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

Understanding IgAN & FSGS: Pathophysiology and Emerging Therapies

Announcer:
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[Chapter 1]

Dr. Barratt:
Immunoglobulin A nephropathy, or IgAN, and focal segmental glomerulosclerosis, or FSGS, are leading glomerular causes of kidney failure. Today we're going to answer some important questions about these diseases, such as how can we reach an earlier diagnosis of IgAN or FSGS? What are the limitations of current therapies? And how can emerging therapies achieve proteinuria remission and shape our treatment decisions?

This is CME on ReachMD, and I'm Dr. Jonathan Barratt.

Dr. Kohan:
And I'm Dr. Donald Kohan. So we have a lot to discuss today, so let's begin. Jonathan, what's the disease burden of IgAN and FSGS, and what do you think are the unmet needs of patients with these diseases?

Dr. Barratt:
So thanks very much for that question, Don. I think there is a significant unmet burden in patients with IgA nephropathy and FSGS. These are 2 diseases that affect young adults predominantly, and with them bring a significant lifetime risk of kidney failure. We often only get to see these patients late in their disease trajectory. They often have advanced disease, which is much more difficult to treat. And we know that the treatments we have available are not as effective as we would like, they come with significant risk of side effects, and patients find them often almost intolerable due to the side effects.

Patients tell us they are desperate for new treatments. We as clinicians really do not have that many treatment options. And what we very much want to do is to be able to identify these patients earlier, make the diagnosis earlier, and to be able to intervene at a point where the kidney is able to respond to therapies and not develop fixed, irreversible fibrosis that ultimately leads to kidney failure. So now let's focus on the mechanism of action of endothelin antagonists because these agents promise to give us a new treatment option for the management of both of these conditions.

Don, can you give us a little background about the endothelin system in health and disease?

Dr. Kohan:
Sure. Endothelin and its receptors are very highly expressed in the kidney. They regulate many aspects of renal function including renal hemodynamics and fluid and electrolyte excretion. Renal endothelin expression is increased in almost all forms of kidney disease. Many factors increase renal endothelin production and some can even form a vicious cycle. For example, both proteinuria and angiotensin stimulate renal endothelin production, while endothelin in turn can increase proteinuria and angiotensin. In general though, endothelin can elicit a wide range of pathophysiological effects leading to things like cell proliferation, apoptosis, inflammation and fibrosis. I think most importantly, these effects are largely mediated by activation of the endothelin A receptor.

Dr. Barratt:
Fascinating. Thanks, Don. I think that really does give us an insight into the importance of this system in kidney health and in kidney

pathology. And one of the questions I have is does endothelin act primarily on the renal vasculature? Or does it have effects on other renal cell types?

Dr. Kohan:
This is a really good question. First, endothelin is produced by and acts upon virtually every cell type in the kidney. Endothelin preferentially stimulates efferent arteriolar constriction, thereby increasing interglomerular pressure. This effect is really very similar to that we all know of with angiotensin. Endothelin also directly stimulates mesangial cell proliferation, contraction, and extracellular matrix production—effects that are important in the pathophysiology of IgAN. Endothelin also directly acts on podocytes, where it can promote slit diaphragm and cytoskeletal disruption, podocyte loss, and proteinuria—actions that characterize FSGS. Further, endothelin acts directly on endothelial cells where it can damage the glycocalyx and the endothelial barrier. Finally, endothelin directly stimulates tubular cell production of profibrotic factors.

Dr. Barratt:
Now you mentioned that endothelin and angiotensin have similar effects on glomerular hemodynamics. Do they interact with one another? And is this involved in kidney injury?

