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Advancing Research and Novel Therapies for C3G

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode in our complement mediated kidney disease series titled, *Advancing Research and Novel Therapies for C3G,* is provided by KDIGO and supported by Apellis and Sobi. Here's your host, Dr. Carla Nester.

Dr. Nester:
Hello and welcome to KDIGO Conversations in Nephrology. I'm Dr. Carla Nester, professor of Internal Medicine and Pediatrics, Stead Family Children's Hospital, University of Iowa, and joining me to discuss Advancing Research and Novel Therapies for C3G is Dr. Nicole van de Kar. Dr. van de Kar is a pediatric nephrologist at Radboud University Medical Center, Nijmegen, the Netherlands. And her clinical and research interests include thrombotic microangiopathy, and the complement mediated kidney diseases. Dr. van de Kar, welcome to this podcast.

Dr. van de Kar:
Thank you, Dr. Nester. It's a pleasure to be in this podcast

Dr. Nester:
Let's begin our discussion today with, well, let's just take the first question. Let's start with your view of what the next decade, as compared to the last decade of course, in therapeutics will look like in the treatment of C3G.

Dr. van de Kar:
Well, thank you for this question. I think this will be really an exciting decade which we're going into because now we can make the diagnosed by kidney biopsy in C3G and we have already supportive therapy, which we know as RAAS blockade and low salt diet. And we have already for years the immune suppressive treatments as Prednisone and MMF but that is all non-targeted treatments. And you can read all these protocols in the KDIGO guidelines, for example. But what is now intriguing is that we have now the first-time targeted treatment available for C3G. And that's because of those two new drugs which have now entered and then they ended almost the clinical trials.

And then for the first time, we have a targeted therapy, which will target the overactive complement alternative pathway, as we know and we heard before. This is the driver of the disease. So this next decades having these complement inhibitors available for the treatment will be exciting, and I think it'll lead to less chronic renal damage, less end stage kidney failure, and hope for those C3G patients who need a kidney transplant and hope for a better future for all C3 patients. So I think this next decade will be really promising.

Dr. Nester:
I think you're exactly right. This idea of targeted therapeutics for the first time in our lives in this set of diseases is amazing. A small question and, and, and I don't want that you to have to think about it too hard, but do you think there are going to be issues about how to use them? For instance, are you going to consider primary therapy? Are you going to consider whether you have to do X, Y, or Z first?

Dr. van de Kar:
I think for us, as clinicians, it'll be very important to draft good protocol when to use these new drugs. For whom? On which, on which conditions, and how to follow them up and how to monitoring them. Because in the trials it was not in the patients were not mostly

primary having the disease for only a couple of weeks or months. Some were already having them for years and entered the trial. So I think there will be definitely people who can use it in the first weeks of the disease, but then will well, guided by protocols, I guess, what would be the criteria to use for.

Dr. Nester:
Yeah, I think that's an excellent approach, this idea of developing protocols. So, then the next question, which is a little bit unfair, you know, because, you know, obviously neither one of us are, are pharmaceutical people, but when designing these trials, you know, for these agents, what's your impression of how the sponsors decided upon the end points that they decided upon?

Dr. van de Kar:
Well, I was not involved designing the clinical trials, but I participated, as well in an international working group organized by the Kidney Health Initiative in 2021 to address the challenges needed to say what do we need from these trials and what outcome do we need and what are the best endpoints? And we had a lot of discussions in working groups and it went back and forth and we came actually at the end, we came up with three endpoints, which might, for C3G might be very valuable. And those are also endpoints you see in the trials.

And for me, I think the most important one is proteinuria. It's a risk marker for disease progression across various glomerular disorders. So not only C3G, and we know that large treatment effects on proteinuria are believed to predict treatment effects on disease progression. If you then look at C3G, then, we have not that much data in time, how patients are doing on the treatments. But we see that from cohorts in the United Kingdom and also from Iowa that if we can reduce the proteinuria and if you can reduces 50% or even more, I think then it'll at the end will benefit also your eGFR, so your kidney function and it will at the end, will be of health for your kidney function.

The problem is for proteinuria that it's not really an endpoint, which is much used in clinical studies. So what is it then good? Is it a bad endpoint? I think it's the best we have at the moment, and I think you would expect an effect at six months at least. So for that, I think it will be a good endpoint and the best we have at the moment.

Of course, if you ask in our group as clinicians, we also know that proteinuria is, can be difficult because we are aware that of course, if you have sclerotic regions in your kidney, you also have proteinuria and together with declining kidney function. We know that this is a different proteinuria. This is proteinuria because of fibrosis, and so this will always be an issue having proteinuria as an endpoint. But I think looking at creatinine function, at kidney function, looking probably, well also at histology it might help, but I think proteinuria is a good one.

