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# FSGS: Interpretation of Proteinuria Reduction Thresholds

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**Dr. Tesar:**
This is CE on ReachMD. I'm Dr. Vladimir Tesar, and I'm joined by Dr. Meghan Sise. Today, we are going to be discussing proteinuria and its correlation to disease progression in FSGS. In addition, we'll cover why assessing and reducing the urinary albumin-creatinine ratio, or sometimes called UACR, can be important.

I would like to stress that we have remission, the decrease of activity of the disease in FSGS, defined in different ways. So traditionally we have defined complete remission proteinuria lower than 0.3 g/g of creatinine. And partial remission, which was traditionally defined as a decrease of proteinuria to less than 3.5 g/g and by at least 50%. And there are now some new data and new analysis showing that another definition of partial remission, lowering of proteinuria to lower than 1.5 g/g and decreased by at least 40%, is most closely associated with the outcome of the patient. And this is the outcome which was also used in trials with sparsentan, which will be discussed later on.

And we know that reducing proteinuria to any of these endpoints is associated with improved outcome, and we can clearly show on the data from sparsentan trials that if any drug is successful, it usually is successful on each of these levels and better than the comparator.

So I have a question to Dr. Sise. There are emerging therapies that can act as dual endothelin and angiotensin receptor antagonists. Can you talk about this mechanism of action and the management of FSGS?

**Dr. Sise:**
Sure. Dual endothelin angiotensin receptor antagonists, or DEARAs, are medications that target endothelin type A receptor pathways and angiotensin 2 receptors. ACEs and ARBs have long been used to treat proteinuric kidney disease, and I think nephrologists have a good understanding of renin-angiotensin-aldosterone blockade in the management of kidney disease. But endothelin-1 is a potent vasoconstrictor and a pro-fibrotic peptide that's produced by endothelial cells, podocytes, and mesangial cells, and it can be an important contributor to glomerulosclerosis, vasoconstriction. And so data have shown that there is benefit to targeting both angiotensin 2 receptor pathways and endothelin-A receptor pathways at the same time. There's an interaction between these 2 signaling pathways, and by blocking them, you can potentiate the beneficial effects of each pathway.

Sparsentan is a dual endothelin angiotensin receptor antagonism, a DEARA, and it's currently approved to slow kidney function decline in IgA nephropathy. It's under review by the FDA, not yet approved. It's under review for the treatment of FSGS. We know that

proteinuria reduction, as you mentioned, Dr. Tesar, is really important in FSGS. It's a part of what the FDA considers when approving new drugs for IgA, FSGS, and other glomerular diseases.

We now have the PARASOL collaborative, which is a working group initiative backed by the FDA but also by important kidney associations, such as the National Kidney Health Initiative, ISN Glomerular Disease section, and the National Kidney Foundation. And this group is pooling data to help us understand how we should look at proteinuria reduction in response to novel treatments for FSGS and how those proteinuria reductions correlate with long-term clinical outcomes, such as prevention of kidney failure

**Dr. Tesar:**
Yeah. We have, now, exciting data showing that sparsentan really is better in terms of reducing proteinuria. For instance, based on this only mentioned recent analysis, complete remission is achieved in much, much more frequently in patients treated with sparsentan compared to irbesartan. It's 18.5% versus 7.5%. It is 2.5 times more frequently.

And also partial remission, and here sparsentan was 1.5 times more successful than irbesartan.

And what is also important is that there's a very early response to sparsentan. And when we look at the course of proteinuria, the curves separate quite early at 6 weeks. Already, there is an advantage of sparsentan compared to irbesartan.

So we believe that these early changes must be translated also in long-term outcome, and this was also the case in this recent analysis showing that patients with complete or even only partial remission had much better outcome in terms of slowing down the CKD progression.

So I think that it was a very nice discussion. Thank you, Dr. Sise, once again for joining me and thanks to our audience for listening today.

**Announcer:**
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