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IgA Nephropathy Care: A Shift Toward Proactive, Targeted Treatment

Announcer:
Welcome to *Clinician's Roundtable* on ReachMD. This episode is brought to you by Vera Therapeutics. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and today I'm joined by Dr. Jonathan Barratt to discuss a recent review on early and targeted treatment for IgA nephropathy, or IgAN, that was published in *Kidney International* in April 2025. Dr. Barratt is the Mayor Professor of Renal Medicine at the University of Leicester in the UK and a co-author of the paper we'll be discussing today.

Dr. Barratt, welcome to the program.

Dr. Barratt:
Hi, it's great to be joining you again, and I look forward to our conversation.

Dr. Turck:
Well, let's start with some background. Historically, IgAN has been managed with a watch and wait approach, but this paper points out that most adult patients have already lost at least half of their nephron mass by the time of diagnosis. What does that tell us about the limitations of deferred treatment and why a more proactive model might be necessary?

Dr. Barratt:
I think it reflects clinical practice both here in the UK but also in the United States. IgA nephropathy is an asymptomatic disease. We generally only see patients as nephrologists, by luck more than anything, because they happen to have had a urine dipstick, a blood pressure check, or a blood test. So by the time we as nephrologists meet the patient for the very first time, they've lost half their nephrons on average. If we delay treatment, they're going to have lost even more nephrons before we even get to the treatments that are going to make a real difference.

So, the two aspects really are, as soon as a patient hits a nephrologist, we need to treat them quickly and effectively, but we also need to go looking for these patients and find them much earlier because we can never return the nephrons they've lost. So it's really a call to action. Treat early when we see the patients, but also think, how do we go out and find those patients in the community, in primary care, and with our secondary care colleagues?

Dr. Turck:
Now, building off that, the review highlights that even patients with proteinuria of less than a gram per day may progress to kidney failure. What sort of implication does that observation have for our current treatment thresholds and guidelines?

Dr. Barratt:
So what's become apparent from a number of registries, both from the UK, from other European countries, and from the United States and China, is that that one-gram threshold we used to think was the threshold upon which we should start getting worried about IgA nephropathy is in fact too high. And actually, there is no safe level of proteinuria. So, we need to intervene at much lower levels of proteinuria, and we need to aim for a much tighter proteinuria target when we are treating and assessing treatment response. So it really is completely changing the paradigm in terms of what our goal should be for early intervention, but also what our goal should be when

we instigate treatment.

Dr. Turck:
Now, the paper also highlights poor tolerability and limited long term benefit with high dose steroids, making the case that emerging agents, like iptacopan, delayed release budesonide, and sparsentan are more targeted, better tolerated, or both. How is that knowledge shaping a more proactive first line approach?

Dr. Barratt:
I think we've accepted for some time that systemic steroids are a necessary evil for some glomerular diseases, but in an ideal world, we would never use them again if we had safer and more effective choices, because patients dislike them—they're associated with many, many side effects, both short term and long term. And even though they can reduce proteinuria, as the low dose testing study showed, the proteinuria just comes back six months, 36 months after stopping them. So, they're a short-term fix for a chronic disease and we're not going to be able to give repeated courses of systemic steroids.

What's fantastic about the new drugs is we have very robust safety data now. We have very robust tolerability data from the Phase 3 trials, and even more importantly, we have very clear efficacy data. And so we know with these new therapies that they are effective at reducing proteinuria and slowing the loss of kidney function. And we have a very good idea about their safety profiles, which means we can have a sensible conversation with patients when we're talking to them about the treatment choices. And we can give them a good idea about potential side effects that they might experience, whether they're reversible, and how we might manage them. And that, again, is really important when you're talking to a person who feels well and you're going to give them a drug. You don't want them to feel less well on the treatment because they'll just stop taking it. So having that information is really important.

And I think we'll really encourage the use of combination approaches when we know the safety profiles that we're looking at. And some of these drugs have complementary profiles. Some are associated with fluid retention, others are associated with making you pee more, so it's a perfect combination to counteract side effects of two different treatments. And that's factoring into how we might use these in clinical practice at the moment.

