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Navigating IgA Nephropathy: Pathogenesis, The Role Of APRIL & The 4-Hit Process, & A Patient Case Study

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You're listening to ReachMD. This medical industry feature titled *Navigating IgA Nephropathy: Pathogenesis, The Role of APRIL & The 4-Hit Process, & A Patient Case Study* is sponsored by Otsuka. And now, here's Dr. Abigail Yancey and Dr. Kartik Kalra.

Dr. Yancey:
Hello NephU community and welcome to today's webinar. Today's webinar will explore the evolving science and clinical variability of IgA nephropathy, from pathogenesis, risk factors, and noninvasive biomarkers to a real-world case. This session will equip you with the knowledge to better understand, assess, and manage this heterogeneous disease.

We will be joined by our eminent expert, Dr. Kartik Kalra. We are so glad to have you join us. My name is Abby Yancey, and I will be moderating today's discussion. I am a Medical Science Liaison with Otsuka.

Before we are joined by our expert, we will take a few minutes to go over some rules of engagement and housekeeping items. This program is paid for by Otsuka Pharmaceutical Development and Commercialization—OPDC. Speakers are employees and/or paid consultants of Otsuka Pharmaceutical Development and Commercialization. The information provided is for educational purposes only. No CMEs are provided, and it is not intended nor a substitute for a medical diagnosis or clinical advice specific to a patient's condition. Those seeking medical advice should consult with your physician or other healthcare provider. While conducting this program, our speaker aims to provide you with content that is accurate, not misleading, and does not promote Otsuka products.

It's my pleasure to introduce our expert for today's presentation, Dr. Kartik Kalra. Dr. Kalra is a Clinical Associate in Nephrology and serves as the Associate Program Director of the Nephrology Fellowship Training Program at Geisinger Medical Center in Danville, Pennsylvania. Additionally, he is an Assistant Professor of Medicine at Geisinger Commonwealth School of Medicine. Dr. Kalra completed his internal medicine residency at St. Peter's University Hospital in Rutgers, New Jersey, and then pursued a nephrology fellowship at the University of Pittsburgh Medical Center. He further specialized in glomerular disease through the GlomCon Fellowship, where he currently acts as a faculty mentor. His primary areas of interest include glomerular disease, peritoneal dialysis, ICU nephrology, and electrolyte abnormalities. He has published peer-reviewed articles and presented numerous posters at both national and international conferences. Dr. Kalra has been honored with an Award for Excellence in Clinical Teaching and is featured on the Internal Medicine Faculty Honor Roll. He is a Senior Member of the Geisinger Cabinet of Educators and a fellow of both the American Society of Nephrology and the National Kidney Foundation.

My name is Abby Yancey, a Nephrology Medical Science Liaison with Otsuka Pharmaceuticals. In today's webinar, we will explore the evolving science and clinical variability of IgA nephropathy. We will review the epidemiology and the underlying pathogenesis of IgA nephropathy, and we will highlight the heterogeneity in the initial presentation of IgA nephropathy. We will also discuss the role of noninvasive biomarkers in assessing prognosis and monitoring progression. This session will equip you with the knowledge to better understand, assess, and manage IgA nephropathy.

Dr. Kalra, to get us started, can you tell us a little bit more about IgA nephropathy and the incidence in the U.S.?

Dr. Kalra:
Thank you, Abby, for the wonderful introduction and appreciate the opportunity. Exciting times for IgA nephropathy with the upcoming uh KDIGO 2025 update.

So IgA nephropathy is a progressive autoimmune chronic kidney disease and the most common primary glomerulonephritis worldwide.

It's still under the rare kidney disease umbrella—rare kidney disease because the overall numbers are low because we are not biopsying enough. It's the leading cause of chronic kidney disease, often diagnosed in ages 20 to 40 years. A majority of these patients will develop kidney failure within their lifetime, and we will go over data during this presentation.

Etiologic pathogenesis is multifactorial. You have ethnic differences; you have a greater proportion of patients from Asian descent, just because of the biopsy protocols and, in general, universal screening protocols. The prevalence of kidney biopsies showing IgA nephropathy varies worldwide due to the same reason. So your threshold to biopsy will actually define how much of IgA nephropathy you actually are seeing in practice, or the prevalence of IgA nephropathy.

So annual incidence of IgA nephropathy globally is 2.5 per 100,000 people; in U.S., it is about 1.29 per 100,000. Male-to-female ratio is 2.5:1 in the U.S. and Europe, and in East Asia it's about 1:1 because of rigorous screening regimens.

