A number of immune labs may be next on your list of things to do prior to the biopsy. For instance, you may be testing for the hepatitides, human immunodeficiency virus (HIV), ANCA disease, or antiglomerular basement membrane (anti-GBM) depending on the age of your patient.

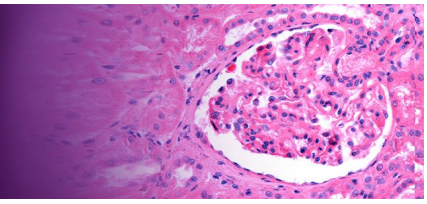
The trigger for a kidney biopsy will be if the proteinuria is greater than 500 mg/day. This threshold generally applies to adult and pediatric patients. It may also be triggered by a reduced estimated glomerular filtration rate (eGFR), such as a high creatinine based on a patient's age group. In the setting of a persistently low complement value, particularly C3, it may make a clinician think we are not dealing with postinfectious GN and therefore need to find out what we are dealing with.

Further evaluation of the C3G patient may include a comprehensive assessment of the overall complement activity. There is a lot to be learned before we can completely translate this comprehensive assessment directly to patient care; however, understanding where in the complement pathway the system is dysregulated may actually serve to establish the concept of a targeted therapeutic. A very high serum C5b-9 may trigger interest in the use of eculizumab. If you have C3 nephritic factors, it may make sense that the target needs to be at the level of the nephritic factors or the amplification loop. If we move towards a complement protein level or pathway assessment, we must think about screening for antibodies. Autoantibodies in C3G include the nephritic factors, in which C3 is the most common one, C5 being the next most common, but C4 is also present in some patients. It is becoming clearer that proteins are the driver of disease when genetic abnormalities are absent. They make up the larger portion of the driver of disease compared to the genetics. We must also think about Factor H and Factor B autoantibodies because they have been reported in isolated cases as also being the drivers of disease.

More recently, genetic testing has been recommended in most patients. Components of genetic testing for the general population may include C3, complement factor B, complement factor H and complement factor I. Complement factor H-related 5 may be very important in some subpopulations, such as considering the heritage or the background of your patient.

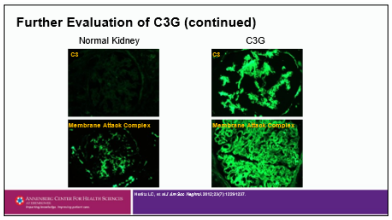
If you happen to have a familial case, such as our 24-year-old patient had a father who had disease and had a grandfather or a grandmother who had disease, you may now be thinking about the C5HR region, as this has been well reported in familial cases. As our science moves forward, we may actually be thinking more of whole genome sequencing for patient populations. If this is the case, we may not have to be very specific about the genes in a gene panel.

Electron microscopy is very important in separating your patients' disease categories into DDD vs C3GN. Electron microscopy is not



required for the diagnosis of C3G and may not be available across the world for this setting. It may add additional information related to the type of C3G disease. For the DDD patient, electron deposits are very dense and tend to be intramembranous. As opposed to C3GN patients, less dense intensity is observed on electron-dense deposits and may frequently have mesangial densities and capillary wall deposits that appear to be more endothelial or subepithelial. For immunofluorescence, the C3G diagnosis comes from this concept that the biopsy is 2 orders of magnitude of C3 deposition greater than any other immune reactant in a patient who does not have a postinfectious picture or monoclonal gammopathy.

Here is our picture of what this may look like for you when you're thinking about the diagnostic testing on the biopsy.



For instance, you see the normal kidney and that C3 deposition is either absent or very mild. In fact, membrane attack complex may be present on a normal kidney, but it would not be a significant presentation. If you skip over now to a C3G patient, the C3 deposition at least 2-plus but often 3-plus to 4-plus and the membrane attack complex deposition is very significantly deposited in this setting.

Let's return to that patient case. She is a 24-year-old who presents with the chief complaint of hematuria. She has elevated blood pressure at 160/100 mmHg. We already know that she has urine blood and urine protein. She has dysmorphic hematuria, so we think that she has a GN and she is presenting with fatigue. What specific testing should be ordered to diagnose whether this individual has C3G?

You can think about routine, prebiopsy screening labs, but at the end of the day, your trigger to figure out whether this patient has C3G or not is whether they have greater than 500 mg/day of urine protein, a significantly reduced GFR or a persistently low complement greater than 12 weeks or 3 months after an infection.