And next we have the eGFR. We discussed it as well in our working group. And, of course you would expect if the inflammation in your kidney caused by the overactive complement activation, will decline by using these drugs, you could imagine that your kidney function will in time improve and the slope of your eGFR will then get less steep. So your kidney function will improve. We don't have data retrospectively data to see what will be the best follow up time. But I think also here's six months is fair to mention that you probably would not need a very deterioration of your EGFR because if that's the case, if your EGFR is deteriorating of going badly with the new drugs, you might wonder if something is wrong and you have to rethink again. So, that's very important, I think.

And then you have the histology. It's a rare disease and you only do kidney biopsy if you think really it's needed. So we don't know what we have to expect in kidney biopsies. You might think the new complement blockers inhibit C3 activation. So there might be a reduction in C3 deposits in the kidney, and you might think in time you will be seeing that in histapathology, but that means that you have to re-biopsy patients again. And I think this is something which we really need to think of if we want to do it and what we want to see.

So I think what we see in the trials is that they looked at histopathology and that was mostly the secondary endpoint. And they had, for example, they had an histological activity index. But in this score there's also a necrosis or fibrosis mentioning. So, we have to define what do we want to see in histopathology which could improve the kidney health. And probably the deposits is one of the most important things, but less fibrosis if there's already something there would be benefit as well.

Dr. Nester:
Yeah, I think you know, all of your points are very important. I think we weren't as fortunate as, for instance, IgA to have that proteinuria is already a selected surrogate endpoint for our regulatory agencies. And when you think about the GFR, you can't wait, you know, the years it takes for the GFR to decline enough for you to get to dialysis, right? So you have to think about, you know, what measure of the

GFR are you going to pay attention to? And you kind of already brought up the important point. Because one of my questions was going to be if you rely on histology, which certainly the animal models would've supported that if you stop the alternative or if you block the alternative pathway that maybe the histology goes away. That means you have to go back to re-biopsy. Two small questions about, and, and they're actually not small questions, but so you've already told me you would re-biopsy. Are your patients in general going to agree that that's okay?

Dr. van de Kar:
I think I would re-biopsy if I don't see enough, improvement in proteinuria or if I hardly see any improvement in proteinuria. I would also re-biopsy if I see, the kidney function is declining. This is really for me, a must to biopsy because that has consequences. If everything is going well then you might wonder, are we going to biopsy? And this is a difficult point because we should. In the ideal world, if biopsies would not do any harm, if it would be easy doing it, I think it would be good to do because we could see what the effect is in time of these new drugs on the histopathology. But that might be difficult to get patients and also clinicians into re biopsy, when things are going well.

Dr. Nester:
Yeah, I think you're exactly right, but you also make the point that we need the real-world experience to help us solve some of these issues. So, perhaps you can share a brief overview of the clinical trial results in general. I know, some of that, like you've said, has been published and some of them are, are waiting for publication. But if you wanted to share just a little capsule of that for our listeners.

Dr. van de Kar:
Well, it already started a couple of years ago with I think the first international trial on complement blockade in, in, in C3G was the Avacopan trial. And it was a phase two trial. Avacopan, we know now because it's now implemented in ANCA vasculitis treatment, but it's an oral blocker of the C5a receptor blocking the effect of C5a. And it was thought it might have a role in C3G.

And it was designed really good. I mean, double-blind, placebo controlled, and the endpoint was, there we come to the histology again, the endpoint was an improvement in histological activity at six months of using the product. And, this endpoint was not achieved. I mean, there was no significant difference between Avocapan and placebo. Although there was reduction in proteinuria by those who were treated by Avocapan in comparison with placebo. But, this trial did not made it further on.

And then we had, I think mostly at the same time actually, there was a trial, also a multicenter international trial on Danicopan. And that's a small molecule inhibitor of the complement factor D of the, also of the alternative pathway. I mean, not also because avacopan is targeting the terminal pathway, but the Danicopan is it's more upstream. That, Danicopan is cleaving factor B, it prevents cleavage of factor B and therefore it reduces the C3 convertase formation, which is seen as the culprit of C3G.

And this trial was a phase two trial. Also double blind placebo controls, but the efficacy was found to be limited. It was probably failing achievement in complement inhibition. And although there was some patients showing a decline in proteinuria, I think it was not showing good results, so it was stopped.

So, and then I, I think where we all have been waiting for and what we see those results of two phase three trials of complement inhibitors targeting at the level of C3. So at the C3 convertase, those are the iptacopan and pegcetacoplan, and both trials have reached now the occlusion rate of patients, and they are finalized or getting finalized and are almost ready or far ready to publish their results.