Dr. Kohan:
Yes, this is a really important point. Endothelin and angiotensin elicit many similar pathophysiologic effects in the kidney, which include vasoconstriction and injury of mesangial cells, podocytes, and the tubulointerstitium. As I mentioned earlier, endothelin and angiotensin can stimulate one another's production. Importantly, the pathophysiologic effects of angiotensin and endothelin, although they're similar, are mediated by different cell signaling pathways. So the effects of angiotensin and endothelin can be additive and even synergistic. This means that targeting both angiotensin type 1 and endothelin type A receptors in kidney disease makes a lot of sense.

Dr. Barratt:
Great. Well, that makes a lot of sense, actually, in terms of how we think about both of these mediators and these pathways in both health and in terms of driving kidney disease. And you briefly mentioned that endothelin's effects on mesangial cells and podocytes could be important in IgAN and FSGS. Is there any evidence that blocking the endothelin system is protective in these diseases?

Dr. Kohan:
This is really a crucial point. Yes, indeed there is quite a bit of emerging preclinical evidence showing this. Endothelin A antagonism reduced proteinuria, preserved podocyte number, and decreased fibrosis in animal models of FSGS and IgAN. Importantly, endothelin A blockade also reduced the mesangial cell proliferation that was induced by galactose-deficient, IgA-containing immune complexes. And most importantly, as I'll discuss later in this session, there are exciting results of clinical trials targeting endothelin A receptors in IgAN and in FSGS.

Dr. Barratt:
In Chapter 2, we'll focus on how to diagnose patients with IgAN and FSGS earlier to improve their prognosis. Stay tuned.

[Chapter 2]

Dr. Kohan:
Well, welcome back everyone. In the first chapter, we learned about the role of endothelin and angiotensin signaling pathways in IgAN and FSGS pathophysiology. Now we're turning to diagnostic approaches.

Jonathan, how can we diagnose adult patients with IgAN and FSGS early, and how important is it to perform a renal biopsy in a timely manner?

Dr. Barratt:
Yes, Don, I think that that is a really important question: how do we diagnose these patients earlier? And we absolutely need a kidney biopsy to make a diagnosis of either IgAN or FSGS. Now, fundamentally, we need to start rethinking the threshold at which we as nephrologists want to do a kidney biopsy, because I think with potentially new therapies coming online, we need to have the diagnosis made as early as possible to be able to provide disease-modifying therapies at the very beginning of the disease. And we know most patients who present to us, and when we're making that decision about kidney biopsy, have already had the disease for quite some time. So waiting and deferring a kidney biopsy, in my view, is not the right approach. We need to make that diagnosis quickly, inform the patient about their condition, think about what their prognosis is like, and intervene as quickly as possible.

I think we also need to think how do we raise awareness of the potential for a diagnosis of IgAN or FSGS? And this comes down to educating our primary care and our secondary care colleagues to understand the importance of an abnormal urine analysis, an abnormal serum creatinine result, or an elevation in blood pressure. All of these factors can be quite subtle signs of underlying kidney

disease, but actually, they're things that we perform in routine clinical practice all the time, no matter what our specialty. And we just need to raise awareness that if we start seeing high blood pressure, we see blood and protein in the urine, we see minor impairments of kidney function, we, as nephrologists, want to see these patients early. Because if we leave it too late, that is when kidney scarring has occurred and that's when it becomes far more difficult to alter the trajectory of kidney function decline, particularly in these 2 diseases.

Dr. Kohan:
Thanks, John. That was very helpful. And what criteria do you think people generally use to decide whether a kidney biopsy should be performed?

Dr. Barratt:
I think we do need to start thinking, as we are getting new therapies, particularly for IgAN and for FSGS, that we need to be standardizing the approach to kidney biopsy, and we need to be lowering that threshold to perform a kidney biopsy. Traditionally, it's been if you have more than a gram of proteinuria, if you have an impaired kidney function, or you've got sign of end-organ damage, such as hypertension, that would trigger a kidney biopsy.

