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Transforming Care in Pediatric Patients With C3 Glomerulopathy: Targeting C3 at the Source

Dr. Daga:
This is CE on ReachMD, and I'm Ankana Daga.

With me today is my friend and colleague, Dr. Richard Lafayette.

So I'd like to start off with a case. We have a 13-year-old girl who has no past medical history, has been healthy all throughout her life, and has now developed swelling on her face and feet for a couple of weeks. This concerns the family. The family sees their physician, and what they find out, after a host of testing and a specialist referral, was that she's now diagnosed with C3 glomerulopathy after multiple blood tests and undergoing a kidney biopsy.

The kidney biopsy results show that on light microscopy, she has a membranoproliferative pattern of injury. And on immunofluorescence, there's C3-dominant deposits and mild IgG staining. And on electron microscopy, she actually has multiple deposits that are present in the mesangial space and the subendothelial space, and there are certain deposits that are found in the subepithelial cells.

In terms of how she's doing kidney function-wise, she actually has normal kidney function with a creatinine of 0.6 mg/dL, she has an albumin that is low at 2.2. She has an incredible amount of protein in her urine, with a UPC of 5.5. Fortunately, she's not hypertensive, but she is quite swollen, and she's about 5 pounds above her estimated dry weight.

So, Richard, what are your thoughts on this case?

Dr. Lafayette:
Yeah, thanks for sharing that with me. This is really a devastating presentation when a young girl, adolescent, comes in with nephrotic syndrome and swelling, and then ends up with a diagnosis of C3 glomerulopathy that obviously is very frightening to her, to her family, and, as you know, to clinicians. And I'm an adult doctor, I know this is a pediatric case, but again, there's very much similarity.

Again, C3 glomerulopathy was recently described within the last decade as a pattern of membranoproliferative glomerular nephritis that, just as you described, is C3 dominant. And we really define it that way because it guides prognosis, and it guides treatment decisions more and more these days. And when we see that membranoproliferative pattern, and we see C3 dominance, we really think that this is something that is high risk, is likely to progress. And we've seen progression rates, both in children and adults, of over 2/3 of the patients can end up dialysis-dependent within a decade. So again, it's a very, very serious diagnosis.

Obviously, in this girl, we want to treat her nephrotic syndrome, get her a low-salt diet, give her some diuretics, make sure, as you mentioned, her blood pressure stays well controlled. But when the proteinuria stays even more than 1 g, let alone nephrotic syndrome, then patients are really at high risk. And so I think that's the concern.

There are similar considerations. You want to see if this is really C3 glomerular nephritis versus dense deposit disease. This sounds more like C3G without the band-like electron microscopic findings of dense deposits in the glomerular basement membrane. But overall, my feeling is that those are similar diseases, treated similarly with similar prognosis. In children, there may be even worse prognosis with dense deposit disease.

So I think that's our background. And this is a big challenge. Ankana, would you agree?

Dr. Daga:
Absolutely, I think you summed it up really well.

Just briefly wanting to review, in addition to the treatment that you had laid out in terms of salt reduction, making sure blood pressure is well controlled, perhaps considering some diuretics to help the weight gain, the current existing guidelines around treatment of C3 glomerulopathy that we've been following, most recently from KDIGO's version in 2021, what has been considered standard of care for patients who, say, have this diagnosis of C3 glomerulopathy is to treat them with high-dose glucocorticosteroids as well as mycophenolate mofetil.

These recommendations have not been approved by the FDA. These are off-label use, but this comes from data that exist that these therapies perhaps do improve the amount of protein in the urine, or to reduce the inflammation that's going on in the kidney, perhaps in a nonspecific way. And in addition to doing that, consider some RAS inhibition.

But my question to you, Richard, is now that we have, finally, targeted complement inhibitors approved for treatment for C3 glomerulopathy, namely iptacopan and pegcetacoplan, Richard, what do you want to share with the listeners about these 2 recently approved therapies?

Dr. Lafayette:
Yeah, I think it's really, really exciting to have new therapies, because, just as you mentioned, and similar to adults, when we have these patients with worrisome prognosis, of course, we first make sure they don't have a reversible, treatable infection, even in very young adults, and there are cases in children of monoclonal gammopathy driving this, which might be separately treated.

But if this is typical C3G, in the past, we've treated them heavily with immunosuppression. It often doesn't work and has devastating side effects. And we've tried eculizumab, which, as you know, sometimes seems to have worked, but not frequently enough to rely on. So developing drugs more aligned to the pathophysiology, which is dysregulation of the alternate complement pathway, having agents that more directly address that, particularly iptacopan, an anti–factor B agent, and pegcetacoplan, an anti–factor 3 and 3b agent, this is really, really critical. It gives us, for the first time, targeted therapy that we really can look at this disease as dysregulated alternate pathway, and now we have agents that can stop that dysregulation by slowing the production of activated C3, therefore stopping the complement pathway right in its tracks, stopping C3a and C5a, which are inflammatory peptides, and stopping the terminal complement pathway, C5b through 9 from being active, which goes and is directly cytotoxic to kidney cells. So again, the iptacopan is a little more upstream at factor B in the alternate pathway, C3 blockade will block all the pathways, block C3a, C5a, and complement. So I think these are really exciting to have these agents.