The need for biopsying is early. Patients with IgA nephropathy have a high burden of kidney disease, and often the presentation is CKD stage 3 and beyond. We need to rethink our approach. Most of the patients that we are seeing in our clinical practice have already CKD stage 3 before we are diagnosing them as IgA. A great disproportion of patients have advanced CKD versus other countries; we have CKD 3 and beyond, about 25 to 40% of these patients have already had nephron loss before they are diagnosed with IgA nephropathy. So we are way late in our spectrum to diagnose these patients.

Dr. Yancey:
Dr. Kalra, in recent years, there have been a lot of advances in the understanding of IgA nephropathy and specifically the four-hit process and the role of APRIL. Can you delve a bit more into the four-hit process and the role of APRIL in the pathogenesis of IgA nephropathy?

Dr. Kalra:
Absolutely. I think what we have now in IgA nephropathy is thoroughly because of a better understanding of the disease process, whereby what you just referred to as the four-hit hypothesis, we have drugs that are targeting different hits, and that has been the cornerstone, or the overarching therapy in managing IgA nephropathy per se.

So what we talk about is different hits. So hit 1 is the production of pathogenic IgA, which is the galactose-deficient IgA1—has a deficient moiety in its hinge region. So the pathogenic galactose-deficient IgA1 are elevated in patients with IgA nephropathy. These galactose-deficient IgA1 are thought to originate in the mucosa and is also produced by the antibody-producing B cells, or the plasma cells.

So what happens to this response is once they are mistrafficked into the system, or there is greater product of these galactose-deficient IgA1 and they reach the circulation, there is synthesis or production of anti-IgA1 or IgG, which is the part of our antigenic response to any antigen in the body. So this is the immune response to any antigen in the body. You have anti-galactose-deficient IgG uh and IgA1 molecules or antibodies that produce.

And anti-galactose-deficient IgA1 IgG levels also correlate with IgAN disease severity, specifically the degree of proteinuria and also with the kidney biopsy findings in terms of mesangial and endocapillary proliferation. That is hit 2, which is the synthesis of autoantibodies against this. Now you have the binding of these autoantibodies to these pathogenic galactose-deficient IgA1 polymers, and they form the antigen-antibody complex.

And hit 4 is finally the deposition of these complexes in the kidney. The kidney's mesangial region has affiliation for the Fc portion of the antigen. So it goes and deposits in the mesangium. It also has certain molecules like fibronectin, which it attaches to. Once it goes and attaches, it goes and binds and activates mesangial cells, it goes and activates the complement system, basically the alternative and lectin pathways. It also causes a cascade of inflammation interleukin 8 potentiating overall kidney injury in IgA nephropathy, leading to proteinuria, leading to hematuria, and eventually leading to kidney failure.

So very important is the role of APRIL, which is a proliferation-inducing ligand in IgA nephropathy. We will be talking about APRIL, which is a key driver of this four-hit hypothesis. We just talked about the four-hit hypothesis, but now we are talking about a fifth hit, or we can call it a hit 0, or basically a pre-hit 1, how the galactose-deficient IgA1 are being formed. So APRIL is one of the molecules that allows that.

So what happens here is in the pre-hit 1, the antigens are encountered by the mucosal tissue, which could be in the GI tract, respiratory tract, or the mucosal surface. The antigen-presenting cells, which are the dendritic cells in the mucosal tissue, they become activated, they migrate to lymphoid tissue, and they release cytokines like APRIL. What APRIL does, it helps promotes cell survival and prevents apoptosis of immature B cells. It also enhances survival, proliferation, and differentiation of activated B cells to promote class switching, eventually to form galactose-deficient IgA1. So, this can be through a T-cell-independent or T-cell-dependent cell-switching—it can be

through either of these pathways. So, hence, APRIL provides a very pivotal role in the four-hit hypothesis and this supports that APRIL as a potential therapeutic target in the IgA pathway consortium.

As we know, as we just spoke about, the role of APRIL proliferating-inducing ligand in IgA nephropathy, APRIL is a key driver of the four-hit hypothesis. APRIL promotes the production of pathogenic galactose-deficient IgA1 and immune complex formation through the T cell-dependent and T cell-independent class-switching of B cells. And APRIL is an important initiating and sustaining factor in IgA nephropathy progression, and that is why blocking APRIL makes more sense in the therapeutic armamentarium. And serum APRIL levels are elevated in patients with IgA nephropathy. Higher APRIL levels are associated with higher galactose-deficient IgA1, which is eventually translated as a rapid progression to kidney failure.

