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Optimizing Outcomes in Patients With IgAN: Novel Therapies and Evolving Guidelines

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Dr. Floege:
Given that IgA nephropathy is a leading cause of kidney failure, early diagnosis and treatment are, of course, essential. In the landscape of these many evolving treatment guidelines, how can clinicians use emerging evidence and emerging therapies to achieve proteinuria remission and maintain eGFR to improve outcomes of our patients? Today, we'll answer these questions by reviewing a real-world clinical patient case.

This is CME on ReachMD, and I'm Dr. Jürgen Floege.

Dr. Barratt:
And I'm Dr. Jonathan Barratt.

Dr. Floege:
John, as we eagerly await the updated KDIGO guidelines, can you provide some insight on what we can expect in terms of IgAN treatment?

Dr. Barratt:
Yeah, so, Jürgen, I think the real driving focus of the KDIGO guideline is to acknowledge all these fantastic new treatments we have and how they might fit into a treatment paradigm, but also to raise the urgency with which we need to diagnose this disease by the level of proteinuria we need to trigger a kidney biopsy; what defines a patient at risk of long-term kidney function loss in terms of proteinuria threshold; what the target should be for new treatments in terms of the level of proteinuria we wish to achieve with these new therapies. And then thinking about the treatment in a very broad way in terms of treatments that are going to treat the immunology, the actual IgA nephropathy itself, and those treatments that are better suited to manage the CKD consequences of IgA nephropathy.

And I thought it would be really good to think about a case that I saw last week. So I had referred to me a 20-year-old young lad. He wanted to join the police force, so we had a medical. He had a urine dip. And he was seen to have blood and protein in the urine. I think this sounds familiar to you as well. And so he came to see me. I quantified the proteinuria. And on a spot UPCR, he had equivalent to 2.5 g of proteinuria. He had hematuria. His GFR was 68 mL/min for a 20-year-old lad.

Dr. Floege:
For a 20-year-old?

Dr. Barratt:
Yeah.

Dr. Floege:
Whoa.

Dr. Barratt:
He was feeling fit. He didn't understand why he was seeing me. He thought he was fine. He was ready to go, was a very fit young man, but that level of kidney function, that degree of proteinuria. We did a biopsy, and it showed confirmed IgA nephropathy.

Dr. Floege:
Hypertension?

Dr. Barratt:
Blood pressure was good.

I had to explain to him his diagnosis, to explain the fact that, from what I could see in front of me, he was at significant risk of progressive kidney loss. So faced with that, what's going through your mind about priorities of treatment and how you might approach the treatment with the available therapies you have?

Dr. Floege:
The fundamental thing is we now have two boxes. We used to call it supportive therapy and then steroids. Now we call it CKD therapy. And for this guy, it's lifelong treatment.

Dr. Barratt:
Absolutely, I was thinking CKD treatments. What is the safest thing? Because in the past, if you look, they all say KGIDO guideline. The only other option there was systemic glucocorticoids. Ideally, we'd have put him in a clinical trial, and that's still an option for him. But we now do have therapies that are targeting the fundamentals of the immune system.

So do you think this gentleman warrants one of those therapies?

Dr. Floege:
Oh, absolutely. I mean, this guy is on the way downhill. He has an eGFR of 68 at the tender age of 20. That's a nightmare. That's a catastrophe for this guy. So he has a very, very good chance of being on dialysis between 30 and 40.

Dr. Barratt:
Yeah. And even if we looked at a 20-year horizon and thought we've done a good job keeping him off dialysis 20 years, he's still going to be 10 years younger than me when he develops kidney failure, and that's a disaster. So and we can never replace the nephrons that he's lost or that we'll lose if we delay treatment.

Dr. Floege:
I believe that's the most fundamental change we're proposing in KDIGO, that we no longer slowly build up treatment and optimize this and then wait 6 months and whatever. But we become rheumatologists, hit hard and early before the joint is damaged, now replace joint with nephron before a nephron is lost because it won't come back.

What about the biopsy, the MEST-C score? Shouldn't you take that into account when you plan your treatment?

Dr. Barratt:
So the MEST-C score is scored for all our patients, not surprisingly; Leicester's John Feehally helped design the study. So we do see that. We help and use that to prognosticate in terms of that information going into the risk prediction tool.

But actually, there is no evidence that making treatment decisions based on the MEST-C score makes any sense in terms of data that we have available. So I look at it, but I'm not going to make a decision on one treatment over another simply on the basis of the MEST-C score.

Remember, this is a score that was designed to able prognostication not to able treatment decision-making. A lot of people confuse that. I don't know. I mean, you must have seen –

Dr. Floege:
Very important point. And I think you can't stress it enough: there is not a single prospective trial where the MEST-C score was used to guide treatment.

We have, for CKD, sparsentan or a RAS blocker. And then what next?

Dr. Barratt:

Well, you see, I think we need to be treating the immunology of the disease. And at the moment, the drug we have is Nefecon, targeting the pathogenic production of IgA in the gut.

