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The Role of the Complement System in Kidney Diseases

Announcer:
Welcome to KDIGO Conversations in Nephrology. This episode in our complement mediated kidney disease series titled, The Role of Complement in Kidney Diseases, 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 Nestor, professor of Internal Medicine and Pediatrics at the Stead Family Children's Hospital, University of Iowa. And joining me to discuss the role of complement in kidney diseases is Dr. Matthew Pickering. Dr. Pickering is Professor of Rheumatology and Welcome Senior Fellow in Clinical Science at Imperial College London, UK. And his clinical and research interests include complement and kidney injury, C3 glomerulopathy, and systemic lupus. Dr. Pickering, welcome to the program.

Dr. Pickering:
Thank you very much, Carla. Delighted to be here.

Dr. Nester:
I think we'll get started right away with our first question for you for this afternoon. What do we need to know about the complement system?

Dr. Pickering:
Thanks. Okay, so firstly, it's a protein network that contributes to immunity. And we know this because when we look at what happens in complement deficiency states, we see that there's an increased susceptibility to encapsulated bacterial infections, streptococcus pneumonia, haemophilus influenzae, and a very strong association between terminal pathway deficiency. That's deficiency of the proteins C5, 6, 7, 8, or 9 and increase susceptibility to meningitis due to neisserial infection. And we need to pay attention to these observations since these infections will occur when we generate acquired complement deficiency states through using complement inhibiting therapy, and of course, we can reduce this infection risk through vaccination and antibiotic use.

Secondly, the system needs to be switched on, activated and switched off, regulated with great precision to make sure that its damaging effects are directed appropriately against pathogens and prevent, and minimize any damage to our own tissues like the kidney. It is switched on by immune complexes. That's the classical pathway. Carbohydrate patterns are long bacterial surfaces. That's the lectin pathway and the spontaneously active, but carefully regulated alternative pathway. And the key effective proteins are important. Remember, a C3 important in opsonization and C5 from which the C5a anaphylatoxin and the membrane attack, complex derive.

And thirdly, defective regulation of complement is the driver of pathology in several diseases. These include age-related macular degeneration; rare anemias like paroxysmal, nocturnal haemoglobinuria, and our subject today, kidney disease.

Dr. Nester:
Thank you for that excellent description. As I'm listening to you, I'm wondering, do you think it will be important for the clinician to understand the difference between the various pathways?

Dr. Pickering:
I think this will be key. We are now, in a situation where we're able to target inhibit activation of those pathways with great precision. So the question will therefore arise, which pathway is relevant to kidney injury in a given disease? Do I need to switch off, for instance, complement that's derived from immune complexes target the classical pathway? Or is it the alternative pathway? Or maybe it's downstream activation through C5. So I think as always, understanding the pathophysiologywill be critical to allow us to accurately and precisely target the complement system to get the beneficial effect.

Dr. Nester:
Excellent point. Excellent point. So, so why don't we just jump in then to, how should we think about complement and kidney disease specifically?

Dr. Pickering:
Okay, well, complement's very common of course, in glomerular inflammation. You see complement staining in the kidney biopsy meetings. So a key question is what is its contribution to glomerular damage and subsequent kidney failure? And in this setting, I like to think about glomerular disease into those in which we have evidence that complement activation is the key mediator of kidney injury would refer to those as complement driven kidney disease and those in which it may be one of many different ways in which the kidney injury is occurring. Complement associated kidney disease is a term I like to use there.

So where it's the primary driver, complement driven kidney disease. While examples are atypical hemolytic uremic syndrome, which in most cases is associated with complement activation along the glomerular endothelium and is strikingly responsive to C5 inhibition and C3 glomerulopathy, C3G, where you have abnormal regulation of the alternative pathway. And this results in excessive glomerular complement activation, and subsequently inflammation and structural damage. And perhaps important examples of complement associated kidney disease include IgA nephropathy, lupus nephritis, ANCA associated vasculitis. Now in these examples, complement activation is contributed to kidney injury, but is not the key disease driver, which would be the abnormal IgA antinuclear autoantibodies and ANCA respectively.