Studies show APRIL acts as an important initiating and sustaining factor in IgA nephropathy pathogenesis. The APRIL levels were evaluated in about 166 patients with IgAN and 77 healthy age- and gender-matched volunteers at one of the university hospitals. Plasma APRIL was undetectable in a portion of patients in both groups, with a greater number in the healthy control group. You have the plasma APRIL levels had a strong positive correlation with adjusted galactose-deficient A1 levels. And the last figure we have the retrospective study of patients with primary biopsy-confirmed IgAN from four of our referral hospitals. Patients were divided into four groups based on plasma APRIL levels, and risk of ESKD and serum creatinine doubling was measured. So patients with highest plasma APRIL levels in the third quartile had significantly greater risk of ESKD and serum creatinine doubling compared with patients with lower APRIL expression.

Dr. Yancey:
So from a patient perspective, how do patients with IgA nephropathy normally present?

Dr. Kalra:
IgA nephropathy has a very heterogeneous presentation, and it can have a very variable clinical presentation. Patients can come after an episode of dark bloody urine following an upper respiratory infection, which is called synpharyngitic hematuria, mostly seen in patients aged 20 to 40, which is a relatively young onset. They can have non-visible hematuria, or proteinuria, or edema, fatigue. They can also vary from something called as lanthanic IgA, which refers to a subclinical or asymptomatic form of IgA nephropathy, characterized by presence of IgA without any clinical evidence of kidney disease, to full-blown disease.

So they can have a very variable and heterogeneous presentation, but one needs to understand that even minor effects like a loss of appetite, aching joints, or nausea can be detrimental in a young patient who's going to school or college.

We have hematuria and proteinuria, which are common presentations of IgA nephropathy. While we can have macroscopic, visible hematuria in 40 to 70% of patients, which is kind of after upper respiratory infections—synpharyngitic hematuria. Bleeding can also be triggered by intense exercise.

We can have proteinuria which is about 75 to 80% of patients—very sensitive indicator of progression of the disease; it forecasts a poor prognosis. It's rare for proteinuria to occur without microscopic hematuria. Right now, our main biomarker for IgA nephropathy prediction, or in general, how IgA nephropathy will progress, is by measuring proteinuria. It's one of those markers that we are using most of the trials are using, is the 9-month decline in proteinuria for accelerated approvals.

We can also have asymptomatic microscopic hematuria, or we can have frequent episodes of macroscopic hematuria in between microscopic hematuria. And the importance of early screening—or the importance of dipstick screening, we can catch early microscopic hematuria in those.

Dr. Yancey:
Can we formally diagnose a patient with IgA nephropathy based on the hematuria and proteinuria symptoms alone?

Dr. Kalra:
Unfortunately, no. The assessment and true diagnosis of IgA nephropathy requires a kidney biopsy, which is gold standard. Unfortunately, we do not have any validated serum or urine biomarkers for IgA nephropathy at this point. Novel biomarkers are being evaluated. Whereas when we do a kidney biopsy, it requires IgA-dominant staining in the glomeruli, and we also assess for secondary causes of IgA nephropathy before labeling a patient as having IgA nephropathy.

So let's go over an interesting patient case. Sarah, who is a 25-year-old with an Asian descent. She is experiencing a self-limiting episode of dark brown urine following an upper respiratory infection 2 weeks prior to her exam—so this is possibly a synpharyngitic hematuria, which we just spoke about. She is currently not menstruating and recalled a similar incident when she was a teenager. Her age at baseline is 25; race is Japanese; eGFR at the time is 70 mL/min/uh/body surface area; blood pressure is 130/80; and proteinuria is 2.1 g/dL. Her dipstick results show color dark blood—dark brown, glucose negative, pH 4.5, 2+ protein, and positive blood.

So clearly, just going by this, we know that this patient, just by virtue of her age, her race, her current eGFR, in a 25-year-old with proteinuria and hematuria, that she is at high risk for progression. The kidney biopsy will give us the final diagnosis. It reveals dominant IgA staining and evidence of mesangial hypercellularity, which confirmed Sarah's IgA nephropathy diagnosis.

So Sarah's biopsy was evaluated using the MEST-C score. Her biopsy showed mesangial hypercellularity greater than 50% of the glomeruli, so she had a score of M1, E0, S0, T0, C0, indicating mesangial hypercellularity. So again, like histopathological features like the MEST-C score can serve as a valuable early prognostication tool which is used for evaluating the risk of progression, but it is not deemed measured to kind of take treatment decisions based on just the MEST-C scoring. It's not being validated for treatment decisions.

