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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

What the Latest IgAN Clinical Trials Mean for Patient Care

Announcer:
You're listening to *On the Frontlines of IgA Nephropathy* on ReachMD. Now, here's your host, Dr. Steve Jackson.

Dr. Jackson:
Welcome to *On the Frontlines of IgA Nephropathy* on ReachMD. I'm Dr. Steve Jackson, and today, we'll explore how to interpret the latest clinical trial evidence in IgA nephropathy, or IgAN for short, with Dr. Andrew Bomback. He's an Associate Professor of Medicine and the Co-Director of the David Koch Jr. Glomerular Kidney Center at Columbia University Irving Medical Center, where he's involved in the care of over 200 IgAN patients. Dr. Bomback, thanks for being here today.

Dr. Bomback:
My pleasure. Thanks for having me.

Dr. Jackson:
Let's jump right in. We've seen a wave of new clinical trial data in IgAN over the past few years. Which developments have you found most meaningful, and how have they influenced the way you think about the disease?

Dr. Bomback:
Well, I think the entire field getting all these new therapies is the biggest development. We have seen therapies that are targeted towards different parts of the pathogenesis of IgA nephropathy, whether at the most initial stages of the pathogenesis or the most distal or later stages of pathogenesis. And the fact that we now have multiple therapies approved for IgA nephropathy has really changed the way we think about managing the disease in the clinic.

But if I were to pinpoint one that particularly has made its way quickly into the way we treat, it would be the approval of drugs that target the BAFF/APRIL pathways. We had a monoclonal antibody to APRIL approved in the end of 2025, and then just this month, the approval of an anti-APRIL, anti-BAFF targeting drug. And these drugs have really remarkable efficacy data in terms of not only clearing the proteinuria associated with IgA nephropathy, but also the hematuria. So in my own glomerular center, we've already put more than 20 patients on these drugs in the last six months—really quick adoption of new therapies.

Dr. Jackson:
Let's talk about clinical trial design. As we look across today's studies, how should we think about the different endpoints being used, and what does each one tell us about a therapy's potential benefit?

Dr. Bomback:
IgA nephropathy has a lot of natural history data which helps drugs now get approved, because the FDA has established a pathway that allows for a surrogate outcome like proteinuria at nine months to get expedited approval of a drug. And then at two years, the eGFR data would get the drug full approval.

What we know about IgA nephropathy is that proteinuria changes at nine months that are clinically significant are expected to yield eGFR or kidney function improvement data at the two-year mark to get the full approval. And to date, there have not been any IgA drugs that have been expedited approval at nine months and not gotten the two-year approval.

So it's really borne out that proteinuria predicts where the disease is heading over the long term. So that's what we look at when we look at outcomes from these trials, and the trials are all designed in the same way. You get a readout of nine months on proteinuria, and that would get the drug expedited approval, and then you get a readout on eGFR or kidney function at two years, which would get the drug

full approval.

The question for those of us who do these trials with IgA nephropathy is, with so many of these drugs now becoming approved and becoming standard of care, what are we going to do for a placebo arm moving forward? Because, traditionally, we've used real placebo, but now, with so many drugs, is it going to be ethical to put patients on placebo? So that's the sort of question for trialists like me to chew over.

But for now, we're continuing to see these trials that are well underway report out very promising data in a typical randomized controlled trial against placebo.

Dr. Jackson:
Sure. All right, now, that proteinuria—how much weight should clinicians give to the reductions in proteinuria when thinking about the long-term outcomes?

Dr. Bomback:
Well, IgA is very unique in this regard, in that we have such great natural history data from large registries that show that the quicker and more profound you reduce proteinuria, the better the long-term effects on preserving kidney function. So we put a lot of stock in proteinuria. That's why the recent KDIGO guidelines, which just came out last year, actually have lowered their proteinuria goals for IgA nephropathy.

You know, when I first started treating IgA nephropathy 15 or 20 years ago, everybody said, "Let's treat to less than a 1,000 milligrams a day of proteinuria." We've learned that that's not a good enough target, and now, the KDIGO guidelines reflect that: the official target is less than 500 milligrams a day. But they actually put a note that, ideally, you want to get these patients under 300 milligrams a day.

And what we know from natural history studies is that the quicker and the more rapidly you get your patient to those targets of low proteinuria, the better the chances of preserved kidney function. So putting emphasis on early proteinuria reductions makes perfect sense, and it's what's going to get you to better long-term outcomes.

Dr. Jackson:
For those just tuning in, you're listening to *On the Frontlines of IgA Nephropathy* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Andrew Bomback about evolving clinical trial data in IgA nephropathy.

Dr. Bomback, based on the evidence we have so far, what makes you confident that a particular therapy has the potential to modify the course of IgAN?

