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Deciphering the Link: Proteinuria and eGFR Dynamics in IgAN and FSGS

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Travere Therapeutics. Here's your host, Dr. Gates Colbert.

Dr. Colbert:
This is *Clinician's Roundtable* on ReachMD, and I'm Dr. Gates Colbert. Joining me to discuss the relationship between proteinuria reduction and the estimated glomerular filtration rate slope in patients with IgA nephropathy and focal segmental glomerulosclerosis, also known as IgA nephropathy and FSGS, respectively, is Dr. Jonathan Barratt. Not only is he the Mayer Professor of Renal Medicine, but he also leads the Renal Research Group within the College of Life Sciences at the University of Leicester in the United Kingdom. Dr. Barratt, thanks for being here today.

Dr. Barratt:
Thank you. It's a pleasure.

Dr. Colbert:
Now if we start with some background, Dr. Barratt, can you define IgA nephropathy and FSGS for us?

Dr. Barratt:
Yes, so IgA nephropathy is the commonest pattern of glomerular disease in the world, and it's defined by the deposition of IgA immune complexes within the mesangium of the glomeruli. And that deposition triggers inflammation and scarring and carries with it a significant lifetime risk of kidney failure.

FSGS, on the other hand, is a pattern of glomerular changes that we see under the microscope. It's defined as focal and segmental, which means that it's a process or a disease that affects some but not all glomeruli, and it affects parts of each glomerulus in terms of generating segmental scars. And we believe this disease is primarily due to damage to the podocytes within the glomerulus that are injured, and that process of injury leads to the generation of segmental scars. And like IgA nephropathy, it carries a very significant risk of kidney failure in the future.

So both diseases are very different under the microscope, but actually both of them affect young people and carry with them a significant risk of kidney failure. And really there's a significant unmet need in terms of new treatments to try and manage these conditions.

Dr. Colbert:
Thank you for that great definition. And as a quick follow-up, what do we need to know about the relationship between proteinuria and the estimated glomerular filtration rate, or eGFR slope?

Dr. Barratt:
So as nephrologists, we've always been convinced, I think it's fair to say, that reductions in proteinuria translate to slowing in the rate of loss of kidney function, and high levels of proteinuria are associated with the high risk of kidney failure in the future, both for IgA nephropathy and FSGS. And now the fact that drug regulators have accepted that as well means that we've seen an explosion in clinical trial activity in these rare forms of progressive kidney disease, with lots of new therapies now being evaluated because we can assess whether the drug works relatively soon after we've started those drugs—within a 9-month time frame.

Dr. Colbert:

So that's an excellent answer, and that leads into the next question of how can the high proteinuria levels help predict the kidney progression and outcomes in these patients?

Dr. Barratt:
So again, for both diseases, we've historically known the more proteinuria, the worse the outcome. But actually, over recent times, we've been able to better quantify what that relationship is. And as an example, we have a Rare Kidney Disease Registry in the UK, and we publish the outcomes for the patients with IgA nephropathy. And what you can see there is the higher levels of proteinuria, the much worse the outcomes are for kidney failure over a relatively short period of time.

So we've even looked at low levels of proteinuria, below 1 gram/24 hours, and 1 in 4 of those patients has developed kidney failure at 10 years. And this really is reinforced by data that was published much earlier from the Toronto Glomerular Disease Registry and from other registries around Europe and Asia.

And the same is true for FSGS. We have looked at a variety of different cohorts from across the world. And in all of those cohorts, consistently higher levels of proteinuria and higher levels of uncontrolled proteinuria that we are not able to reduce with drugs is associated with a much higher rate of kidney failure.

Dr. Colbert:
And can high proteinuria levels also help us guide our therapeutic approach in these type of patients?

Dr. Barratt:
Yes, so it's what I use when I make treatment decisions and when I'm looking at monitoring the response to treatment. Proteinuria changes relatively quickly, which means that I can get a very early idea of whether the changes I've made to a patient's treatment are positively impacting and are helping to preserve nephrons and to slow the rate of loss of kidney function decline. So it's something I use all the time in my clinical practice, and it is incredibly useful because it is a prompt biomarker of change.

I think we clearly do need other biomarkers to help. I think it would be lovely if we had biomarkers that were as specific for glomerular inflammation and for podocyte injury. I think they're a long way off at the moment, but hopefully they will come. But at the moment, proteinuria really is the key biomarker that I look at in my clinical practice in the short term.

Of course, over a longer period of time, it's GFR that really matters. But we can only look at GFR over 2-3 years in a slowly progressive glomerular disease. And so that really limits how we can use that to monitor response to therapy. But what we've seen from a large volume of data is that early changes in proteinuria do reflect quite closely what's going to happen over the next 3 to 5 years in kidney function. So I'm confident if I can give a new therapy that reduces proteinuria that that is going to translate through to slowing in the rate of loss of kidney function for my patients.