So just going over the MEST-C scoring, which it gives us a great framework. It's basically the pathologist talking to the nephrologist in making a clinical decision regarding the biopsy of the patient. This is a histopathological system that evaluates key markers of kidney damage to understand the disease severity and progression. So it's providing a standardized framework here. mesangial hypercellularity you have either an M0 or an M1, depending on the glomeruli; endocapillary hypercellularity depends on the increased number of cells in glomerular capillary lumen. It can either be present or absent; segmental sclerosis adhesion or sclerosis not involving the entire glomerulus, either it's absence or presence; tubular atrophy presence—the presence of tubular interstitial fibrosis in the cortical area, you can either have 0–25, 26–50, or greater than 50. It has three scores: T0, T1, and T2; and then we have the crescents which will be fibrocellular or cellular crescents, either it is present, less than 25%, or more than 25%.

So we can compass this entire score based on the biopsy. It clearly gives us a very fair idea where are we more on the inflammatory side, are we having more Ms and Es, or are we having more of Ss and Ts, which is more of fibrosis. So one needs to use this tool along with proteinuria, eGFR decline, the age, and other features and not take it just independently to make clinical decisions. But however, this tool is excellent to characterize and understand the pathogenic mechanisms that are affecting the kidney structure in general.

So how can it help assess disease activity? I just briefly touched on this. Higher acute activity—the more of Ms and Es—if you have more mesangial hypercellularity and the endocapillary proliferation or hypercellularity, again, this goes to the four-hit hypothesis. Basically, more formation of galactose-deficient IgA1, and then eventually depositing in the mesangium, causing mesangial hypercellularity and endocapillary proliferation. More of M/Es and score kind of warrant the need for more immunosuppression in these patients, or early immunosuppression, whereas more of S and Ts highlights the fact that there is much more ongoing, chronic, irreversible loss.

As I told you early on, that now the KDIGO 2025 wants us to think about IgA nephropathy in the form of a multi-pronged approach. We are halting the immunosuppression pathway, or in general, drivers of underlying nephron loss, which is basically your CKD mechanisms, and also simultaneously, we are acting on the immunological side of it. So it just depends on how the biopsy looks like—if there is a lot of S and T, so we know there's a lot of chronicity, so we can understand the fact that the proteinuria is coming from the chronicity. It is not going to go away, and we need to target more of foundational therapies there, as opposed to more of M and Es, where we can think about something like a disease modification therapy.

But overall arching principle will be to reduce proteinuria. The disease modification and foundational therapies—combining them together and helping out with proteinuria reduction. That's the overarching principle behind the IgA nephropathy consortium, or just how to eventually delay the progression of the disease, to prevent the proteinuria from progressing, and the GFR stabilization, which I mean by decline preventing the decline in the GFR slope.

Dr. Yancey:
So given the variability in patient presentation and progression, can the MEST-C score help with determining the risk of the patient's progression moving forward? And are there any other variables that we may use to help us determine a patient's risk of progression?

Dr. Kalra:
So we have the international IgA prediction tools that combines the clinical, histopathologic, and demographic variables, in addition to the use of treatments like RAS blockers, immunosuppressive therapy, and biopsy. It helps us better stratify patients to make therapeutic clinical decisions. It tells us that there is something more than proteinuria. Patients are assigned to different risk categories which predict the risk of experiencing either 50% decline in GFR or progression to kidney failure up to about 80 months from biopsy.

So again, our same patient, we kind of plugged her numbers in the IgA prediction tool. One can scan to access the IgA prediction tool here. So based on this, we got a 50% decline in her GFR. At the risk of 50% decline in GFR, her progression to end-stage kidney disease after kidney biopsy was 15% for this patient. So Sarah had a 15% risk of progression based on her numbers, based on her biopsy.

So using baseline characteristics at biopsy, Sarah had a 15% risk of progression to end-stage kidney disease at 5 years. So 1 year after the treatment with optimal supportive care, which is basically low-salt diet, RAS inhibitors, uh and foundational therapies, getting the blood pressure in check, putting her on a statin, her blood pressure decreased to about 120 /80, and the proteinuria was reduced to 0.9. So but her risk progression calculated again, an updated post-biopsy risk prediction tool at 1 year after diagnosis, was about 31% at 6 years post biopsy. So there is two different tools here, one at the biopsy and one updated prediction tool post biopsy.

Dr. Yancey:
There seems to be a strong correlation between the proteinuria and that worsening risk of developing kidney failure. Can you delve into this a bit more?

Dr. Kalra:
Absolutely. Actually, we have not had a lot of endpoints. The endpoints we've been using is the doubling of serum creatinine, end-stage kidney disease, or death. And actually, this takes a very long time. So what we use now is a surrogate endpoint, which is proteinuria. And kudos to the initiative that was the combination between the ASN and the FDA, where we were able to justify proteinuria as a surrogate endpoint. And this actually greased the wheels for newer therapies in the space of IgAN. While the other endpoint that we use is the eGFR slope. But proteinuria is a strong prognosticating factor which leads to progression of kidney disease.