Dr. Nester:
I note you make a, a significant point about the distinction between driven versus associated and it's a very important approach, I suspect, but, do you have a concept of what the impact of that distinction may be for the average clinician?

Dr. Pickering:
So, I, I think what we need to consider there, we need to look at experimental evidence that really defines the, the magnitude of, of the contribution, if you like, of complement to kidney injury because that will give us a feeling for what we can expect from complement inhibition. So where you have a condition such as atypical HUS, where we know that when we look at this experimentally, the damage to the glomerular endothelium that triggers the thrombotic phenotype is entirely dependent on activation through C5. Then you'd expect a big effect of C5 inhibition in the clinical setting. In conditions like lupus, it is very important for us to, to think about certain scenarios where, where perhaps complement would be key and other scenarios and where in which it's not driving the damage. And the only way really to address this, I think, is through experiments.

Dr. Nester:
So that makes, a good point also. So you've given us an excellent background, if you will, on the complement pathways and, and their potential roles. So now let's talk about what do we need to know about the complement therapies with respect to the glomerulonephritis.

Dr. Pickering:
Yeah, well this is a really exciting time, particularly with respect to C3G therapy. Since we have phase three clinical trial efficacy data shown reduction in proteinuria reduction in glomerular C3, staining for two complement inhibitors. Pegcetacoplan, a C3 inhibitor that's administered by infusion twice weekly and Iptacopan a complement factor B inhibitor administered as a tablet twice daily.

Complement associated diseases and therapeutic complement inhibition, while we can think of ANCA associated vasculitis and IgA nephropathy, of course in ANCA associated vasculitis with strong proof of concept evidence for C5a receptor blockade in animal models of MPO disease. And that feeds back to my point about the experiments. And then of course, clinical trials showed efficacy for avacopan, which is a C5a receptor blocker administered as a tablet in adjunctive treatment of AAV. And in the trials, avacopan in combination with rituximab and cyclophosphamide markedly reduced the requirement for glucocorticoid.

In IgA, there's a phase three trial of Iptacopan in patients with a 24 hour urine protein creatinine ratio of one gram per gram or more, despite supportive therapy, and Iptacopan showed significant reduction in proteinuria as compared to baseline at the nine month time point. So, 38% lower than changes in placebo.

Dr. Pickering:
And of course, the key question is, what will the effect of Iptacopan be on kidney function over time?

Dr. Nester:
So, you know, as I'm listening to you, I think, you know, coming from the laboratory setting, it was very satisfying for me to hear you talk about the animal models and ANCA associated vasculitis and how they predicted potential success, you know, with these complement inhibitors. Is there a similar model for IgA a that has predicted some potential good events here?

Dr. Pickering:
No, this has always been a major limitation in terms of, at least in Viva modeling of IgA. Is that there is really no, I would argue, no good, animal model of IgA, nephropathy, unlike for example ANCA, C3G, atypical HUS, , and various forms of immune complex nephritis. So that has been a limitation.

Dr. Nester:
Yeah, I suspected you were gonna tell me that. So, let's take a slightly different direction and let's discuss how does measuring the complement system in the circulation help us understand either the complement system or potentially response to the therapeutics?

Dr. Pickering:
Yeah, so measuring, circulating C3 and C4 levels provides useful information, and the reason for that is C4 is part of the classical lectin pathways, but not the alternative pathway. All the pathways result in C3 activation and then downstream of that C5 activation. So measuring C3 and C4 in the clinic is helpful. If you see a low C4 with low C3 levels, then you'll think of classical pathway activation as typically the cause. Immune complexes driving the, the, the classical pathway activation. The most common cause relevant to us would be SLE immune complex associated MPGN. Much rarer but important, what if you see a low C3 with normal C4 level? Well, that tells you there's no classical or lectin pathway going on. The C4 level's normal. The C3 is down because of alternative pathway activation, and then you should think of post infectious GN and C3 glomerulopathy. So just looking at those two molecules, C3 and C4 gives you a lot of information.