So, Jürgen, in terms of, I mentioned the kind of thresholds for what you want to achieve. So you have this gentleman, you've put him on treatment. What do you want to achieve in terms of proteinuria, in terms of hematuria, in terms of long-term GFR decline? What are your goals for therapy?

Dr. Floege:
I think that is the fundamental change in the guideline. In 2021, in the version, we said, the goal is proteinuria below 1 g per day. That is history. Within just 3 years, it was wiped away by your study and the RaDaR data, showing that even at a much lower proteinuria degree, your lifetime risk is very, very significant.

Dr. Barratt:
And in my experience, if a patient doesn't understand why we're giving them the drugs, they usually end up in a packet in a cupboard and they don't take them. So that engagement and discussion is critical, isn't it?

Dr. Floege:
I talk to patients for at least half an hour. I realize I have a luxury situation there, but this is the most important half hour in their life. And we go over what is your blood pressure, what is good exercise, what is your diet, what should it look like? How about smoking? How about salt? Lots of things. And I tell my patients, the aim of the treatment is now to get it into full remission ideally. Full remission defined as proteinuria of ideally 0.3 or less, but 0.5 is something that would already make me happy.

Dr. Barratt:
I couldn't agree more. Anything else in the KDIGO guideline that you think has changed to a point that is important for people to understand in terms of new ways we're thinking about IgAN?

Dr. Floege:
I'm certain that this dichotomy of having CKD and having an immune disease, and both of these need different treatments; that's really important. And it's very clear that we're talking complex decisions on how to combine. Actually, this is the one question I get most of the time.

Dr. Barratt:
So in terms of those treatments, so I tend to think now of the treatment paradigm as the left-hand box and the right-hand box. The right-hand box is CKD treatments. The left-hand box is how we treat the immunology of the disease.

And at the moment, we have Nefecon and we have systemic steroids. And so I think the guideline tries to discuss the pros and cons of both approaches and what we need to think about if we're going to use either.

Did you want to just summarize for us the kind of pros and cons of each approach and where that might be appropriate and what we need to do when we talk to a patient, when we're going to prescribe those?

Dr. Floege:
In many countries, the question will still be steroids or not steroids. If steroids, then use the so-called low-dose TESTING scheme, but really tell your patient about this. Even with the low-dose TESTING scheme, we had very significant adverse events. We had lethal infections. And there are now at least 4 European studies showing that, prospectively, like our STOP-IgA study and 3 retrospective studies, showing that steroids don't affect long-term outcome, whereas TESTING delayed kidney endpoints by 2.5 years. So it’s kind of a controversial situation.

Nefecon is an alternative, because the adverse events are much less, obviously. Yes, you do see some typical steroid effects. I had a woman stop because she didn't like her face anymore. But you don't have serious infections; you don't have diabetes.

The phase 3 study was 9 months of treatment and then taper down quickly and then stop. Does it make sense to stop, or do we need some kind of maintenance therapy? Nine months is a short time in the life of a patient.

And we know from the phase 3 study that the moment you stop Nefecon, eGFR starts to fall again. So this is something to find out. I cannot give you conclusive answers.

Dr. Barratt:
It's a real challenge, isn't it, that Nefecon at 9 months does not cure IgA nephropathy. I think we need to make everyone aware of that and that you might need repeated cycles or chronic maintenance.

We've got this young lad that I've mentioned to you, 50-60 years of life ahead of him, am I really going to want to give him a continuous therapy for the rest of his life and interfere with his immune system? Absolutely not.

Dr. Floege:
Absolutely. I mean, so far, we're talking 2 years, 3 years. We have to talk 20-30 years of treatment. And I think the most exciting data are the B cell modulators, BAFF/APRIL antagonists, or CD38, where at the ASN Congress, we have the first instance where eGFR was absolutely flat and stable for 96 weeks. And I think that is something important. So we will have therapies that, at least for these relatively short periods, look really promising.

Dr. Barratt:
Yeah, it is really exciting. But the key – you've hit the nail on the head. It's for a short period. It's a drop in the ocean for a 20-year-old.

Dr. Floege:
So obviously combining a RAS blocker, irbesartan, with sparsentan doesn't make any sense, because that would be hitting the one thing twice, namely the angiotensin receptor.

Dr. Barratt:
Good point. And what about the sequencing of a RAS inhibitor and a dual endothelin angiotensin receptor? Do you need to do one first always, or can you choose which of those you would want to start a patient on?

Dr. Floege:
Well, there's no evidence that you cannot start with sparsentan right away. In fact, if I were that young guy, I would want to have maximum protection of my kidneys. And very clearly where, in the PROTECT trial, irbesartan led to a GFR loss of 3.8 mL/year, it was 1 mL less per year with sparsentan. And what we also see frequently, and I hear this from real life now, that sparsentan has a huge drop in proteinuria way beyond what you see with the RAS blocker.

Dr. Barratt:
And indeed, my colleague Chee Kay has ran the SPARTAN trial, which is taking patients at the time of diagnosis who are RAS naïve and starting them immediately on sparsentan. And he presented data here at the ASN showing 60%-70% reduction in proteinuria as sparsentan as first line.

