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Innovations in IgAN Care: Addressing Challenges with Therapeutic Advances

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

Dr. Turck:
This is *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the current challenges and innovations in the treatment of IgA nephropathy, or IgAN for short, is Dr. Pietro Canetta, an Associate Professor of Medicine at Columbia University Medical Center in New York. Dr. Canetta, welcome to the program.

Dr. Canetta:
Pleased to be here.

Dr. Turck:
So to start us off, Dr. Canetta, how do we typically treat patients with IgAN?

Dr. Canetta:
So there's a stepwise process that we use, but generally, you start with supportive care. This is a chronic disease in most people, and so we use medicines that are sort of low risk that'll improve outcomes over time. And classically, that's been medicines like ACE inhibitors or ARBs, which are protective for the kidneys, decrease protein in the urine, and prolong life of the kidneys in most proteinuria kidney diseases like IgA nephropathy. And then there's options for additional treatment for more aggressive disease, including immunosuppression with things like corticosteroids, and now in the past year or two, we have a couple of FDA-approved options as well.

Dr. Turck:
And as a follow-up to that, would you tell us about the limitations that are associated with some of the treatments you mentioned?

Dr. Canetta:
IgA nephropathy is generally a chronic disease. It sort of comes out of nowhere; it affects people generally when they're younger. And what patients want is they want to hear that we have a cure, and we largely don't have a cure. Most of the medicines that we use to treat it are medicines that will improve outcomes over time and reduce the severity of the disease but don't necessarily make it go away entirely. So that's the big limitation of the treatment paradigm that we have.

Dr. Turck:
Now how did the Kidney Disease Improving Global Outcomes, or KDIGO, treatment guidelines utilize proteinuria in assessing patients in making treatment decisions? And do they have any limitations?

Dr. Canetta:
KDIGO uses a couple of cutoffs of proteinuria as recommendations to guide therapy. Now these are guidelines so you have to make them simple and accessible. And they have to be based on the best, most validated evidence, but they use a guideline of 0.5 grams a day of proteinuria as their cutoff over which everybody should be treated with an ACE inhibitor or an ARB, for example. And then they use 1 gram a day of proteinuria as a cutoff over which more aggressive therapies should be considered, and in particular, glucocorticoids.

One thing we have to recognize is that proteinuria is not a variable that actually is associated with these hard cutoffs where there's a distinct change in the disease right above or right below these cutoffs. And what I mean to say is that proteinuria is a continuous

variable, and its effects are probably continuous as well in IgA nephropathy. And that the more proteinuria you have, the worst the prognosis, the less you have, the better the prognosis. So I don't think there's anything really magical about 0.5 grams a day. I certainly treat patients even below that level with ACE inhibitors or ARBs if it's appropriate for that patient and individual level. And I don't think that that's inconsistent with the guidelines in that guidelines are meant to be just that: guidelines, blueprints, but they're not meant to be set in stone. And certainly on an individual patient, you have to be able to adapt the themes of the guidelines.

Dr. Turck:
For those just joining us, this is *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Pietro Canetta about the current treatment challenges in IgA nephropathy, or IgAN.

So, Dr. Canetta, given the challenges we discussed earlier, what therapies are on the horizon that might help us address some of the limitations you mentioned and slow disease progression in IgAN?

Dr. Canetta:
So there's a group of different types of drugs that are being studied, a whole lot of them right now. We have two drugs that have come to market already. These are both accelerated conditional approvals based on these drugs' ability to reduce proteinuria. And the full approval will depend on the drugs in follow-up and in practice being shown to actually improve GFR outcomes. So those two drugs are already out and available. And it's exciting that we actually have two FDA-approved therapies.

And then there's a whole slew of other new drugs coming up. They kind of fall into different categories. There's many that target B cells through a pathway called APRIL or BAFF. And these are drugs that interrupt signaling of the B white cells that are important in downstream antibody production. And there's at least half a dozen drugs that target the complement pathway of the immune system that is important for activating inflammation and generating inflammation in the kidney itself. And that's been shown to be very important in IgA nephropathy.

So those are two big areas in which there are many, many drugs being developed.

Dr. Turck:
I was wondering if you would highlight some of the key clinical trial data that come to mind involving some of these newer and emerging therapies?

Dr. Canetta:
Even as we start with newer and emerging therapies, I think a really important clinical trial to look at is a study called the TESTING study that was published in JAMA, and this was a large study of an old therapy, glucocorticoids, but it stands out as a clinical trial on IgA nephropathy because of its size and because it's really set out to definitively show the effect of drugs that have been used for years but had never really been sort of carefully described as far as their risks and benefits.

So the TESTING study randomized people, it was double blinded, to glucocorticoids or placebo in the background of maximal supportive care. It actually paused during the course of the study because after a few years of follow-up, it was recognized that patients who were getting the glucocorticoids were having more adverse events as far as infection events, including serious infections. They did not stop the trial altogether, but they paused it and reconfigured the study a bit to make it a little bit safer. They reduced the dose of the steroids, added some antibiotic prophylaxis, and then continued the study.

And those results were published - both the initial results and the final results - in JAMA. And they really showed a substantial impact on kidney outcomes with glucocorticoids. There were more side effects, yes. And that's completely unsurprising to somebody who's experienced these drugs or who uses these drugs. But the effect of the glucocorticoids on renal outcomes was really substantial. Proteinuria dropped, and hard outcomes improved. There was less renal failure outcomes.

So I think that's an important study to look at because when you compare newer studies and newer drugs coming out, you have to think of what's available and what should be considered standard of care. And I think for aggressive IgA nephropathy, the kind of standard against which new drugs should be thought of should be a new drug versus what we are already able to do with glucocorticoids.

Dr. Turck:
And before we close Dr. Canetta, are there any final thoughts you'd like to share with our audience today?

Dr. Canetta:
So I think that if you are a clinician who treats IgA nephropathy or if you're a patient living with IgA nephropathy, it's an incredibly exciting time right now because of the number and diversity of drugs that are being actively investigated to treat this disease. Many companies with many different drugs with different mechanisms of action, often complementary mechanisms of action, are being studied. And so this really leads to a lot of hope that we will come up with not just one but potentially several drugs that could work in

concert with each other in order to control this disease and improve outcomes over time.

Dr. Turck:
Well as that brings us to the end of today's program, I want to thank my guest, Dr. Pietro Canetta, for joining me to discuss how the latest innovations in IgA nephropathy may help us address common treatment challenges. Dr. Canetta, it was great having you on the program.

Dr. Canetta:
It was my pleasure to be here. Thank you.

Announcer:
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