Dr. Nester:
Excellent. That's actually a very straightforward depiction of how to think about these circulating biomarkers, if you will. And, so I can't help but ask, do you want to comment on the more expanded biomarker panel options?

Dr. Pickering:
Yes, of course. I think these are very, very important. There's a lot of work going on, to search for biomarkers that help us, identify in the circulation whether or not there's ongoing glomerular complement activation. That's a subject of research. So, investigators are looking at complement activation fragments. So for example, if you want to understand whether C5 five is activated, a good way to look at that is to measure C5 activation in the circulation. And soluble C5 B9 levels rise when C5 activation is occurring. And that's again, useful information if you're thinking about targeting C5. If the C5, B9 is up that emboldens you with that approach. Then there are other important biomarkers which are, which are disease specific, if you like. So for instance, in C3 glomerulopathy and idiopathic immune complex associated MPGN, we should be thinking about measuring C3 nephritic factors. These are very, very helpful and they come in two flavors. Those that cause C3 activation alone typically seen in things like DDD and those that result in C3 and C5 activation. Typically seen in C3 glomerular nephritis and IC-MPGN.

Dr. Nester:
Very good. Thank you for that explanation. For those just tuning in, you're listening to the KDIGO podcast on the role of complement in kidney diseases. I'm Dr. Carla Nester, and I'm speaking with Dr. Matthew Pickering. Dr. Pickering , so my next question for you is, why is the alternative pathway such an attractive therapeutic target in C3 Glomerulopathy?

Dr. Pickering:

This is because abnormal regulation of the alternative pathway is so strongly associated with C3G. The causes of the abnormal regulation include autoantibodies, most commonly C3 nephritic factor. This binds to, it stabilizes the alternative pathway enzyme that activates C3. We call this a C3 convertase. So C3 NEF stabilize the C3 convertase, and this causes uncontrolled C3 activation. So if you measure C3 levels in these patients, they're low. Some nephritic factor stabilize the C5 convertase causing low C5 levels too. Nephritic factors, as I mentioned earlier, causing only low C3 levels are typically seen in Dense Deposit Disease. Those causing C3 and C5 activation are typically seen in C3 glomerulonephritis. There are also genetic causes which interfere with the normal regulation of the pathway by factor H, and it's important to consider these. These are very rare, but you should consider these if there's a family history. Paraprotein is an important association to consider in adults with a C3 dominant glomerulonephritis on biopsy. And then important for me to point out in up to perhaps 40% of of cases we don't identify a cause for the abnormal alternative pathway activation.

Dr. Nester:
So in the terminology that you have used previously, is it fair to say then that C3G is driven by abnormalities that affect the alternative pathway?

Dr. Pickering:
Yes, I would agree with that. And this can be modeled experimentally. So if you want to dysregulate the alternative pathway, a good place to start is to take away the key negative regulator of that pathway. Uh, and that's a protein called factor H. And if you interfere with factor H function experimentally in in animals, you get uncontrolled C3 activation through the pathway C3 levels fall in the circulation and these animals spontaneously develop accumulation of C3 in the glomeruli and a C3 Glomerulopathy.

Dr. Nester:
So at the end of the day, what are the pros and cons of targeting C3?And or C5 in C3 Glomerulopathy?

Dr. Pickering:
that, that's an excellent point., C five inhibition prevents the production of the pro-inflammatory anaphylatoxin C5a and the formation of the membrane attack complex. And we know that inhibiting C5 with eculizumab in C3G reduces glomerular inflammation. Kidney biopsies on Eculizumab, serial biopsies, show resolution of glomeruli macrophages. And the same is true in IC-MPGN, but, and this is the key, the abnormal glomerular C3 doesn't change. And so the C3 driven glomerular damage continues. The kidney failure risk remains in the presence of C5 inhibition. And this is what is seen in experimental models of C3G too.