Dr. Daga:
For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Ankana Daga, and here with me is Dr. Richard Lafayette. We're discussing complement-directed therapies in the treatment of a pediatric patient newly diagnosed with C3 glomerulopathy.

Yeah, absolutely. And can you tell us a little bit about the clinical evidence that led to the approval of these therapies for treatment of C3 glomerulopathy?

Dr. Lafayette:
Yeah, Ankana. As you know, this has been a really exciting year. We've had 2 randomized controlled trials of these agents, for the APPEAR-C3G trial for iptacopan. Again, a group of patients—and remember, this is a very rare disease, only happening about 1 in a million people—so they were able to gather over 100 patients to screen. Nearly 80 patients were randomized with biopsy-proven C3G, and they were given a placebo vs iptacopan. And there was a very nice reduction in proteinuria, stabilization of GFR, biopsy evidence

that C3 deposition and disease activity were somewhat quelled and looked really nice and led to regulatory approval of iptacopan for C3G.

In the case of pegcetacoplan, there also was a randomized controlled trial published this year called VALIANT. Here there was a similar number of patients overall, slightly more. It included both C3G and immune complex glomerulopathy, included adolescents and adults, and included some patients posttransplant. And across all of those populations, again, it was a pretty spectacular reduction in proteinuria by about 2/3, again, a very clinically and statistically significant stabilization of kidney function with a really high number of patients reaching proteinuria remission and stable kidney function, and again a very impressive reduction of C3 deposition within the kidney.

So again, in both cases, really, really nice results, giving us new FDA-approved tools to use for our patients. And at the same time in both programs, there was a requirement for vaccination against meningococcus, antibiotics until the vaccines took hold. And in that situation, there was really beautiful safety with good tolerance of the medications, and this held for the C3G, the immune complex as well, children and adults, and so really, really nice options for us to treat our patients.

Dr. Daga:
Yeah, it's finally an exciting time, as you alluded to how rare this disease is and how severe this disease is, to actually have targeted therapy with such incredible, convincing data. Specifically for the pediatric world to have adolescent patients included in a trial with good results also is promising.

Practically speaking for our patients, iptacopan is an oral medicine; pegcetacoplan is a sub-q infusion taken twice a week for 30 minutes. That's how the infusion lasts, actually easy to do at home with a pump. And pegcetacoplan you know had the trial for pediatrics.

So for the pediatric world, when there is a medicine available, then discussing with the family that it’s a subcutaneous infusion, always is met with a little bit of hesitancy in the beginning, but overall has been very well tolerated among the patients who were studied, and in my experience the patients who I've been able to start them on this therapy.

And thank you for bringing up the infection risk, because similar to eculizumab, which has now been approved for more than a decade in patients with a different condition, there is risk of increased bacteremia from these encapsulated organisms, but with the right vaccinations, which is an important requirement for being on these medications, most patients have done really well.

The trials didn't mandate patients needed to be on antibiotic prophylaxis, so that is sort of left at the discretion of the prescribing physician, and sometimes the practice is that until they're fully immunized, they get the whole series, it may not be a bad idea to have them on some prophylaxis for that period of time.

I wanted to ask you, in this specific case, a 13-year-old, if you were going to consider starting her on pegcetacoplan, what would that look like? How would you counsel the family in what that exact strategy would mean for this patient?

Dr. Lafayette:
Yeah, I think you covered it very well. And we would go over the options, talk about iptacopan off label for kids, compare it to eculizumab, compare it to systemic immunosuppression, but it would be a wonderful choice. Talk about those twice-weekly infused subcutaneous injections. And just make sure they understand that in a trial it was well tolerated, that it was with great safety when the child is well vaccinated, that everything is going to be closely, closely monitored for safety and tolerability. And that we expect these days, really remarkably, we can have an expectation for a really nice response, a reduction of risk, and in many children and adults, control of the disease to where the GFR will be stable. So great expectations.

Dr. Daga:
And as you probably know that the trials are great, but I think when you look at what the patients were already on, I think that part is a little bit hard to understand whether these patients were already on some form of what was considered standard of care in terms of being on mycophenolate or steroids. And so I think with time we'd know how those therapies would pan out as to whether those patients would continue to need those therapies, or would a complement-directed therapy by itself be enough for these patients, and kind of thinking about whether we should start them on this therapy at the get-go if we can, would they require additional glucocorticoid

therapy, or would they require MMF? I don't know, Richard, if you have thoughts around that, but it's something that I think about.

Dr. Lafayette:
Yeah, a major issue with VALIANT is that many of the patients were indeed status post immunotherapy, and many still were on immunotherapy to get the wonderful results that we saw, but some weren't and still had very robust responses. So I do think you could try this as primary therapy, and still the expectations will be great, but we're going to have to see some real-world data and get further experience for sure.

Dr. Daga:
This is great. Thank you for this. And thank you to the audience for listening. Thank you, Dr. Richard Lafayette, for sharing your extremely important insight and expertise.

Dr. Lafayette:
Okay, thank you. Goodbye.