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Optimizing Outcomes in Patients with FSGS: A Case-Based Approach in the New Era of Targeted Therapy

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Dr. Latus:
Nowadays, everybody's talking about IgA nephropathy and about remission in IgA nephropathy, but now we have a lot of patients with primary FSGS. And as well, it's a progressive disease and a lot of patients ending up at dialysis. So there were no effective treatment options available in the past. It was RASi, it was SGLT2, but nowadays we have a completely new drug available, sparsentan. Sparsentan showing a very significant proteinuria reduction and reduced loss of eGFR.

This is CE with GLC, and I'm Dr. Jörg Latus.

Dr. Norouzi:
And I am Dr. Sayna Norouzi.

Dr. Latus:
So yes, let's begin by taking a look at a typical adult patient with FSGS. Sayna, I know you have one in mind.

Dr. Norouzi:
One of the patients that's standing out right now to me is a patient that I saw recently in the clinic. She was in her 30s and was diagnosed with primary FSGS, possible primary FSGS, by a kidney biopsy. Came to the clinic for a second opinion. She was really nervous and upset at the time. It's the prime of her life. She's in her 30s, has a lot of plans, wanted to have another kid. She was planning to get pregnant, exercising every day, going to work, traveling around the world, and all of a sudden she got severe swelling on her legs and came in with severe fatigue as well, got a kidney biopsy, was told that she has a really rare disease called primary FSGS, and was there to see what are her options.

The fatigue is real. She wasn't able to exercise anymore. She wasn't able to perform at work. She was calling in sick all the time because she had multiple appointments. She had a lot of swelling and was getting a lot of questions about it, and that's not fun.

Dr. Latus:
So I like your patient case very much because you're not talking about eGFR and proteinuria, so that's very important for us as

nephrologists, but you're talking about quality of life, getting pregnant. And I think when we look—and I think this is a big problem. When we look at the current standard of care we have available for our FSGS patients, several important limitations become crystal clear for us.

So yes, of course, when we go back, we have, of course, the supportive therapy. We have RAS inhibition. We have blood pressure control, which is always a big issue in our patients. We have an SGLT2 inhibitor. And yes, we see a reduction of proteinuria. And on the other hand, we have broad but nonspecific immunosuppressive therapies available, including, of course, corticosteroids, calcineurin inhibitors, and other steroid-sparing agents.

But I believe when we talk about the treatment it's a major challenging track, therapy, because yes, there might be some, let's say, partial remission and partial responses in many patients, but of course there is—so I believe I'm not only talking about efficacy. It's always a problem with the safety because we have substantial toxicity with our patients. They have prolonged corticosteroid exposure. They have weight gain, again, talking about quality of life, diabetes, hypertension, infections, osteoporosis, so significant quality of life impairment.

So yes, in addition, treatment responses in FSGS was present or was available in some of the patients, but it was highly heterogeneous. So some patients, they have progressive loss of kidney function despite aggressive therapy, and there are currently limited targeted treatment options addressing the underlying disease mechanism.

And so as a result, up to now, many patients continue to face ongoing proteinuria. Of course, they lost kidney function, increased risk, of course, of kidney failure and being dialysis patients.

So the unmet need is particularly relevant in not only adult patients, even in pediatric patients. And even in these patients, long-term exposure to immunosuppressive therapy can interfere, of course, with growth, development, and overall well-being.

Dr. Norouzi:
I completely agree with what you just said, and this patient was already started on systemic corticosteroids at the time that she came to my clinic, and she wanted to know if she has any other options as an add-on therapy to bring down the proteinuria.

And hearing that the sparsentan has the FDA approval for FSGS is great news for us as nephrologists and for our patients as well. So as we were discussing her options, sparsentan came up as well. And having this option, we can talk about this and it might help you to bring down the proteinuria, and we do have clinical trial results on this, that was such fantastic news to her.

And sparsentan is indicated for treatment of primary FSGS to bring down proteinuria.

The dose that we use for sparsentan depends on how much our patients weigh and their age as well. For adult patients and for patients who are older than 8 years old, if their weight is more than 50 kg, we start with 400 mg per day, and then we're going to up-titrate to 800 mg per day. If they are lighter than 50 kg, then you're going to start with a lower dose, 200 mg daily, and then you can up-titrate to 400 mg daily.