Treatment of C3G

Andrew S. Bomback, MD: The treatment of C3G involves a number of different ways to approach the disease, none of which have been approved by the US Food and Drug Administration (FDA) for C3G. Virtually all patients should be given supportive care with an ACEi or ARB. Many patients will be exposed to nonspecific, general immunosuppressive therapies. The field is moving towards using complement-targeting therapies and, as we go through these complement-targeting therapies, it's helpful to think of them as C5-directed therapies, which block or target the alternative pathway at the more distal components, and C3-targeted therapies, which block the alternative complement pathway at the more proximal components.

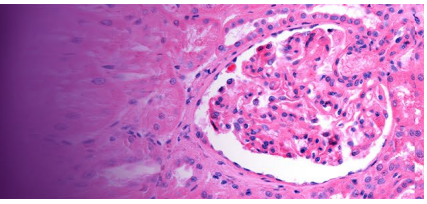
A healthy lifestyle should be encouraged and virtually all will be initiated on renin angiotensin aldosterone system blocking agents like ACEi or ARBs. Typically, this is done mostly for proteinuria reduction, but if patients also have high blood pressure, it will give blood pressure reduction as well. It's been shown to improve kidney survival in patients with C3G as has been shown essentially in patients with any form of glomerular disease. These drugs improve the overall kidney survival.

We generally push the doses of the ACEi or ARB to what we call a maximal tolerated dose. This is essentially how high we can get the dose and that is influenced by how the patient's blood pressure and kidney function tolerate the medicine. Many patients will also be given lipid-lowering therapies to reduce cholesterol levels that may be elevated in the setting of a proteinuric kidney disease. Recently there's been an enthusiasm of using sodium-glucose cotransporter-2 (SGLT2) inhibitors, in patients who don't have diabetes, across a spectrum of kidney disease. In C3G, this would apply to patients who have clear evidence of CKD which would be a sustained GFR less than 60 mL/min/m^2 with or without proteinuria.

Let's discuss the general or nonspecific immunomodulatory approaches to treating C3G. In the past, plasma exchange has been used. The data is limited in treating C3G and mostly focuses on case reports where plasma exchange has been effective in patients who have an identified genetic variant in factor H. The plasma exchange is essentially serving as a form of replacing factor H.

The reduction in circulating C3 nephritic factors with plasma exchange removing a pathogenic autoantibody would require very high intensity therapy that generally is not feasible. The big problem with plasma exchange, particularly in a patient with a factor H defect, is that once the infusions stop, the disease will come right back. Plasma exchange is a costly therapy, which involves some degree of permanent access and access to either inpatient hospitalization or outpatient infusion centers. It's not really a viable long-term treatment strategy for patients.

People have looked at using general immunosuppressive therapies that have been used in other glomerular diseases to treat C3G. The nonspecific immunosuppression with the most available data is glucocorticoids. Glucocorticoids have been a mainstay of treating MPGN for decades. There are many patients who are diagnosed with MPGN as children who now, when we look back on their biopsies, would clearly be reclassified as C3G. These patients received anywhere from 2 to 4 years of glucocorticoid therapy and saw a significant reduction in hematuria, proteinuria, and stabilization of kidney disease; now, in their adult years, they still have preserved kidney function with low levels of hematuria and proteinuria, despite evidence of low complement.



The problem with a 2- to 4-year course of glucocorticoids is the toxicity. You can't keep patients on 2 to 4 years of high-dose glucocorticoids and not expect to see very significant toxicities which, themselves, adds significant morbidity to the disease. Replacements for glucocorticoids had to be sought and again, glucocorticoids are not really considered to be disease-modifying. They're functioning as an anti-inflammatory, but do nothing to address the underlying etiology of the disease. We do not expect that glucocorticoids will actually interfere with the activity of a hyperactive alternative complement pathway.

Combination therapies have been tried with glucocorticoids and other nonspecific immunosuppressants, including calcineurin inhibitors, rituximab, and alkylating agents; but the one with the most data and the best results is combining corticosteroids with mycophenolate mofetil. This is essentially borrowing the regimen that we use in lupus nephritis and applying it to C3G. There have been series, both from the United States and Europe, that have shown using a mycophenolate and glucocorticoid-based regimen appears to reduce the risk of progression to ESKD compared to either no immunosuppression or other nonspecific immunosuppressive courses. The problem with this regimen is that like corticosteroids, mycophenolate does not actually target complement protein. They're not considered to be disease-modifying, but rather disease-stabilizing therapies.