And I think we really need to educate our colleagues that we need to be performing kidney biopsies. I would suggest even with proteinuria above half a gram for 24 hours. Because if I can make that diagnosis earlier, I can then intervene earlier, and I can potentially alter the trajectory of the kidney function decline. Now remember, we're talking about young adults here that have the next 40-50 years to live with their kidney function as it is, and we need to be thinking about nephron-preserving therapies as soon as we possibly can in these people with chronic progressive glomerular disease.

Dr. Kohan:
What findings do we need to look for on renal biopsy to make the diagnosis of IgAN and FSGS?

Dr. Barratt:
Yeah, so both of these conditions are diagnosed by kidney biopsy. I'll deal with IgAN first. So in IgA nephropathy, the defining feature is a dominant or codominance of mesangial IgA immune complex deposits. You may see C3, you may see IgG, you may less commonly see IgM. But actually, it is a dominance or codominance for IgA that makes the diagnosis.

Once you've made the diagnosis of IgA nephropathy, you then want to use the kidney biopsy to try and look for prognostic features that will help you and help you educate the patient about what is likely to come in the future. And so in the diagnosis of IgA nephropathy, we will classify the kidney biopsy using the Oxford classification which looks at 5 parameters: mesangial proliferation, the M; endocapillary hypercellularity, the E; segmental glomerulosclerosis, the S; tubular interstitial inflammation and fibrosis, the T; and the presence of crescents, or C. And we abbreviate this to the MEST-C score. And in my practice, I will have that report and that score given to me with the kidney biopsy diagnosis. I will then use the International IgA Nephropathy Risk Prediction tool, where I'll input that data alongside some basic clinical features, and that will give me an indication of what's likely to happen to my patient over the next 5 years. And I can use that to help discuss with the patient what we'll think is likely to happen in the short term in their disease and how that might influence decisions regarding clinical trials, regarding treatment.

Now, FSGS, it's a very different story. FSGS isn't a diagnosis; it is a pattern of change that the pathologist sees under the microscope. And it can have many different causes. And I've not got time to go into the many different causes, but we generally think of it as either a primary or soluble factor-mediated disease, where the patient presents with nephrotic syndrome and with an FSGS pattern where we think there's a soluble podocytopathic mediator that is causing acute podocyte injury and development of severe proteinuria. And then we have those secondary causes of FSGS that may be due to a maladaptive glomerular response to stress such as obesity to nephron loss for any other reason. We then have a group of diseases that are driven by monogenic genetic disorders, where there are very clear genetic changes that lead to the development of FSGS. And we commonly see those in childhood. And then finally, there's this group of conditions that cause FSGS, but we don't know what the fundamental cause is.

But the difference here is, of course, FSGS is just a pattern. And we can see FSGS in IgA nephropathy, we can see segmental lesions in a lot of other forms of glomerular disease, and so it does require a lot of thought. It requires integration of the clinical data with the pathology to come up with what is likely to be happening in the patient with FSGS and whether it's due to a genetic cause, a maladaptive response, or a soluble mediator.

Dr. Kohan:
So, John, a natural question that follows from this is, does the kidney biopsy help outside of allowing a diagnosis to be made?

Dr. Barratt:
As I said, Don, in IgA nephropathy, we absolutely use the MEST-C score to feed into the International IgA Nephropathy Risk Prediction

tool. And that is a tool that's been developed using data from over 3,000 patients from across the globe, looking at outcomes and looking at features that, independent of each other, predict outcome in terms of loss of kidney function and loss of GFR [glomerular filtration rate]. And so as I've said, I have the app on my phone; it's freely downloadable. And you can then input the data, once you get the biopsy report back. And you get a personalized risk of the likelihood of a 50% decline in GFR, end-stage kidney disease, or death for that patient over the next 5 years. And I find that particularly useful in my practice.