So to effectively treat the condition we need to target and prevent C3 activation, and we can now do this using eitheriptacopan or pegcetacoplan. In these trials, we saw for the first time resolution of glomerular C3 on repeat kidney biopsy in some patients, and if this is sustained, based on everything we know, this would be expected to stop kidney failure. I mean, you can't get C3G without the C3. Important to restate whether or not we target C3 or C5, it's important to mitigate the risks of bacterial infection, particularly meningitis.

Dr. Nester:
Very good. You, you've actually made the point very well that it may well be important to know what is driving a given disease. In order to know at what level of the complement system , you should, you know, target or you should attempt to block. So since therapeutics, that may block, various levels are becoming available, what do you suppose is the best way that we can get this distinction out to the clinician?

Dr. Pickering:
I, would think about, for instance, there will be the elephant in the room, if you like, with, with considering how we might use these drugs will be accessibility due to cost. But let's pretend for a moment that these were freely available. Then I would say in situations where you're seeing glomerular inflammation in the presence of complement, so you're seeing glomerular macrophages, for example. Uh, and if you stain for it, you'll see evidence of C five5 activation. Then C5 inhibition would be a very effective anti-inflammatory therapy. And unlike, for instance, courses of glucocorticoid, I can't see any long-term side effects of that approach. It may be used for a, a limited amount of time to reduce glomerular inflammation, which then resolves and patient comes off the C5 therapy.

For conditions like C3G, where you have ongoing C3 activation, then I think the most appropriate is to target at the level of C3 because then you are preventing the C3 mediated damage, the mesangial expansion, the deposition of C3 within the mesangial matrix and the basement membrane and so on, and also preventing any downstream C5 activation, which is driving the glomerular inflammation.

Dr. Nester:

This has been an absolutely excellent discussion. Thank you very much for all of your contribution here. Before we close out the session, Matthew, are there any final messages you'd like to leave with our listeners?

Dr. Pickering:
Absolutely. I think most important is that is to emphasize we're at a very exciting time in the therapy of C3G, but there there is lots to do.

Critically important is to demonstrate that the beneficial changes in the trial surrogate endpoints translate into what we want to know: reduced kidney failure. And this will require long-term monitoring, perhaps best done using registries. We need to diagnose promptly and treat patients with these drugs at an early stage before any kidney damage occurs. And it's my view, I don't think we can justify indiscriminate immunosuppression in this patient group anymore. We need to consider understudied groups, children under 12, patients with paraproteins and patients with a kidney transplant. And we need to think about when we might stop therapy and whether there's any role, as I referred to earlier, for C5 therapy during periods of acute inflammation.

We need to understand how to recognize success. Should we use proteinuria targets or would we still be concerned, for example, about a patient with significantly reduced proteinuria, but ongoing C3 activation in the circulation? And this speaks to the need for biomarkers. Ideally something in the blood or the urine that we can measure that tells us if we have stopped C3 activation in the glomeruli, and of course then would reduce the need for repeat kidney biopsy.

And perhaps the most important point we need to make sure patients can access these therapies, and this will require coordinated effort between patients and physicians, and, which I'm pleased to say is a very active area with excellent work from organizations such as NephCure, CompCure, KDIGO, and the International Society of Glomerular Disease.

Dr. Nester:
Excellent. You've highlighted all of the critical aspects that we need to be paying attention to coming forward, and in fact, that's a great way to round out our discussion today. I want to thank my guest, Dr. Matthew Pickering for joining me, Dr. Pickering, it was just great having you join our program today.

Dr. Pickering:
A pleasure, Carla. Thank you very much.

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