One of the signals that has emerged from the data on mycophenolate as a treatment for C3G is that it appears to work best in patients who have autoantibodies. In C3 nephritic factor-positive patients, the response to mycophenolate appears to be significantly better than patients who do not have detectable C3 nephritic factors. That may influence your decision to use mycophenolate in the treatment of C3G. However, most people who see and treat a lot of C3G don't consider mycophenolate to be the ultimate answer for our patients and really are encouraging our patients to look into getting onto complement-targeting therapies as a way to get to a disease-modifying therapy.

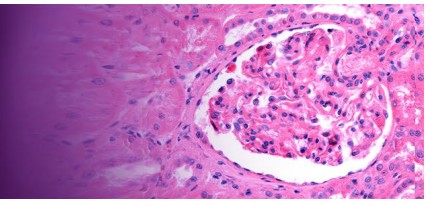
The first available complement-targeting therapy was eculizumab, which is a monoclonal antibody that targets against C5. There's a newer version called raviluzumab which has the same target, but different pharmacokinetics, so it can be dosed less frequently than eculizumab. When I talk about eculizumab in this slide and in coming slides, you can assume that similar results would be seen with raviluzumab. Eculizumab has efficacy in other diseases that are mediated by alternative complement pathway hyperactivity, such as atypical HUS and paroxysmal nocturnal hemoglobinuria. In theory, there is a reason to have some hope that eculizumab could help patients with C3G. In the very least, by blocking the production of C5a, which is a potent anaphylatoxin, you will get some anti-inflammatory response from eculizumab and a reduction in proteinuria and glomerular inflammation. But the real question that we wanted to see out of eculizumab is whether the blockade of C5b and the subsequent blockade of the formation of the membrane attack complex will lead to significant disease modification.

The efficacy of eculizumab for C3G mostly comes from case reports and case series, and some of these have shown a reduction in serum creatinine, proteinuria, and soluble C5b-9 levels. Some of them have coupled those clinical improvements with histopathologic evidence of improvement as well on repeat biopsies. To me, some of the robust data is actually coming out of Europe where they show that if you look at a larger sample, roughly about 25% of patients will have a partial response, roughly about 25% will have close to a global response, but at least half of the patients will have no response to eculizumab. The longer-term data that have emerged from European and United States cohorts have shown that some benefits you see with eculizumab are mostly in the first or second year of therapy and then efficacy appears to wear off. What that suggests is that some of the early benefits may be solely through that C5a blockade as an anti-inflammatory, similar to what we see with steroids, and we're not really seeing the blockade lead to disease modification.

However, there are a number of patients who have been treated with eculizumab off-label to treat C3G, particularly patients who are what we would call crashing, who are progressing towards ESKD despite being on conservative therapies, such as corticosteroids or mycophenolate. There have been a number of patients who have been prescribed eculizumab and been able to get it even though it's being used off-label. If you are going to use eculizumab or any complement-blocking therapy, it is required to have vaccinations against *Neisseria*, meningococcal A, meningococcal B, pneumococcus, and *Haemophilus influenzae*. Those are the bare minimum for vaccines that patients would need to go on complement-targeted therapy.

There are some factors in considering whether to put a patient on eculizumab. The data suggests that at least half of patients will not respond. Some of the responses appear to be temporary and not in long-term data. A real issue with the current availability of entry into clinical trials is that 1 of the exclusion criteria considers whether or not patients are on eculizumab and the need to be washed off of complement-targeting therapy before clinical trial entry. These are factors that must be considered before thinking about using this drug off-label.

As I mentioned that the data on eculizumab is mostly from case series and retrospective cohorts, one of the first prospective, randomized, double-blind, placebo-controlled trials in C3G uses a drug called avacopan. Avacopan is a C5-targeting drug, like eculizumab. Unlike eculizumab, it has no effect on C5b. It is only a C5a receptor antagonist. It has already been approved for the treatment of ANCA-associated vasculitis and it is used as a steroid substitute. The idea of could you use avacopan in C3G would again be as a steroid substitute. Remember, I said that in the past, children with MPGN, who would



now be called C3G, were treated with high doses of steroids for 2 to 4 years and many of them had good responses. Could you get that same sort of response using avacopan as a steroid substitute?