As with FSGS, that's a slightly different picture, because we use the biopsy here to try and give us an indicator of what the underlying cause may be. As I said, there are certain features that might indicate a primary podocytopathy in a soluble mediator, particularly on the electron microscopy when we look at FSGS. And there may be other patterns that perhaps may be more aligned to a maladaptive response, as we might see, say, in uncontrolled hypertension or obesity. The biopsy features don't generally help when we're thinking about genetic causes, but that's usually obvious because we're looking after children and young adults with steroid-resistant nephrotic syndrome. And now it's standard practice in a lot of countries to perform a genetic panel, looking for those common genetic mutations that can drive steroid-resistant nephrotic syndrome, which gives an FSGS pattern on kidney biopsy and is due to an underlying genetic defect.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jonathan Barratt, and here with me today is Dr. Donald Kohan. We're discussing how to diagnose patients with IgA nephropathy and FSGS earlier and how emerging therapies can help address the current unmet needs of these patients.

Dr. Kohan:
Thanks, John. That was very useful. And finally, how does the diagnostic approach differ in children?

Dr. Barratt:
So pediatric nephrology have quite a different approach to kidney biopsies, for obvious reasons. Kidney biopsies are invasive. Children often have to be given a general anesthetic to go through the procedure. And therefore, there needs to be a very good indication for a kidney biopsy that's likely to alter management in pediatric practice.

In IgA nephropathy, often the kidney biopsies are reserved for those with more aggressive disease, those with persistent heavy hematuria, proteinuria with clear signs of end-organ damage, elevations in creatinine, and development of high blood pressure. And actually, the pediatricians use the biopsy much more than adult nephrologists to determine treatment decisions. And indeed, the guidelines that are just coming out around the management of IgA nephropathy very much centrally place the kidney biopsy features in determining the treatment approach for children. That's not the case in adult practice yet.

With regard to FSGS, really, children presenting with nephrotic syndrome are invariably given a course of corticosteroids as a first treatment option, rather than going for a kidney biopsy. And then their following course is really related to their steroid responsiveness. If they respond to steroids, then a kidney biopsy is not necessary. But if they don't respond to steroids or they become steroid resistant or steroid dependent, then those children will have a kidney biopsy to look for diseases other than minimal change disease. And of course, at the same time, there will be greater thought about genetic causes for the nephrotic syndrome. And actually, a genetic panel is now becoming part and parcel of the evaluation of pediatric nephrotic syndrome, and particularly in those who are steroid nonresponsive, and will precede a kidney biopsy.

Dr. Kohan:
Thanks, John, for that great explanation in both adults and children. Now, in Chapter 3, we'll discuss challenges with current treatments and take a look at what's on the horizon for patients with IgAN and FSGS. Please stay tuned.

[Chapter 3]

Dr. Kohan:
Welcome back, everyone. In Chapter 2, we learned that performing a renal biopsy early is critical to a timely diagnosis of patients with IgAN and FSGS. We're now turning to treatments.

Jonathan, what can you tell us about the current treatments for IgAN?

Dr. Barratt:
Yeah, so whenever I'm thinking about treatment of glomerular disease, I automatically defer to the KDIGO [Kidney Disease: Improving Global Outcomes] clinical practice guidelines. And these were last written in 2021 and are currently going through a continual cycle of updates. And if we think about IgA nephropathy, what does KDIGO tell us? Well, it tells us that all patients with IgA nephropathy should have good general supportive care. So that's good blood pressure control to a target of 125/75 mm Hg, they should be given lifestyle advice, ensure they're a healthy weight, dietary sodium restriction, ensure they exercise regularly, and they don't smoke. We need to

make sure that they are taking the maximal tolerated dose of a renin-angiotensin system [RAS] inhibitor, whether they're hypertensive or not, to try and reduce proteinuria. And we need to ensure that we are addressing any cardiovascular risk factors that they might have.

And then if we have done all of that, and the patient identifies themselves as being at high risk for progressive kidney disease by the presence of persistent proteinuria—and in the current guideline, this is above 1 g per 24 hours—then we should offer that patient the opportunity to enroll in a clinical trial of a new therapy, because we are in desperate need for new therapies for this condition that are both safe and effective.

