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A Case-Based Discussion on Managing Adult Patients With C3G or IC-MPGN in the Era of Complement Inhibition

Announcer:

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Dr. Jhaveri:

Welcome to this case-based discussion on managing adult patients with C3G and primary immune complex MPGN in the era of complement inhibition. Through a practical patient case and a review of emerging clinical evidence, we will discuss how to individualize treatment decisions, optimize the use of complement-targeted therapies, and translate the latest data into everyday clinical practice.

This is continuing education with GLC, and I am Dr. Kenar Jhaveri.

Dr. Wadhwani:

Hello, everyone. I'm Dr. Shikha Wadhwani.

Dr. Jhaveri:

So I'll begin telling you about a recent patient case, Shikha, and then you can tell me what you think, and we'll go back and forth.

So this is a 29-year-old woman with biopsy-proven C3 glomerulonephritis. So her initial presentation was a creatinine of 1.4 with a GFR of 52 mL/min and a protein creatinine ratio of 4.8. Her serum albumin was 2.9 with microscopic hematuria. Her serum complement markers showed a markedly low C3 at 32 mg/dL and a normal C4. Her ANA, ANCA serologies were all negative. C3 nephritic factor was negative, and the free light chains were within normal range.

A complement workup showed an elevated soluble C5b-9 and evidence of alternative pathway activation, but there were no pathogenic complement gene mutations that were identified. A kidney biopsy was done, obviously, that showed an MPGN pattern of injury with endocapillary hypercellularity and focal crescents. The IF showed C3 dominance. C3 was 3+ and immunoglobulin staining was negative. EM demonstrated mesangial and subendothelial deposits, and the IFTA was probably 10% or so. So the diagnosis was a C3G.

Given her age and aggressive nature of the disease, we did treat the patient with mycophenolate and glucocorticoids. I titrated up the MMF to 1.5 g twice a day, and I treated the patient for 8 months. The proteinuria after 8 months is only down to 4.1 g, and the creatinine 1.7 from 1.4, so it actually got worse. C3 remains markedly low. It is persistent microscopic hematuria.

Dr. Wadhvani:

I assume this patient really did not get to you at the onset of their disease. It takes quite a long time for these patients to actually get referred to a nephrologist, and by the time you saw her, I think you said her creatinine was already 1.4, which for a 29-year-old, she's lost 50% of her nephrons already.

And then after several months of what could be considered standard of care therapy, at least in the past, her kidney function's worsening. I think, as you know, this has been a really challenging condition for us to treat. One, just to get these patients into our offices and make a diagnosis. A lot of these children do present in childhood, or sometimes I've had situations where the diagnosis was missed in childhood and they're now presenting to us as an adult, as your patient.

I think just hearing the case I'm sad that your patient did not respond to mycophenolate and glucocorticoids. But I'm also not surprised because I've had the same situation happen to me, and I've had patients progress all the way to end-stage kidney disease, and we've been having conversations about transplant which is really challenging at such a young age.

I think some of the pearls that you brought up were definitely some classic things we think about with C3G, the low C3 level, the elevated soluble C5b-9. And what I think is remarkable is when you initially biopsied this patient, it was clear C3-dominant staining, and there wasn't other features that were necessarily confusing, and initially you had minimal IFDA. But in just a few months, you already started to see kidney function worsening. And I'm kind of concerned that we're losing time by sort of treating this patient with all we had for many years, which is sort of this cookie cutter, throw mycophenolate and steroids when we don't know what to do, and it's not a targeted approach. You mentioned the C3 was low, the C4 was normal, and you had evidence, obviously, of complement activation is what we expect in C3G. We know there's alternative complement pathway dysregulation. So I'm really thrilled that now we don't have to approach every patient up front with mycophenolate and glucocorticoids, and we have new options.

So I'm curious. Did you have access to any newer therapies that are more targeted for the complement system? And what did you do next after she clearly wasn't responding to mycophenolate?

Dr. Jhaveri:

The standard of care at this point is mycophenolate and steroids for C3G. But in the last 1 year, or a little bit more than a year, we have had 2 clinical trials: one, an oral factor B inhibitor, and another, complement 3 inhibition, that's been approved for C3G and immune complex MPGN.

And that might have changed the way we actually treat these patients. So I actually had access to the factor B inhibitor, the oral, and treated the patient given the inadequate response to this mycophenolate and steroids. And mycophenolate is discontinued. We started the factor B inhibitor. The C3 levels drastically improved from 32 to 88, and the soluble complement factor 5b-9 normalized. The proteinuria unfortunately remained the same, around 3.8 to 4 g, and the creatinine actually rose to 2, and the GFR dropped to 32.

Any thoughts on the recent 2 drugs that are approved for C3G and then how this patient responded?

Dr. Wadhvani:

I think the factor B inhibitor data show that it did work for a number of patients.

I wonder if we had access to that sooner and we could have given that up front instead of the mycophenolate and glucocorticoids when she sort of had more of a chance to respond, perhaps the outcome would've been different. But I think at this point you've had, I think you said, something like 8 months or so of the mycophenolate and glucocorticoids, then you've tried another 6 months of a factor B inhibitor.

So I might say at this point, I would have a conversation with her. Should we get a repeat biopsy, see is there still activity, or is this all chronicity? Because the other thing to consider is are we putting someone at risk for side effects from a medication that isn't necessarily doing something? Or now that we have multiple approved therapies, could we switch her to another therapy that's also approved that you mentioned? So that would be the conversation. I love kidney biopsies, so I would probably be interested to see if the patient would be willing. Now that it's been a year and a half or so, we may not be dealing with the same thing.