And earlier thought was based on the Canadian registry we had was that proteinuria less than 1 gram, we have less risk of progression, and that's why we were trying to target the proteinuria of less than 1 gram and continuing supportive care in those patients.

The new radar data from UK tells a different story. It's a UK-based registry, or to participates in RaDaR any patient with proteinuria of greater than 0.5 gram or a GFR less than 60, these are high-risk patients. Every renal unit across UK can leverage this data, so we have time average proteinuria, we are dividing the proteinuria into different levels greater than 2, 1-2, 1 to 0.5 to 1, and less than 0.5. So what RaDaR showed that even at lower degrees of proteinuria, less than 1 gram, or even less than 0.5 gram, 20% of these patients were requiring dialysis in their lifetime, or even 30% of the patients with proteinuria of 0.5 to 1 gram, were having adverse kidney outcomes during their lifetime.

So this was actually eye opening, because we were not even biopsying these patients prior to this, less than 1 gram of proteinuria, and everybody was calling it quits and trying to stabilize it from there. But the RaDaR data tells a different story. So if your threshold of proteinuria has gone down, the threshold of biopsy also should go low. So one needs to get the proteinuria down to the lowest limit, ideally 0.5, or even less than 0.3 with a maximum able unit, with the help of these newer therapies that we have.

There's another way of looking at it, is the GFR stabilization. You have higher levels of proteinuria are linked with increased risk of eGFR decline and faster progression of kidney failure. The more the proteinuria, the faster the eGFR decline. As we see, we increase the risk by 2x to 3x.

There's also a very powerful way of looking at it. This Heat Map basically tells us that what is the likelihood that one will develop kidney failure in their lifetime if they have a set loss of kidney function for the rest of their life? So if they are losing—for example, Sarah was losing about 3 ml/minute /year decline in kidney function. So she had 100% chance that she will land up on dialysis or she will have kidney failure during her lifetime. Whereas even if you see a patient who has a GFR drop of 1 ml/minute. So if they are less than 50—40 years of age, or even they are less than 50 years of age, 40% of those patients with a GFR decline of 1 ml/minute will require kidney replacement therapy during their lifetime, or they will reach kidney failure during their lifetime.

So ideally, you need to drop down the GFR decline to physiologic goals of less than 1 ml/minute/year to avoid dialysis, potentially during their lifetime. So 100% of the patients less than 40 years with a GFR decline of greater than 3 ml/minute will reach kidney failure in their lifetime. Imagine this patient who is just barely 20-25 she will reach kidney failure in her lifetime before she gets 40. Again, decreasing proteinuria. What we just spoke about, decreasing proteinuria and stabilizing GFR, can reduce the risk of kidney failure or death.You reduce the proteinuria by 20%, you reduce the risk of kidney failure at that by 21%. And sequentially, the more and better you decrease the proteinuria and that she has to be sustained over time, the better are your chances of preventing kidney failure or dialysis during her lifetime. For every 10% drop in proteinuria, the risk of kidney failure or death decreases by 11% approximately.

Dr. Yancey:
This has been some really great information. I know we're almost out of time, but really appreciate you taking the time to discuss um IgA nephropathy with us today.

Dr. Kalra, before we conclude, do you have any final thoughts for the audience?

Dr. Kalra:
This was a great summary of this talk. IgA nephropathy, again, is a progressive kidney disease with variable clinical presentation. Early

recognition of this disease burden and risk of progression is critical for management. We spoke about the four-hit hypothesis and spoke about how APRIL plays a pivotal role in contributing to the overproduction of pathogenic IgA1, linking it to the early stages of disease development, the pre-hit 1 what we spoke about.

We are often asked about whether we should rebiopsy patients in IgA nephropathy. What I would say is, if you want to consider rebiopsy, do it not for the MEST score, but do it to understand the activity—you want to get a feel of what the biopsy looks like. It's more of immunological activity or the inflammatory activity or chronicity.

We have a plethora of medications right now. We are actually kind of not talking about the glomerular disease per se, but it's actually the patient mortality at a young age which needs to be identified. If we are not thinking long term for these patients, we are going to undertreat and not serve our patients very well. So really, the time to diagnose them is early, so we can diagnose them early and treat them accordingly with the right medication. And the importance of individualized therapy, we have to select the right therapy for the right patient.

Dr. Yancey:
Thank you, Dr. Kalra, for the informative presentation and discussion today and this valuable resource for our NephU community. To our NephU viewers, thank you for joining us.

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