And I think iptacopan, for example, an oral factor B inhibitor, selectively blocks the formation of the C3 convertase of the alternative pathway. This phase three trial has been performed in adults, and this is now already the drug which is registered because of the results by the FDA and the EMA in the treatment of C3G in adults. And we have to await for the adolescent trial, which is still going on, but already very far ahead for their results.

So then we have pegcetacoplan it's a C3 blocker, activation level of C3. And this drug, I actually acts on C3 and therefore acts on all three complement pathways, including alternative pathway. And that's a drug you need to give subcutaneously, twice weekly. And for this phase three trial is in adolescence and in adults, so they combine it and it's in C3G, but they have also primary immune complex MPGN. And they have also included patients who are known with C3G and but have already a renal transplant. And actually those drugs have already shown good results, as you probably aware of. And I think the design was for both trials was they all had a six months, so 26 weeks or placebo or drug. And then after 26 weeks, all got the drug and I think the results have been published for the

first six months of both drugs.

Dr. Nester:
Yeah, so, so thank you for that overview. If you are just tuning in, you're listening to the KDIGO Podcast on Advancing Research and Novel Therapies in C3G. I'm Dr. Carla Nester and I'm speaking with Professor Nicole van de Kar, pediatric Nephrology, Nijmegen. So I'm going to ask you, and I might be able to guess, since you're a pediatric nephrologist, can you share with us some of the distinguishing features between the studies that end up being important given what kind of patients you're approaching?

Dr. van de Kar:
Well, I think what they did in both studies, I think the trial design was, at quite some similarities. Adolescents need to be above 12 years, so we don't have data on below 12 years, and you and I know that we see children which are younger than 12 years as well. They all wanted to have an active disease, all wanted the EGR above 30 ml per minute. They all want to have more than one gram per gram proteinuria in 24 hours or in first morning. Urine also, more than one gram per gram.

So that makes it you already have an exclusion of patients who have less than this one gram or don't have the age of 12. You need mandatory vaccination. I think that's very, very important. We are aware of that for the other diseases, atypical HUS and PNH, that you need vaccinations against the meningococcus, pneococcus bacteria, and hemophilus influenza. So that was all in all of them.

So that was one thing, and I think the exclusion criteria were almost all the same as well. So, you were excluded if you had more than 50%, sclerosis in your kidney biopsy. Secondary forms of C3G, so mostly in post infectious and the monoclonal gammopathy were excluded and you need to not have to have an exposure to other complement inhibitors. But you were allowed to have ACE or ARB inhibition or SLGT2 at least for adults. We are not allowed to use it in Europe for children. And you were allowed to have prednisone or corticosteroids and MMF, but you need to be on a stable regimen for those drugs. So those were actually having somehow the same results, the same inclusion or exclusion criteria.

But of course, the way of action is different. One, attacks factor B, the other attacks C3. Iptacopan orally, pegcetacoplan, subcutaneously and that means that you have already have some differences between those drugs. If we look at the results, I mean the results for both studies look good. Iptacopan had a 35% reduction in proteinuria change in proteinuria compared to the baseline, and versus the placebo. It had a stabilization on the EGFR in 12 months, so that's very good. The pegcetacoplan were in C3G and immune complex MPGN is included showed a reduction from 67% reduction in proteinuria compared to the baseline as compared to placebo. And they could show a small improvement on eGFR at six months and they had already looked at more biopsies Iptacopan at this time. And they could show less staining, or in a lot of zero staining on C3G, in kidney biopsies. So both drugs do really work as it looks on the complement overactivation we found in C3 glomerulopathy. So that's very good.

Dr. Nester:
Thank you. That's a very good representation of the trials, and I agree. You know, they both work very well. I'm curious, and I recognize we don't have data for this, but you mentioned they both require a one gram of urine protein, somewhat like the IgA world these days. Do you think once we get to real world we'll be interested in using it before a gram? Or do you think most of us will stick to the gram?

Dr. van de Kar:
Depends. I think if you have new patients and it's above the one gram. I think always you start, with ACE or ARB. And probably you will get already quite some patients having reduced proteinuria and maybe even below 0.5 gram a day.

And then becomes the questions and are we going to give those then already immediately a complement inhibition? Are we doing it instead of prednisone and MMF, which is at the moment standard therapy? Or we add first with the ACE and the ARB, we add prednisone and MMF and together with complement inhibition?