Dr. Bomback:
So the most definitive evidence that you've modified the course of IgA nephropathy is by doing a second biopsy. And sometimes we do that in patients, but it's an invasive procedure, and we really reserve it for patients who are not showing the kind of clinical behavior we would expect. But if you do a second biopsy and you see no disease activity—no change in the chronicity or scarring on a biopsy—you know you've modified the disease. But most patients don't want to do a second biopsy, and most clinicians don't want to subject their patients to a second biopsy unless it's clinically crucially needed for the management.

So with the absence of that kind of invasive marker—and since there's really no disease-specific biomarker for IgA nephropathy—we do rely on proteinuria, we do rely on eGFR, and we also look at hematuria. That's why some of the newer clinical trials that are coming out, which report out not just resolution of proteinuria but also resolution of hematuria in patients, are really remarkable. Because what that suggests is that you truly do have control of the disease, and you have cleared out any of the active IgA nephropathy.

It's very hard to conceive of a patient with active IgA nephropathy who has no hematuria or no proteinuria. Those are the hallmarks of disease activity. So if a drug is able to take patients from significant proteinuria and significant hematuria to absence of proteinuria or hematuria in that nine-month phase—in the early parts of these trials—that's a sign that the drug establishes control of the IgA nephropathy and makes the disease quiet.

Dr. Jackson:
And as more therapies emerge and enter the treatment landscape, what's the best way for clinicians to compare studies that use different endpoints or the best way to enroll different patient populations?

Dr. Bomback:
Well, to your first question, it is not a straightforward thing to compare one study against the next. The good news is that they're all generally designed the same way: placebo-controlled, nine-month proteinuria data, two-year GFR data. But there are slight nuances in these trials, a lot of which are due to when they started.

So, for example, in some of the more recent studies on IgA nephropathy, you're seeing much more background use of SGLT2 inhibitors than was seen in earlier studies, which may influence some of the proteinuria data. I expect that some of the future IgA trials are going to see more background use of endothelin receptor antagonists, which may also influence some of the proteinuria data.

So it's going to be a little bit of—not apples to apples, but more different types of apples, and different types of oranges maybe. That being said, there's still a way to look at these trials and say, "Am I getting significant proteinuria reduction in nine months? And long term, am I seeing significant slowing of any GFR decline at two years?" Those are still very definitive signs that the drugs are working.

To your second question, how do we get patients more enrolled in trials? It's going to be a bit of a challenge. You know, when these trials that have gotten the drugs approved originally started five or six years ago, there weren't a lot of IgA drugs. It was really just corticosteroids. So it was much easier to get patients into trials when there were no new drugs for them to use.

Now that we have five or six new IgA drugs, we're going to have to figure out which patients want to be in trials when there's so many options available. So some of the things that we would say is, for example, if you're a resistant patient with IgA nephropathy, or if you're someone who has IgA nephropathy, and it's mild enough and you feel like you want to make a contribution to science, maybe you want to be in a clinical trial. But I think that is going to be a challenge moving forward.

Dr. Jackson:
Yeah. Before we wrap up here, let's look ahead. What upcoming trials or emerging research do you think will have the greatest impact on how we care for patients with IgAN?

Dr. Bomback:
Well, I think now that we're doing so well with efficacy, the next question is, can we get that same efficacy and potentially have even better safety data than we're seeing from the trials that have been done? Most of the trials that have been done have pretty good safety data, but from a theoretical standpoint, there are some new products in development that promise even better safety signals than what we've seen.

For example, I know of at least one product that's called a trap degrader, where, basically, this therapy is trapping the galactose-deficient IgA1 that begins the pathogenesis of IgA nephropathy and leverages the body's natural clearance mechanisms to selectively target and remove that galactose-deficient IgA1 with really no other effect on the immune system. So you're basically taking away the first step of the pathogenesis with this therapy without affecting the rest of the immune system. So that would potentially give you a very nice way to target the disease without affecting the rest of the immune system in a very safe way.

There is at least one complement drug that's been already approved for IgA nephropathy. The expectation is that another complement drug will be approved for IgA nephropathy within the next year based on its early study results. And these are systemic complement inhibitors, which require vaccinations and more surveillance for infection. But in development are tissue-based complement inhibitors, which, basically, would only inhibit complement at the level of the kidney without systemic complement inhibition. And those, again, should promise some better safety signals than the systemic complement inhibitors.

So I think now that we've gotten so many drugs with great efficacy, the next step is, can we keep that efficacy and maybe get a little bit better of a safety signal—particularly less immunosuppression involved in these agents?

Dr. Jackson:
Very encouraging final thoughts there. And with those in mind, I want to thank my guest, Dr. Andrew Bomback, for helping us better understand today's IgAN clinical trial landscape. Dr. Bomback, it was great having you on the program.

Dr. Bomback:
Thank you for having me.

Announcer:
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