The ACCOLADE study has been completed. The results have been presented as abstracts at national meetings, but the final publication has not been published and we will wait for that final data. But it is an important study in the very least because it shows that you can do rigorous clinical trials in this disease state. They actually over-enrolled from their initial projections because there was such an enthusiasm from the C3G community to try a new drug even in the form of a clinical trial.

Iptacopan is an oral factor B inhibitor and this is a drug that targets at the level of C3. We have had some data presented at national meetings from an early phase 2 study where they're essentially trying to see if there is a signal of response to actually fuel a larger phase 3 study. This study actually had 2 different cohorts, in which 1 included patients with disease in the native kidneys and 1 with patients who had disease recurring in the kidney transplants. They showed that in most patients there was a significant reduction in proteinuria, stabilization of kidney function and improvement in C3 levels; but it was at a very short time frame of 12 weeks. We've learned from the eculizumab experience that you want to see longer-term therapy. This was clearly enough of a signal, especially seeing both efficacy and good safety data and a blocking at the level of C3, with a factor B inhibitor. They moved on to do a phase 3 study, called the APPEAR-C3G study.

This is a study that is being done in a rigorous, randomized, placebo-controlled trial setting. It is comparing placebo against iptacopan for 6 months. But I want to note something here. You can see there's a very important second period of the study called open-label extension where all patients will be put on iptacopan for an additional 6 months. This is based on some of the things that patients voiced to caregivers, providers and representatives from the FDA and pharmaceutical companies at the Voice of the Patient meeting that I talked about earlier. They said we are willing to do placebo-controlled trials, as long as we are guaranteed that we will get access to the drug when the placebo period is over. So, all of the trials that I'm talking about now with complement inhibitors have this open-label extension. What we would hope is that when patients are brought into the open-label extension, if they show a clear response after that 6-month period, they will be given even further access to the drug as we wait for it to get approved.

Pegcetacoplan is another C3-targeting drug. This is a drug that targets at the level of the C3 complement protein itself. It's a C3 inhibitor. The drug has already shown very nice results in other alternative complement pathway-mediated disease and it's been FDA-approved for the treatment of paroxysmal nocturnal hemoglobinuria. This is a subcutaneous-administered drug. As we saw with iptacopan, there was a phase 2 study which showed good results in terms of a signal of efficacy and safety. Based on that phase 2 study, they've actually moved on now to a randomized phase 3 study in 2 different forms. One is called the NOBLE study which is looking only at patients who have been transplanted and have recurrence of the disease in the transplant. One study is called the VALIANT study and enrolls both patients with native disease and transplanted disease.

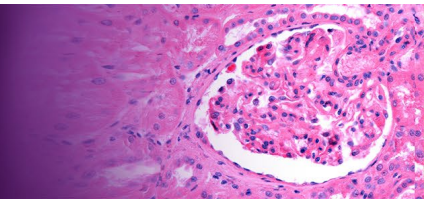
The NOBLE study has a 12-week, placebo-controlled period and the VALIANT study has a 6-month, placebo-controlled period. Both of those studies have open-label extension for the duration of the first year of study. Our hope is that we will see even more robust responses from C3-targeting therapies and continue to see the safety responses that we're seeing in earlier phase 2 studies.

Kidney transplantation is clearly a part of disease management for many of our patients who go on to ESKD. As was mentioned earlier, the disease is expected to recur in the overwhelming majority of patients with C3G who undergo kidney transplant. It's actually the rare exception of the patient who doesn't get recurrence of their disease in the allograft and this is because there's ongoing dysregulation of the alternative complement system. The transplant itself, nor any of the antirejection medications, have actually stopped that ongoing hyperactivity of the alternative complement pathway.

A series from Columbia University, where I work, reported on 19 patients who underwent kidney transplant for ESKD due to C3G, and we saw 85% of the patients recurred within a 5- to 6-year period. We saw slightly greater rates of kidney transplant loss, what is called allograft failure, in patients who had DDD vs C3GN with earlier graft loss in that subgroup. Although I will tell you that if you follow those C3GN patients over a longer period of time, they will also eventually lose the graft. It's very important that the studies that are being done enroll patients who have the recurrent form of the disease in kidney transplants, in addition to patients who have the disease in their native kidneys.