So I think this is really stuff to have good thinking about what we are going to do. It's also, I mean, those drugs are cost lots of money. And if we want to have it available for a good treatment in our C3G patients, probably, we should not use those complement inhibition drugs in those who have less than 1.5 gram a day, and maybe even not with one gram, we should start with ACE and ARB and see what comes out And then progress, with maybe Prednisone and MMF. But I know there are also colleagues who would like and love to start, with the complement inhibition right away.

But depends if attacking of the overactivated complement system would be enough in the first weeks of your disease, if there is such an inflammation already there, which is broader than only the over activation of the complement, should we then still need immune suppressive drugs, for example, for a short while. What would be the best protocol?

Dr. Nester:
I think you're exactly right. I think at the end of the day, we still have some thinking to do on this. We still have to figure out, you know, is attacking inflammation critical? Is targeting the complement system critical? Is targeting the protein critical? Or even for that matter, the CKD aspects. As you've kind of indicated,there's a number of supportive cares. So, the final point on that might be that will the standard of care change? I mean, we know what has been set by KDIGO currently. We have to decide what happens next, don't we? And more to come, I'm sure.

But, then maybe one of the final questions I'll have for you is that if you could pick one or two or maybe just a very few what are the biggest challenges you think that we're going to face? And, you know, we started this discussion about what's the next decade look like. Well, what's the next decade look like when it comes to challenges in this setting?

Dr. van de Kar:
I think I want to play out for all the clinicians treating patients with C3G, unite yourself to gain more data on C3 patients and the treatment, whatever treatment it is. I mean, if it's ACE, if it's ARB, if it's prednisone, corticoids.

And we really need good well thought of treatment protocols. We have to collaborate with each other to make those protocols. And I think there, there are initiative already going on, which I really encourage and I really think they're very important and we really have to work together on an international way to make this collaborative databases, because then we can see what the landscape looks like and what the drugs will do.

I clearly think that the standard treatment care will change for C3G and complement innovation will find its place somewhere in those protocols as well. But then we'll be very that like we discussed when to start. Which complement inhibitor use? Is there a moment to stop? Can we stop? Do we have to treat those with auto antibodies against the C3 convertase? Do they need the same treatment as those with genetic variation, for example? And I'm very curious, can we get complete remission in all C3G treated patients with complement inhibition, for example? And this is a more important challenge for us as clinicians.

We clearly have to monitor the efficacy, I think as well and the side effects, and that's what I told earlier. If you don't see a benefit, let's say in three, six months your therapy, reconsider. Maybe you need to re-biopsy again. You need to think if this drug is effective enough. Also if you think of complement inhibition in a long time, is it safe in your growing, child, in adolescent? I still don't know. I mean, we have just started with atypical AHUS of course and PNH and we, we are still figuring out, and I think we are very lucky for seeing these results of this new therapies, but it doesn't change anything on the presence of the auto antibodies against the C3 convertase. So, at the overactivation of the complement system, we can act with those blockers, but we can not do anything on those auto antibodies.

So that might be a challenge for future trials, maybe in combination with complement inhibition to see if we can get rid of this and to auto antibodies as well. Some will disappear by themselves in time, but some will stay there for a long time and will continue to over activate the complement system and possibly ongoing C3 glomopathy. So I think, well it's really, an interesting decade, which we are going into as clinicians and as patients, but promising. Very promising.

Dr. Nester:
That's exciting. Even hearing you talk, it gets very exciting. So what I hear you say is, for one thing that's going to be important is this idea of global teamwork. This idea of all of us collaborating to get the answers that we need. But also, I think you make a very good point of, you know, just surveillance of what happens and you know, what do we need to do next? So those are all fantastic points and I thank you very much for identifying all of those challenges.

We are about to wrap up. So before we wrap up completely, Dr. van de Kar, I thought I would ask you very quickly, do you have any final messages that you want to share with us? Perhaps you've said most of them, but if you have a few that you'd like to add, please do.

Dr. van de Kar:

I think if you, those who are listening, have patients with C3G in your practice and you're looking, clearly, you're looking out for this new, promising, new treatment options, but please try to contact your colleagues in expertise center or reach out to other colleagues who treat C3G patients and try to do it in a protocol way. Whatever protocol, but make one and stick to that or look for it.

And then I think make sure that your patients is somewhere in a national, international database because we have to learn from now on how to use these treatments. And this learning has just begun.

Dr. Nester:
I think that's an excellent message. So, thank you Dr. van de Kar for joining me for this session. It was really great having you here and you clearly have a number of wonderful insights into what this new decade will look like for us. Thank you for joining us.

Dr. van de Kar:
Thank you. It was a pleasure. Thank you for having me.

Dr. Nester:
I'm Dr. Carla Nester. To access this and other episodes in our series, visit kdigo.org/podcast. Thank you for listening.