Dr. Jhaveri:

So I think, Shikha, you brought up a very good question. What is driving the persistent disease, right? Is it the residual complement activity, or is it an upstream mechanism that's inadequately controlled by the factor B inhibition? Or like you said, could it be an irreversible chronic kidney injury at this point?

The one other thing I would also mention is that maybe we are missing a diagnosis that's driving the C3. So should we reconsider looking at a postinfectious or infectious category or the monoclonal gammopathy? I think those were all persistently ruled out. But we did do the Wadhvani approach and re-biopsied the patient at 15 months, and it did show persistent C3-dominant GN with ongoing activity. But this time there was the 30% to 40% fibrosis.

So now the key question becomes, would you consider alternative therapy or consider this a treatment failure and not do any treatment further? I just wanted to see what your thoughts are on that.

Dr. Wadhvani:

So, yeah, I think that it would be worth kind of chatting a little bit about the VALIANT trial, and there's some newer data also within the last couple of months that I think are important to share.

Dr. Jhaveri:

The VALIANT trial, it was a phase 3—I think it was around 124 patients, but included both C3G and primary immune complex MPGN, both adult and pediatric patients.

At 26 weeks the trial showed that the C3 inhibitor pegcetacoplan reduced proteinuria by 68% versus placebo. And the reduction was over 50% for the proteinuria reduction, which is great. And the stable GFR occurred in 49% versus 3% in the placebo, which is again a game changer, right? And the tolerability of the drug was really great. It was well tolerated from the patient perspective.

In addition, the long-term data was presented at the ERA recently. At 1 year pegcetacoplan produced a sustained 63% reduction in proteinuria with 50% achieving proteinuria less than 1 g, and eGFR remained essentially stable.

So this, and then they showed the 52-week data with consistent safety profile and no meningococcal infections. So the safety profile also was very good at 52 weeks.

Okay. In addition, there was a poster at ERA that also showed the injection site reactions people think about with these agents. Really, there's only one patient discontinued because of injection site reaction. So really, no severe injection site reaction, if that's what people are worried about.

So I think, in general, even the pharmacokinetics of this drug are great in terms of all ages, diagnosis, transplant status based on eGFR. The long-term late data is coming out, which is great. So I would consider this as a strong option for this patient if I would give this patient one more chance before we call it quit in terms of maybe changing therapy.

What do you think? What do you think about, overall, some of the data and what we would do for this patient?

Dr. Wadhvani:

Yeah, no, I agree with you. I think the data sort of speaks for itself. You kind of shared this patient's journey, which I think is not unique. There was significant GFR loss just within 15 months. So your patient, I think, started at 1.2, 1.4 creatinine and was all the way up to a creatinine of 2 just within 15 months while you were trying therapy.

That's not even the natural history of the disease. That's while you were trying mycophenolate, glucocorticoids, factor B inhibition. So, I mean, in terms of how much GFR your patient lost in 15 months, it was almost 20 mL/min, which is terrible. And to see that we have a therapy that at least over the course of a year has stabilized GFR completely, I mean, that's mind-blowing to me.

Dr. Jhaveri:

It's very important for our patients to understand, and all the nephrologists, that compared to—recently we saw the RaDar data from IG, and you saw that even that was thought to be a very benign disease, with hematuria and maybe creatinines running in the ones people

thought there was a benign disease.

But the long-term data showed dismal outcomes even for a proteinuria of 0.5, right? So this, the RaDar data for C3 was presented at ERA, and that even had worsening data. So as 10-year kidney survival was 67%, so the one-third of these patients that were studied in the UK database with C3 and immune complex MPGN, one-third of them progressed to kidney failure within 10 years of diagnosis.

And this is with standard of care, which is not great right now, which is mycophenolate and steroids. So I'm hoping that the newer medications will change this curve and that these patients do not end up on dialysis or needing a kidney transplant, and these traditional immunosuppressions go away and we have more targeted therapies. And I think these therapies are really game changers, and they will really change the way we treat C3G.

Now, in terms of switching, I mean, when would you consider switching in general, when you have one patient on a drug, consider switching to another agent that's more targeted? Would it be in a case like ours, or do you have other scenarios where you would do the switch?

Dr. Wadhvani:

I've had patients with C3G who have been stable on mycophenolate, so it's not a one-size-fits-all. But I think if I was starting up front knowing what I know now in someone who's treatment-naïve, I would go for targeted therapy over mycophenolate and glucocorticoids up front because those are actually FDA-approved for C3G; mycophenolate is not. And then I think if I already had them on a factor B inhibitor, they were doing well, I'd probably continue, but I wouldn't wait too long, just as you did, when I have other options available.

Dr. Jhaveri:

Before we wrap up, let's each of us offer a final take-home message. Shikha, why don't you tell our listeners what you will take away today.

Dr. Wadhvani:

It's really important that we try to diagnose these patients early, refer patients with hematuria, proteinuria, and definitely abnormal serum creatinine to a nephrologist as quickly as possible.

But I wouldn't wait for the creatinine to be abnormal because, unfortunately, then we're already catching them late. And then I think as soon as we have a diagnosis, I think we need to have the conversation with our patients about the options that are now available that are FDA-approved, they're safe, and, I think, really have potential to change outcomes for patients.

Dr. Jhaveri:

Thanks, Shikha. I think my takeaway is really simple, is treat the target. I would use more targeted therapies and not beat around the bush with steroids and mycophenolate.

And that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Shikha Wadhvani, for joining me.

Dr. Wadhvani:

Thanks for having me.

Announcer:

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