It's amazing that you do have this indication for the pediatric population as well. As you mentioned earlier, we do have a lot of FDA-approved medications, for example, for IgA nephropathy these days, but we don't have these options for pediatric populations at this point. At least we don't have the FDA approval for the pediatric population. But for sparsentan in the setting of FSGS, having this option for the pediatric population, that's amazing.

Dr. Latus:
Absolutely.

For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Jörg Latus, and here with me today is Dr. Sayna Norouzi. We are discussing how to optimize outcomes in patients with FSGS.

Dr. Norouzi:
Okay, so moving on to this, we already talked about the effective treatments for FSGS, but I was wondering if you could tell us about the

mechanism of action of sparsentan and how it works in patients with FSGS.

Dr. Latus:
So I think this is a very important question because we have to communicate this new drug to our patients.

So first of all, sparsentan represents a novel approach. It is the only non-immunosuppressive oral therapy designed to directly target podocyte injury through dual blockade of the endothelin A receptor and angiotensin type II receptor 1. This dual mechanism is important because pathways contribute to ongoing podocyte damage, proteinuria, glomerular scarring, and loss of kidney function.

And in the DUPLEX trial, sparsentan demonstrated a significant greater—and I think this is very important—sustained reduction of proteinuria compared—this was not a placebo-controlled trial; it was compared with maximal dosed irbesartan. And at week number 36, more patients achieved the FSGS partial remission endpoint. This was 42% in the sparsentan group compared to 26% in the irbesartan group.

And over 2 years, proteinuria reduction reached approximately 50% with sparsentan compared to only 32% with irbesartan. And complete remissions were higher in patients treated with sparsentan compared to irbesartan.

However, there was one problem. The trial did not meet its primary endpoint of a statistically significant improvement in eGFR slope after 2 years despite a numerical trend favoring, of course, sparsentan, and fewer patients progressed towards kidney failure.

So these findings have sparked important discussions all over the world in our community about the role of proteinuria as a surrogate endpoint in FSGS trials.

And I think this is very important because FSGS is such a heterogeneous disease with variable progression patterns. So that's not so easy to do a trial in these patients, but it's very important to do a trial in these patients. Demonstrating differences in eGFR decline over relatively short trial periods can be a challenging problem, and therefore there was not so many trials done in FSGS patients.

This has led to the PARASOL initiative, a collaborative effort involving the FDA and leading kidney organizations aiming to validate the proteinuria reduction we saw in the DUPLEX trial as a meaningful surrogate endpoint for future FSGS studies. And overall now, sparsentan represents, I believe, a major milestone for the FSGS community, for our patients, and offering now a targeted, well-tolerated non-immunosuppressive therapy with consistent antiproteinuric effect in a disease where we didn't have any effective treatments in the past. So I think it's a good time for our patients.

Dr. Norouzi:
I agree. I feel like the results of the studies are really significant, and I completely agree with what you said about having proteinuria reduction as a surrogate endpoint marker for patients with FSGS. We do see a lot of variation in the eGFR of our patients, and the phenotype of our patients are so different with primary FSGS.

One thing that we just wanted to add, that I think our understanding of FSGS and primary FSGS is evolving as well, and hopefully we can see better clinical trial results and more clinical trials on FSGS as well. It's such a heterogeneous disease, as you say, and I always see primary FSGS with different phenotypes in my patients, and probably there are some genetic factors that we still don't know about it, and it's affecting the phenotype of the disease and how they're going to respond to the medications. And that's what's making FSGS really fascinating, at least to me.

So are there any other studies contributing to this indication for sparsentan that you'd like to share with us?

Dr. Latus:
Yeah, so I'm happy that we not only have one trial, so we have phase 2, the DUET trial. This was a trial done in more than 100 patients, not only adult patients and even included pediatric patients with a primary FSGS ranging from 8 to 75 years. And this was again a randomized, double-blind, active-control study. And again, it's active control, it's not placebo; it was compared to irbesartan, sparsentan.