If we return to the patient case that we've followed through during this session, based on the labs and testing that was recommended, SL was diagnosed with C3G on a biopsy. The question now would be which therapy should be initiated for the treatment of her newly diagnosed C3G. Well, I think putting her on an ACEi or an ARB would be a very obvious choice to start out with and we'd have to counsel her in terms of the risk of teratogenicity with those agents. The real branching point after that is whether you would put her on a mycophenolate and glucocorticoid-based regimen as an initial option or would you tell her to consider enrollment into a clinical trial of C3-targeting drugs. In many ways, it would come down to what the severity of the disease is and how you would prognosticate where the disease is going to be in 1 year, 2 years, 3 years from now.

If I thought she had a very mild form of the disease, I might treat her only with an ACEi or an ARB. If I thought she had a mild-to-moderate form of disease, I might suggest let's put you on a mycophenolate and



glucocorticoid regimen rather than automatically enroll you in a trial and wait to see what the trial results show. But, if I thought she was at significant risk, I would tell her that her best option at this point is to get into a clinical trial of a C3-targeting drug and try to get early access to that drug in the hopes that that will work to modify the natural history of her disease.

Carla M. Nester, MD: That was an excellent presentation, Dr. Bomback, of our current approach to this particular case. For instance, I think it's worth talking about that you make it very clear if we have a concept of where the patient's going to be in a year or so or how aggressive their disease may be, it probably does make sense to do it exactly like what you've said. The problem we all face, and certainly people who even have less experience with C3G, is that we really don't right now have the ability to prognosticate where that patient's going to be in a year. There absolutely could be 24-year-olds who are at end-stage in a year, or they could be 20 years into their disease and not be terribly compromised, if you will, with kidney disease. So, really the point I just wanted to throw out there is that this concept of we're not yet very good about prognosticating. We don't yet have the biomarkers that we need to figure it out. I believe that we all are hoping that either there will be large cohort reports of what's happening with the natural history or even, as these clinical trials admit and study these patients in the longer-term, very controlled data will give us a better sense of what is the natural history of this very heterogeneous disease.

Andrew S. Bomback, MD: I completely agree. I think, in 2022, really the best data we have to try to prognosticate is probably the biopsy. We can look at a biopsy and say, okay, this is a very aggressive lesion, or this is a mild lesion, but we really need disease-specific biomarkers, as you alluded to, that will give us a better clue as to how to prognosticate and try to get our patients onto the right therapies.

Carla M. Nester, MD: We need the same advantage that other glomerular diseases have with biomarkers. Of course, the initial biopsy's necessary, but wouldn't it be nice if we had these surrogate markers that told us how the disease was going? With biomarkers, we could keep good tabs on the patient without having to biopsy them frequently. But you're right, the best right now is the biopsy, just unfortunately you can't do a daily one.

Supportive Measures and Faculty Summary

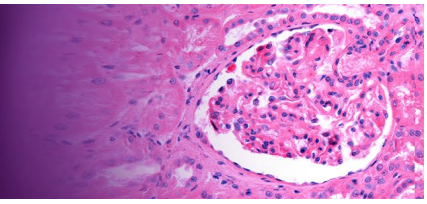
Carla M. Nester, MD: We are going to finish up our presentation of the glomerular nephritides and specifically C3 glomerulopathy by talking about supportive measures that may help your patients deal or understand the direction of their disease or why you're treating them in such fashion.

Many of your patients, because it's an ultrarare disease, will rely heavily on you to educate them about what this disease is like, what its natural history may be or response to therapy may be. They also can use public databases or public forums to actually meet other patients. Like Dr. Bomback mentioned earlier, this idea of the Voice of the Patient session that was held by the FDA was critical because it actually got patients together to begin talking about their experience and what it was like dealing with the disease. But it also just got them together so that they could actually begin sharing stories even going forward. I am aware that a number of these patients have stayed in contact. They've bonded with each other and continue to share with each other what their experience is. Other national organizations include the National Organization for Rare Disorders. They also have a group of patients that can glean support and information from this entity. The National Kidney Foundation not only has a C3G steering group, but they also have a family support group that's led by C3G patients with opportunities to discuss what's going on with you in a forum setting. I think that this not only takes some of the pressure off the physician to educate the patient, but also brings education to a very personal level for the patient.