Dr. Floege:
Which for our 20-year-old, would be wonderful.

Dr. Barratt:
Absolutely.

Dr. Floege:
If we get him down from 2.5 to 0.5.

Dr. Barratt:
Yeah, and we saw that with young people that were recruited into the study.

Dr. Floege:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Jürgen Floege, and here with me today is Dr. Jonathan Barratt. We're discussing on how to optimize outcomes in patients with IgA nephropathy in light of evolving clinical guidelines.

So in terms of CKD therapy with SGLT2 inhibitors having this really nice effect on kidney protection, can we combine it with these newer drugs like sparsentan?

Dr. Barratt:
Yeah. I mean, a great question again. And of course, a lot of these trials started recruitment when SGLT2 inhibitors were either not approved or were really making little penetration, so we don't have the data from the phase 3. But thankfully, many of the studies of these CKD drugs are now looking at combinations. So we have studies examining the combination of sparsentan with SGLT2 inhibitors, both in the open-label extension of PROTECT but also in a separate SPARTACUS trial.

We have the ASSIST trial, which is looking at atrasentan with SGLT2 inhibitors. And there is, in fact, a large study looking in general CKD, which will undoubtedly include a lot of IgAN patients called the ZENITH High Proteinuria study, which is looking at zibotentan, dapagliflozin, and a RAS inhibitor. So we are going to get data over the next few months that are going to show us both the efficacy and the safety of combining all of these drugs.

Dr. Floege:
And we'll have first real-life data in my wonderful journal where I'm the editor. *CKJ* will publish a case series of close to 20 patients where the combination of sparsentan and SGLT2 inhibitor was given. Great effect.

Dr. Barratt:
Yeah. And it makes sense, doesn't it? Because the thing you're concerned about with an endothelin receptor antagonist –

Dr. Floege:
Is edema.

Dr. Barratt:
Yeah, salt and water retention. And what do the SGLT2 make patients do? They make them pee. So actually, there's a perfect combination.

Now, the key thing is, do we need to have that patient on that treatment for the rest of their life to achieve that, and what is the risk from a safety perspective of doing that? But for the first time in the history of IgA nephropathy, we're going to have drugs that we can actually use. We can combine.

Dr. Floege:
Are there any biomarkers that can help us beyond proteinuria?

Dr. Barratt:
That's the question I get asked the most. We have a serum creatinine and an eGFR and proteinuria, albuminuria. We need to be cautious, of course, about the value of proteinuria. It's a great prognostic marker, and we can use it to monitor treatment response. But there is no magical number that determines when the tipping point is.

Dr. Floege:
Well, we just had that, right? Even the magical number of 1 g/day is blown away.

Dr. Barratt:
Absolutely. It's now 0.5. And if we have enough data, it may well go lower. But of course, nothing changes in the kidney when you have 0.45 g of protein or you have 0.55.

Dr. Floege:
So it remains our best prognosticator.

Dr. Barratt:
It does, and it's a guide to what we should do. So if I have a 22-year-old and his proteinuria is 0.45 g, I'm going to be as worried for that guy as it was, because, just because there's a magical number of 0.5, it doesn't mean that I should ignore the value, and that's a really important message. And the guideline is a guideline. It's there to help guide, but it's not meant to be a rigid bar upon which clinicians should base every single decision.

Dr. Floege:
Before we wrap up, let's offer a final take-home message. So, John, what do you hope our listeners will learn today and leave with today?

Dr. Barratt:
I think if they take anything away from today, the first thing is, you need to think about making a diagnosis early in your patients. Any patient with more than 0.5 g of proteinuria justifies, in my view, if you're considering IgA nephropathy as a diagnosis, a kidney biopsy to make that diagnosis, because there are treatments available now for those patients. Any IgA nephropathy patient with more than 0.5 g of proteinuria has identified themselves as being at significant risk of progressive kidney disease and justifies treatment. And if we are going to treat, we need to aim for the lowest possible proteinuria that we can achieve, below 0.5 would be where we'd want everyone to get to, below 0.3 in a perfect world. And when we think about treatments, at the moment, the way I describe it is for when nephrologists think about IgA nephropathy, the CKD side of their brain occupies 90% of their thought process, and the immunological side occupies a very small amount of their thinking time. We need to shift that so it's 75% immunology treat the disease, and 25%, yes, we must treat CKD, just like we do in a diabetic.

Dr. Floege:
And for me, the most important take-home message is turn the paradigm around. Instead of slowly building up your treatment and losing GFR on the way, turn it around; let those young people like yours not lose GFR, hit hard and early. Even risking that you potentially

overtreat, you can always then decrease and taper treatment quickly. But a nephron lost is a nephron lost forever. To me, that seems logical.

So thank you for joining us. It was great listening to you, John, and sharing all your expertise. And it was just, I think, a really nice discussion today. Thank you.

Dr. Barratt:
Thank you, Jürgen. As always, a pleasure. I'd like to thank the audience for watching us, and goodbye.

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