If a trial isn't available, then you can consider the use of systemic glucocorticoids. We know that these come with significant side effect risks, we know that patients find them often very difficult to take because of the side effects and the tolerability. But there is some evidence that they can reduce proteinuria, albeit over a temporary period. And that this can impact in the short term on the rate of loss of kidney function.

Dr. Kohan:
These are the 2021 KDIGO guidelines, to my knowledge, and I assume there are going to be important new information with the guidelines that'll be out in 2024, so we're all looking forward to hearing about that.

Finally, to cover our bases, what treatment options do we have for patients with FSGS?

Dr. Barratt:
Yeah, so it doesn't get much better with FSGS, I'm afraid. Again, we have limited options. We know that these patients can have significant proteinuria. They can present with nephrotic syndrome, particularly those with a soluble factor that targets podocytes. So we do need to do some general things well, which is control the symptomatology, control the edema with diuretics, control the blood pressure, dietary sodium restriction. And what we really have other than that are high-dose glucocorticoids, which is recommended that we would try for a maximum of 6 months to see whether we could get the proteinuria under control. We know that often that is just intolerable for patients in terms of side effect profile. We have second- and third-line agents which, really, we have very little strong data on, and most of the data is from small trials. And these are—calcineurin inhibitors have been used. And we have some data on mycophenolate mofetil and even less data, although there is some, on B cell modulators such as rituximab.

But it is really challenging to manage this disease, and KDIGO recognizes that. It recognizes the massive unmet need in terms of safe and effective therapies. But so in my practice, when I look after a patient with FSGS where I think this is due to a soluble mediator, I will give them a trial of systemic corticosteroids with a low threshold to stop if I do not see an improvement, and I may well use a calcineurin inhibitor. And if pushed and the patient is really struggling, I may consider rituximab, but not on great quality evidence. Of course, if they have a genetic cause of FSGS, it's going to be symptomatic control. And if they have a secondary cause, such as that related to obesity, diabetes, we treat the primary underlying disease with the hope that that will limit the progression of the FSGS lesions.

Dr. Kohan:
So it appears that there is significant residual renal injury despite the current therapies in both IgAN and FSGS. Do you think this will change in the coming years?

Dr. Barratt:
So absolutely. In IgA nephropathy, we have many different therapeutic approaches being evaluated in IgA nephropathy. We have approaches targeting B cells, the source of the pathogenic IgA that deposits within the kidneys. We have a range of different inhibitors of the complement system, which are designed to control the inflammatory response within the kidneys that occurs due to those immune complexes being deposited, and we have a range of drugs that are targeting the generic changes within the damaged kidney that are not specific to IgA nephropathy but offer us a real opportunity to slow progression of kidney disease. And here I'm talking about the SGLT2 [sodium-glucose cotransporter-2] inhibitors and the endothelin receptor antagonists. And we already have exciting phase 2 data and some phase 3 data showing efficacy of these new approaches and showing that these drugs are well tolerated by patients; they don't come with all the baggage of systemic glucocorticoids with those terrible side effects that patients complain to us about so much.

The treatment landscape and the trial landscape in FSGS is not as plentiful, it's fair to say, as in IgA nephropathy, although some of the approaches that are being looked at in IgA are also being looked at in FSGS. And here, I'm talking about those generic approaches to controlling the general drivers for kidney damage, such as endothelin receptor antagonists. So I think these agents are likely to change our clinical practice and are going to improve outcomes for our patients over the coming years.

So, Donald, you told us about the endothelin system's involvement in these diseases, and there are some new exciting drugs that target this system. What has been the clinical experience with those agents?

