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Talking Through the Therapeutic Landscape of IgA

Announcer:
You're listening to *Clinicians Roundtable* on ReachMD, and this episode is brought to you by Chinook Therapeutics. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Clinicians Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the therapeutic landscape for immunoglobulin A nephropathy, or IgA nephropathy for short, is Dr. Pietro Canetta, who's an Associate Professor of Medicine at Columbia University Irving Medical Center. Dr. Canetta, thanks for being here today.

Dr. Canetta:
Thanks for having me.

Dr. Turck:
So to start us off, Dr. Canetta, what treatments are currently available for patients with IgA nephropathy?

Dr. Canetta:
So the treatment paradigm currently involves a set of steps or layers that we employ. And it starts with something that we call supportive care. Supportive care being a set of things that we tend to do just as good clinical medicine, good nephrology, that's applicable to almost any patient with proteinuric kidney disease. But that's been shown to be very important in IgA nephropathy. And that can be very successful when done right.

So what is supportive care? It's lifestyle changes in order to best protect the kidneys; things like quitting smoking if that's applicable, a low sodium diet, potentially weight loss in the case of obesity to limit a glomerular hyperfiltration, and things like that. Blood pressure control is crucial. The KDIGO guidelines recommend a systolic blood pressure of less than 120, which is often not achieved in practice, and so deserves attention. The use of angiotensin receptor blockers or ACE inhibitors is a key part of therapy. If any degree of proteinuria is present, really the KDIGO guidelines use a cutoff of 0.5 grams a day, but I think in practice, the benefits have been shown to be consistent, regardless of the degree of proteinuria, the relative benefits. So it's the use of a maximally tolerated dose of an ACE inhibitor or an ARB to not just control blood pressure but to reduce proteinuria.

And then increasingly, laying on top of that, SGLT2 inhibitors. That's based on really convincing data from very large randomized controlled studies in proteinuric kidney disease, including studies that have subgroup analyses in a population of patients with specifically IgA nephropathy, like the DAPA-CKD study or glomerular disease, glomerular nephritis, like the EMPA-KIDNEY study. And both of those very large randomized controlled trials, well done randomized controlled trials, showed that in that population of a specific IgA nephropathy population or the glomerular nephritis population, that these drugs, the sodium glucose cotransporter 2 inhibitors had really strong benefits that mirrored the larger CKD population in these glomerular subpopulations. So that's the supportive care layer. And then on top of that, you can add more aggressive therapies as dictated by the severity of the disease. So for patients who have more aggressive, more progressive disease, you may layer on immunosuppression of various types. Historically, we've used a lot of oral glucocorticoids. And I think worldwide, that's probably still what's used most often as a next step, things like prednisone or prednisolone. And then in the United States, in the past year and a half, we have two additional agents that have actually been FDA approved specifically for IgA nephropathy, which has been very exciting. One is a form of targeted oral budesonide. So it's a glucocorticoid that acts particularly in the gut mucosal system. And another is a very recently approved combination endothelin A inhibitor and angiotensin receptor blocker. Both of those drugs have provisional approvals from the FDA based on their success in short-term lowering of proteinuria. And they're being followed to determine if that early success will translate, as we expect it usually does, into GFR

preservation, which is a more definitive outcome that could potentially lead to them being definitively approved.

So that's sort of the spectrum of options of the most validated options. And there's, beyond that, other forms of immunosuppression that have been looked at like mycophenolate, and there are a lot of clinical trials. It bears mentioning they're enrolling for patients interested in being part of the scientific process.

Dr. Turck:
And what are the challenges or limitations associated with these therapies?

Dr. Canetta:
Yes, I think there's several that have to do with the disease itself. So IgA nephropathy has a few aspects to it that make it challenging to develop medications and in particularly, focused medications, to treat it.

So one, it has a long time-course and a relatively slow progression. So that's historically made it difficult to develop drugs because of the power calculation involved in trying to design a study to show hard outcomes. It would have to involve often large numbers of patients with a long follow-up. And that's been addressed rather effectively by the use of well-validated surrogate outcomes like proteinuria.

The disease is a fairly heterogeneous disease with different patterns of progression. So there's the classic patient who will have a slow progressive chronic kidney disease, proteinuric chronic kidney disease, but some patients can have very mild disease that then accelerates at some point, some patients can have flares of disease that wax and wane over time. So that's another challenge. And I think a real challenge has been that the disease is very complex, immunologically, and pathogenically. It involves multiple aspects of the immune system, multiple aspects of glomerular damage and glomerular injury. And so while that gives great opportunity to develop drugs that target all these various systems that are involved, it also means that in any given patient, it's a real challenge in trying to identify what might be the best pathway to target and the best drug that might work specifically in one patient with the disease but might not work as well in the next patient. And we don't really have the biomarkers necessary yet to identify what pathway is most important to target in any given patient.