Finally, NephCure Kidney International has an opportunity to help educate patients with glomerular disease in general. I'll finish up by saying there are family support groups. There's at least 2 that I'm aware of that, if families are interested, they can join these groups. They may not be useful for all patients, but they may actually help you, as a provider, help the patient understand their disease better.

Andrew S. Bomback, MD: I think it's really important to follow up on what we, as the healthcare community, can do to support our patients beyond referring them to these resources. There are some really specific things that we can do to help support them through their disease course. One is to recognize that there clearly global effects from the complement system being dysregulated that we're not really giving due attention to. One of the things we heard from patients when we spoke to them at the Voice of the Patient was how it was affecting their quality of life. There are definitely concomitant health issues outside of the kidney that these patients are dealing with and there is a clear role of specialists in comanaging these patients. For example, one of the complications of C3 glomerulopathy outside the kidney is the development of Drusen in the eyes, similar to what you can see in macular degeneration, and many of these patients need access to retinal specialists.

There are certain centers throughout the country and the world who see a lot of C3G and feel very comfortable managing the disease right from the beginning. That includes making the correct diagnosis at the time of biopsy, doing the appropriate diagnostic workup to look for why the alternative complement pathway may be overactive or hyperactive and getting patients to the right therapies, including access to clinical trials. But there's issues for some of these patients in terms of how they can get to those specialized centers. There can be incredible distances that they have to travel to get to these centers. Now, fortunately, many of the trials build in assistance to get patients to these centers, but we have to encourage them to get to that level of assistance so that they have access to these highly specialized



centers and make sure they have every availability to get the best treatment for their disease.

When we talk about clinical trial enrollment, it involves a lot of education. There's sometimes a mistrust of what a clinical trial means, such as what it means to go on a placebo. One of the things that we want to make clear to patients is that the development of these trials was done by both patients and physicians who have expertise in C3G. We listened to what patients said, and we know that they are willing to do placebos if they are going to get guaranteed access to the drug. We need to show our patients how the trials are designed to encourage them to enroll and generate the data that hopefully will lead to an approval of a drug that could modify their disease.

Carla M. Nester, MD: I agree completely about the clinical trials. It's basically the clinician's job to make the patient understand the trials, what the burden of those trials will be for them, and what the potential advantages will be. They can't possibly figure this out all by themselves, so it is very important for us, as clinicians, to help patients understand what the trials have to offer them and how they might meet their needs. I wanted to add 1 other point when you were discussing global effects of the complement system. Just as an example, fatigue is so very commonly reported by our patients, yet we have really no idea why the fatigue is such an important aspect for them. As clinicians and scientists, we often say, well it's related to inflammation, and we think that if we cut the inflammation down, the fatigue will get better. But, in the meantime, we have to recognize that our patients may be fighting fatigue and we have to just help them with that. We may not be able to get rid of it straightaway, but if we recognize it and make accommodations, I think that we have a wonderful opportunity to partner with our patients to see if we can make them better. I think that that ends up being an important addition to our responsibilities.

First of all, when you're treating the glomerulonephritides, particularly C3G, one of the first things we end up doing is managing HTN and proteinuria before we consider what's next in their case. Even though C3G remains an ultrarare disease, we need to be comfortable with spreading the word about education, the pathology behind the disease, and how we might be able to better support the patient through some of the nonspecific or specific symptoms. We have to position ourselves to better diagnose the disease and be able to move patients towards a more adequate treatment.

We have to think about the kidney biopsy early. We have to think about when we get the kidney biopsy result, what it means and what it might mean for the patient's treatment. Many glomerular disease doctors will be very quick to biopsy. When you get the C3G diagnosis, you need to know what to do with it.

In C3G, we are very likely going to need complement-targeted therapies at the level of the amplification loop or the alternative pathway because that appears to be where the greatest degree of complement dysregulation exists. It makes a lot of sense to us in the clinical world that targeting the alternative pathway at the level of the convertase is incredibly important and therefore entry into trials is going to be incredibly important. Finally, don't forget to point your patients in the direction of these resources that actually may be able to support your ability to educate them, convince them that targeted therapy is possible, clinical trials are possible and doable and how they might get involved in them. I think that is a very, very important role that we play with our patients also.