Dr. Turck:
For those just joining us, this is *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking to Dr. Jonathan Barratt about how proactive and targeted approaches are reshaping how we care for patients with IgA nephropathy, or IgAN.

So, Dr. Barratt, let's continue to dig into this paper. One of the central proposals is that use of early simultaneous targeting of both immune dysregulation and other chronic kidney disease mechanisms as opposed to a stepwise approach is the way to go. How could this dual targeted model impact care plans and long-term outcomes?

Dr. Barratt:
Well, I think it's going to be something that's very new to nephrologists. It is something they're going to need to rethink. They need to understand that there is a sense of urgency in treating IgA nephropathy and that any single approach is unlikely to be effective when we think about lifetime risk of kidney failure. The challenge in terms of implementing it is going to be having young people who feel well coming into a nephrologist clinic, being given a diagnosis of IgA nephropathy—they're not on any medicines—and suddenly, their life is transformed.

So, we are going to need to communicate with our patients well and explain why they need to have these treatments—because we are thinking of preserving their kidney function for the rest of their life. And while they may not notice any immediate benefit, undoubtedly this will protect their kidney function and prevent the need for dialysis. So we are going to need to come up with strategies to introduce these medications in a patient-friendly manner, get the patients on board to understand why they're taking those treatments, and get the patients on board to understand that these are long-term therapies. And even though they feel fine, the drugs aren't going to make them necessarily feel any better. We are protecting them with an eye on the next 20, 30, 40 years. And that's really important in terms of how we communicate that message, to get the patients bought into the idea they need chronic treatment.

Dr. Turck:
And shifting gears to biomarkers and surrogate endpoints, how might those tools be leveraged in tandem with a dual targeted approach to enable earlier, more personalized interventions?

Dr. Barratt:
So I think the goal is to get the loss of kidney function back to what we see in a healthy person. But we can't use that in practical terms. We're on a clinic-by-clinic basis. And so what we have at the moment is proteinuria. So what we are going to be doing is looking at the magnitude of proteinuria reduction with treatment, and we are going to be aiming to get that residual proteinuria as low as possible,

ideally below half a gram in a perfect situation, normalized to less than 0.3 grams. And to do that, we are going to need multiple therapies and that is going to be the way, over the short term, we monitor response to treatment. And we need to get our patients engaged with that and for them to understand that the lower the proteinuria, the better. And if it takes three drugs to get that proteinuria down, then so be it. But we can be confident that by reducing that proteinuria, we are going to see maximal kidney function protection.

Dr. Turck:
Now, before we wrap up the program, Dr. Barratt, let's look ahead for just a moment. If proactive multi-targeted therapy becomes the new standard for patients with IgAN, what clinical, logistical or guideline-level changes will be needed to enable us to transition to that new approach most successfully?

Dr. Barratt:
Well, I think we have recently updated the KDIGO guideline to bring this concept in. I have to say that it's been interesting, the comments from nephrologists, in terms of how they view this because it is a complete change. And remember that we only had two new therapies within the new updated guideline. In the United States, you now have an additional two drugs that aren't included in the KDIGO guideline because they were only recently approved. There's going to be another drug approved in the United States before Christmas and another one approved soon after in the New Year. So, we are going to need to think about how we rapidly update the guideline to make it relevant to clinical practice because we have so many new drugs coming.

And to make it relevant, to make it useful for nephrologists to review, and to help them manage patients, we need to ensure all of the drugs that are approved and available are included in the guideline. But the message will stay the same. Diagnose early, treat early, aim to get that loss of kidney function down to what we see in a healthy patient. And in reality, the only way we will achieve that is with combination therapy targeting the fundamental pathogenesis of the disease, alongside those downstream CKD consequences. And I have no shadow of a doubt that that is the only way we will prevent kidney failure in the lifetime of most patients with IgA nephropathy.

Dr. Turck:
With those key takeaways in mind, I want to thank my guest, Dr. Jonathan Barratt, for joining me to discuss our evolving management approach to patients with IgA nephropathy. Dr. Barratt, it was great having you on the program.

Dr. Barratt:
Yeah, it was a pleasure. Thank you very much. Bye-bye.

Announcer:
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