Dr. Turck:
So then how might we address the unmet needs of our patients with IgA nephropathy and improve their outcomes?

Dr. Canetta:
Well, thankfully, there's a lot of work being done right now in this field. The biggest unmet need for a patient suffering from IgA nephropathy is a cure. If you ask patients, that's what they want. They want to be able to take a medicine that ends the disease or a set of medicines that ends the disease that cures it. We are not there for the most part. Some people are able to obtain really great remissions and then long-term outcomes with certain types of treatments like with steroids, but they don't work for everyone. And so the real unmet need is being able to have a drug or set of drugs that can put the disease into a really strong substantial remission in a targeted way with minimal risk and side effects. And we're not there yet, although there is a lot of work being done to try to develop agents that might be able to do this.

Dr. Turck:
For those just joining us, this is *Clinicians Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Pietro Canetta about the treatment of IgA nephropathy.

So, Dr. Canetta, now that we have a better understanding of the current challenges encountered in IgA nephropathy care, let's switch gears a bit and look ahead for a few moments. How might our knowledge of IgA nephropathy's pathogenesis influence the future treatment landscape?

Dr. Canetta:
I think this is an area where we as clinicians, clinician scientists, and along with colleagues in pharmaceutical development have been really successful in recent years in this disease space. We've gotten a very detailed understanding of the pathogenesis of IgA nephropathy through a lot of excellent work in the basic sciences. In genetics, some of my colleagues at Columbia have been real leaders in this that have elucidated the various aspects of the immune system that are important in causing the disease, as well as local glomerular injury that are important in allowing the disease to progress over time. And so what that has given us is a whole set of targets, druggable targets really that are being actively looked at in clinical trials. And so it's an exciting time because the understanding of this complex pathogenesis has allowed for the application of specific drugs that target the different steps of the disease pathogenesis and that are being studied in clinical trials. We don't know which of the drugs will be successful, which of the drugs will be successful in any given patient; we're not there yet. But the understanding of this general schema of the disease pathogenesis, which is quite complex, has allowed us to come up with many different types of strategies to target the disease.

Dr. Turck:
So with that being said, would you tell us about some of the new therapies on the horizon?

Dr. Canetta:
Sure. I like to think of them in groups. And so the first group I think still bears mentioning is corticosteroids or glucocorticoids, in particular. We have an approved targeted glucocorticoid, a form of targeted budesonide. But also some of the best work and best information on the use of just general oral glucocorticoids has been published in just the past few years. And I'm thinking in particular of the TESTING study, which was very large randomized controlled trial of oral glucocorticoids for IgA nephropathy, and really clearly demonstrated their benefit on kidney outcomes, as well as some of their risks, in particular, infectious risks. So I think there still is a role for the use of these agents and for understanding these agents, and there's ongoing studies of these agents. So that's one group.

The next group, I'll mention the endothelin A antagonists. So these are drugs that have been around for years to treat some forms of these drugs have been around to treat different vascular conditions like pulmonary hypertension. But now there's two that have been investigated fairly actively for proteinuric kidney diseases. And so that's a nice addition to the armamentarium, with a very specific mechanism of action.

Then there's a set of drugs that I kind of lump into the category of complement drugs. So there's at least a half a dozen different drugs that target various aspects of the complement system. The complement pathway of the immune system is important in local glomerular damage, has been shown to be very important in IgA nephropathy. And we have a lot of different drugs of different types that can intervene in this activation of the complement pathway because it's a complex pathway that involves many different proteins.

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

Dr. Canetta:
I think if you are a clinician who treats patients with IgA nephropathy, or if you're a patient who suffers from IgA nephropathy, this is actually a very exciting time because of all this work that's been done in order to identify with really good quality science, very rational targets, druggable targets of the disease. There's a lot of options in advanced clinical development of drugs that might be useful in this disease that are being studied specifically for this disease. And I think also credit has to be given to the regulatory agencies who have allowed for the use of surrogate endpoints, like proteinuria, to allow companies and scientists to more quickly develop drugs and bring them into advanced clinical trials with the understanding that surrogate outcomes may not be definitive, but they can at least accelerate hopeful drugs accelerate their development, and potentially bring them so that they can be used by patients while still respecting the scientific process and following patients under treatment in order to fully elucidate the benefits and the risks over the long-term and end up with approved drugs that are safer and effective than the current therapies that we have.

Dr. Turck:
Those comments are a great way to end our discussion. And with that, I want to thank my guest, Dr. Pietro Canetta, for joining me to discuss current and future treatments for IgA nephropathy. Dr. Canetta, it was great having you on the program.

Dr. Canetta:
It was my pleasure. Thank you.

Announcer:
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