Dr. Kohan:

There are several completed and ongoing trials studying endothelin A receptor blockers in IgAN and in FSGS. Two phase 3 trials using the dual endothelin A blocker and ARB [angiotensin receptor blocker] sparsentan have recently reported important results. First, PROTECT studied approximately 400 adults with biopsy-proven IgAN, proteinuria over 1 g per day, and an estimated GFR over 30. The prespecified interim analysis performed at 36 weeks of treatment found that sparsentan reduced proteinuria by almost 50% compared to baseline, and this contrasts with about a 15% reduction for irbesartan. Based on this, the FDA recently granted accelerated approval for sparsentan in IgAN for patients at risk of rapid disease progression. This really is very exciting, as it is the first time an endothelin receptor antagonist has been approved for any form of kidney disease and gives IgAN patients a new, important option for therapy. Full approval for sparsentan is pending results of eGFR [estimated glomerular filtration rate] later this year.

The other phase 3 trial involving sparsentan is DUPLEX, which studied 370 patients with primary FSGS. The 108-week treatment results were just reported to have a 0.9 mL/min/year favorable difference in chronic eGFR slope, compared to irbesartan. However, this did not achieve significance. Proteinuria was reduced by 50% with sparsentan, compared with 32% for irbesartan. In addition, more patients achieved partial and complete proteinuria remission on sparsentan compared to irbesartan. A full final analysis and plans for a path forward towards agency approval are now pending.

As I mentioned, there are ongoing trials with other endothelin antagonists in IgAN and in FSGS. The largest of these, ALIGN, is studying the effect of atrasentan, an endothelin A receptor antagonist, versus placebo on proteinuria and eGFR in 380 IgAN patients taking maximally tolerated doses of renin-angiotensin system inhibitors. The prespecified interim proteinuria results of this trial should be known later this year. Finally, it is important to mention that no significant serious adverse events have been noted in these phase 3 trials. Fluid retention, which has been described with endothelin receptor antagonists, has been mild, and liver toxicity, which occurred with some of the earlier endothelin receptor antagonists, has not been reported.

So with that, John, let’s shift gears a bit. What other challenges do you think we face when we’re managing pediatric patients?

Dr. Barratt:
Yeah, so that's a really good question, because I feel really sorry for the kids with kidney disease, because in all of the studies that we've talked about, children have been excluded from these studies for valid reasons, because we are using drugs we have no real great data on safety. But actually, all of the studies start and include patients over the age of 18. And it’s great to see that some of the new agents are actually developing pediatric programs and beginning to recruit pediatric patients to studies of new therapies. And as an example of that, we have the EPPIK study, which is a study of sparsentan, the endothelin receptor antagonist, which is looking at a group of pediatric patients with IgA nephropathy, with FSGS, with Alport’s, and looking to evaluate, in the same way that sparsentan has been evaluated in adults, to look for safety and efficacy in this population. And there are other studies where new agents are also being considered to be evaluated.

Well, this has certainly been a fascinating conversation. But before we wrap up, let's each provide a final take-home message for our audience.

Donald, what do you hope our listeners will leave today with?

Dr. Kohan:
I think these really are very exciting times for patients with IgAN and FSGS. We’ve gone from only renin-angiotensin system inhibitors for IgAN to several new, approved therapeutic options, and more new agents may be approved in the next several years. FSGS is a harder disease to define, given it’s a pathology diagnosis with many underlying causes. So defining the role of endothelin receptor antagonists in FSGS, particularly based on subset analysis, will be important. Overall, I’m excited for the future in general and for the use of endothelin receptor blockers in particular.

Dr. Barratt:
I have to agree. I think we are moving to a new era of supportive care and combining RAS inhibitors with endothelin receptor antagonists. My final take-home message is reframe how you look after these patients, think lifetime risk of kidney failure—don't think short term—think lifetime risk and treat accordingly.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Donald Kohan, for joining me and for sharing all of your valuable insights and expertise. It was great speaking with you today.

Dr. Kohan:
Thank you, John. It’s been a pleasure, and thank you to everyone who listened today.

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