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Transforming C3G Care: New Advances in Targeted Treatment

Dr. Colbert:
Welcome to *On the Frontlines of C3G* on ReachMD. I'm Dr. Gates Colbert, and joining me to discuss diagnostic challenges in complement 3 glomerulopathy is Dr. Anuja Java, who is an Associate Professor of Medicine in the Division of Nephrology at Washington University School of Medicine and the Director of the Kidney Transplant Clinic at John Cochran Veterans Hospital in Missouri.

Dr. Java, welcome to the program.

Dr. Java:
Thanks for having me, Dr. Colbert. It's a pleasure to be here today.

Dr. Colbert:
First, Dr. Java, what does the therapeutic landscape for C3G currently look like?

Dr. Java:
So that is a very timely question, Dr. Colbert. Up until a month ago, the treatment landscape was very variable for C3G and was guided by the KDIGO 2021 clinical practice guidelines for glomerular diseases. And based on those guidelines, for patients who had C3G in the absence of monoclonal gammopathy, the treatment was basically any kind of immunosuppression. There were cases of rituximab and the guidance that if these failed, then anti-C5, like eculizumab, could be considered. Additional guidelines recommended that if patients did not respond to any of these therapies, then they should be enrolled in clinical trials.

And this has really changed in the last month because we have the approval of a complement factor B inhibitor, which is called iptacopan. And in the coming months—hopefully before the end of the year, we are hopeful that a second drug will also get approved, which is the C3 inhibitor called pegcetacoplan. And there has been really good clinical trial data for both of these drugs, so the treatment landscape is really going to drastically change with having these targeted treatments.Some of the other immunosuppression just helps with decreasing the inflammation that is an outcome of the complement activation, whereas these drugs are more targeted.

So iptacopan is a drug that works upstream in the complement pathway, specifically targeting the alternative pathway, which is the driver of disease in C3G. And there has been a phase 3 study called APPEAR-C3G, which looked at the efficacy and safety of this drug in patients, and it showed that patients who were on this drug had a 35 percent improvement in proteinuria at six months, which was sustained at 12 months. Additionally, there was improvement in the EGFR trajectory compared to historical declines and a pretty favorable safety profile.

And the second drug, which is an emerging treatment and also has shown very promising results and we're hoping will get approved later this year, is called pegcetacoplan, which is a C3 inhibitor, and C3 is the central molecule of the complement system. So this drug also had a phase 3 trial, and it showed almost a 67 to 68 percent reduction in proteinuria. And they also had histology data that showed that 74 percent of patients achieved improvement in the C3 staining and that 71 percent actually achieved 0—had almost negated the staining. There was 0 intensity staining. So these are two treatments that are really promising that I think are going to become the face of the treatment for these patients.

Dr. Colbert:
For those just joining in, this is *On the Frontlines of C3G* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Anuja Java about current and emerging strategies in complement 3 glomerulopathy treatment.

So, Dr. Java, if we zero in on monitoring patients with C3G, what key clinical outcomes should clinicians prioritize?

Dr. Java:
So the three primary outcomes that have been used in clinical trials for this disease—and even as a field, we consider our most appropriate—are proteinuria, EGFR monitoring, and histopathology. There was a Kidney Health Initiative C3G trial endpoints work group that was put together, and it was stated that a favorable treatment effect on all three of these endpoints would provide convincing evidence of efficacy when you're working with these targeted drugs. So those are the three main things—proteinuria, EGFR, and histopathology—clinicians would be or should be looking at.

Dr. Colbert:
As we wrap up, do you have any last thoughts you'd like to share with our audience?

Dr. Java:
As I mentioned earlier, we have come a long way in our understanding of these complement-mediated kidney diseases. It's really been a game changer, especially with the availability of these drugs for our patients with C3G because a few years ago, there were patients who we couldn't transplant or who actually refused to get a kidney transplant because we knew that there was going to be disease recurrence in the allograft. And now this landscape has completely changed for our patients.

I see this not only with what's happening in the C3G world but what is happening in the nephrology world and with all the therapeutics coming together—I see that we need a change in our mindset as nephrologists. We have always kind of felt satisfied by preventing patients from going on dialysis or preventing from going into ESRD, and we accepted that yes, there is CKD and we treat the CKD. I think we really are at a time where we can actually prevent CKD from happening. And so I almost think that this is a time when we should be able to prevent kidney disease altogether—not just prevent dialysis—and that is something that we have to start thinking about. And that obviously requires being very aggressive with diagnosing these patients and understanding what these diseases are. And we're almost at a time where we can pick and choose these treatments—precision medicine is coming into nephrology, which has been a part of oncology for a long time—I think we are making a lot of headway. So my main takeaway is that I think we have to change how we treat these patients and start thinking about not having kidney disease at all.

Dr. Colbert:
I want to thank my guest, Dr. Anuja Java, for joining me to discuss best practices and emerging strategies in C3G care.

Dr. Java, it was wonderful having you on the program.

Dr. Java:
Thank you very much for having me.

Dr. Colbert:
For ReachMD, I'm Dr. Gates Colbert. To access this and other episodes in our series, visit *On the Frontlines of C3G* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.