And the study demonstrated, as shown in the DUPLEX trial, that sparsentan demonstrated a significantly greater reduction in proteinuria after only 8 weeks of treatment. And so we have good efficacy, but it had a very good safety profile as well. As importantly, but it also

introduced the FSGS partial remission endpoint—I think this is important for future trials—defined as a reduction in UPCR of at least 40% to a level below 1.5 g.

So patients reaching this endpoint showed in the later stage improved long-term kidney outcomes. And again, this means that a reduction of proteinuria means more preserved kidney function in the future.

So it's not only 1 trial; we have at least 2 trials showing good efficacy and, I think, from the safety standpoint, a very good safety profile.

Dr. Norouzi:
I agree. Seeing these clinical trial results are really reassuring and help our patients as well, too, because they always ask about this.

I just wanted to repeat one more time about sparsentan indication, that we do have the FDA approval not only for adults, we do have it for pediatric patients who are older than the age of 8 as well.

Considering the safety profile, the safety profile looked really good on the clinical trials. We do have a REMS program here under the FDA label that we have to check for liver enzymes every 3 months, and there are instructions on how to follow up on the liver enzymes. If it's more than 3 times higher than the baseline, then you have to think about reduction of the dose or holding the dose. And there is a minor risk of hepatotoxicity that I usually discuss with my patients.

There are some other side effects with the sparsentan that is important to consider. It can drop the blood pressure, it can cause hyperkalemia, and in some cases can cause some swelling as well.

And of course, for my female patients, like the patient that we discussed, I always mention that pregnancy is basically a contraindication for taking this medication. So while they're taking this medication, they should make sure that there is no risk of pregnancy.

Any other additional concerns or any comments about the sparsentan as you're prescribing it for your patients?

Dr. Latus:
Yeah, so I think it's overall a well-tolerated drug, and I think this is very important. Yes, you have the drop in blood pressure in some of the patients, but I think you have to take in mind not just stopping the drug. So a lot of patients, they get used to the blood pressure, and the blood pressure is getting in the normal range within several weeks after you start the treatment. And when we talk about hyperkalemia or edema, most of our patients do get sparsentan in a combination therapy with an SGLT2. So may be, I believe, the additive effect in regard to, let's say, efficacy and safety. Makes complete sense for me. So overall, a well-tolerated drug.

Yes, you have to check the liver enzymes, but again, it's non-immunosuppressive, and you can treat your patients with a very, very young age, a reduction of proteinuria and a preserved eGFR. So yes, there is hope, I believe.

Dr. Norouzi:
I agree. It generally is really well tolerated, and the side effects that we mentioned, I always tell my patients that these are potential side effects. It doesn't mean that it's going to happen to you.

Dr. Latus:
Yes, so there is hope. And before we wrap up, let's each offer a final take-home message. So, Ms. Sayna, what do you hope our listeners will leave with today?

Dr. Norouzi:
I just want our listeners to remember that we do have an FDA-approved medication for primary FSGS after many, many years. All of us as nephrologists, we've been treating our patients with off-label medications, and basically when they come to our clinics, we tell them about their options, but we never had an FDA-approved medication for our patients. So this is an exciting time for us.

It's really important to remain updated on indications of these medications, how to prescribe them, how to monitor our patients, and make sure that our patients know about their options, because if we don't know about it, we're not going to talk about it, and our patients, it's really hard for them to figure it out by themselves. This is a really complicated situation.

So our responsibilities these days is much higher than what it was before with all the new FDA-approved medications. So let's try our best to remain updated and being able to offer FDA-approved medications to our patients and come up with the best decisions for them together.

Dr. Latus:
And maybe I can only add that I think FSGS remains a progressive kidney disease, and I think this is a big problem for our patients. We had significant unmet need and historically limited treatment success. And now we have a new drug available, sparsentan.

And I think let's go for remission and not only talking about the age, not only talking about IgA nephropathy. Talk about remission and just go for the new drugs we have now available because otherwise we have the drugs and we don't treat our patients.

Yeah, and that's all the time we have today. So I want to thank our audience for listening, and thank you, Sayna Norouzi, for joining me.

Dr. Norouzi:
Thanks so much for having me.

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