Dr. Colbert:
For those just tuning in, you're listening *to Clinician's Roundtable* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Jonathan Barratt about the complex relationship between proteinuria and the eGFR slope in patients with IgA nephropathy and focal segmental glomerular sclerosis.

So considering the implications we just talked about, Dr. Barratt, can you share some best practices integrating proteinuria and eGFR monitoring into our routine clinical practice?

Dr. Barratt:
Yes. Well, the first thing to say is if a patient comes to a nephrology clinic, they should not escape from that clinic without having a UPCR and the eGFR measures. Now the frequency with which we do that, I think, will vary depending on the type of patient. But for me, a urine dipstick, a urine protein creatinine ratio, and a measurement of eGFR are essential in my evaluation of all patients with kidney disease. They help me risk stratify, they help me determine whether I should intervene or alter treatment, and they help me monitor the response to treatment.

Now clearly GFR is the thing I'm most interested in because it's the one that is clearly very linearly associated with the risk to need kidney dialysis. But of course, it takes much longer to see what happens with the GFR, and we need to wait 2-3 years before we get an idea of the pattern of GFR change for most of the slowly progressive chronic kidney diseases like IgA nephropathy and FSGS. So I need something that I can monitor that changes relatively more quickly, therefore giving me an indication of whether the treatments that I'm doing are actually having an effect. And that's where proteinuria is absolutely critical.

So for me, I want to be looking at proteinuria at each assessment of my patient, I want to be determining whether there's a pattern of increase or decrease, and I want to be able to look at the relationship between the new drugs I've started and what that impact they have had on residual proteinuria, with the goal to get proteinuria as low as possible and maintained at that low level for as long as I

possibly can. Because we know it's not only the magnitude of how much we can reduce the proteinuria; it's whether we can keep it at that low level for prolonged periods of time. So for me, assessing proteinuria is a critical aspect in managing any patient with CKD, but in particular, patients with a glomerular disease.

Dr. Colbert:
And before we close out, Dr. Barratt, are there any final thoughts you'd like to leave our audience regarding proteinuria levels and eGFR slope in these patients with IgA nephropathy or FSGS?

Dr. Barratt:
Well, one thing I would warn our listeners about is that even if you're not paying attention, I guarantee your patients will be paying attention. You're talking to a group of patients here with IgA nephropathy and FSGS who are young, highly motivated, and highly interested and involved in their own disease. And certainly, the work I do with the IgA Nephropathy Foundation and with NephCure is heavily promoting the patient's involvement in their own health. And so they will be asking you, what is their proteinuria? What's happening with their proteinuria? Why is their proteinuria not coming down? What are you going to do about it? And that's very interesting because we've not had that level of patient advocacy before, and I think we're going to see more and more of it because we're seeing lots of new therapies coming. And patients will say in one breath, 'Why is my proteinuria not coming down? And why can't I have this new drug that's just been approved that reduces proteinuria?' And this is going to change because we're going to have new drugs approved, probably two new drugs in IgA nephropathy every year for the next 3 to 5 years.

So we are going to need to make sure we are educated in those new drugs that are coming. We're going to need to make sure that we have the patients on the right treatments that minimize proteinuria as much as possible. And we need to realize that unlike before, we're going to have second, third, fourth, and fifth-line drugs that we could try if the first choice or the second choice hasn't reduced proteinuria by the amount that we want to see. And of course, that's before we start thinking of combining these drugs.

So I think the next 5 years are going to be incredibly exciting. I think we are going to be using proteinuria very closely to risk stratify our patients, as we do already, but also to monitor the response to these new interventions. And of course, what would be perfect would be to have biomarkers to add to what proteinuria tells us, to give us biomarkers that tell us or allow us to give a measure of how much inflammation is actually happening within the glomeruli. In a perfect world, how much IgA has been deposited in the glomeruli for IgA nephropathy; and in FSGS, how much podocyte injury is actually happening? Have we got that under control? I think they're a few years off. And while we're waiting, proteinuria is the absolute thing that we need to focus on. And so I think we are going to need to know about it, our patients will most definitely be monitoring their own proteinuria, and we are going to need to think about how we utilize all the new drugs that we're going to have available to us to get that proteinuria as low as possible and keep it low.

Dr. Colbert:
And with those final comments in mind, I want to thank our guest, Dr. Jonathan Barratt from the UK, for joining me to discuss how proteinuria reduction and the eGFR slope relate to one another in the context of IgA nephropathy and FSGS. Dr. Barratt, it was great having you on the program.

Dr. Barratt:
Thank you. It's been a pleasure.

Announcer:
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