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Released: 03/10/2026

Valid until: 03/10/2027

Time needed to complete: 1h 05m

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Targeting Lower Proteinuria Levels: Shifting the Goalpost in IgAN

Announcer:

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Dr. Suzuki:

This is CE on ReachMD. I'm Dr. Yusuke Suzuki. So we are pleased to have Dr. Richard Lafayette with us today.

So now I'd like to share a specific case. So a 29-year-old man with no significant past medical history is referred to a nephrologist after persistent microscopic hematuria and proteinuria identified on routine evaluation. So he reports intermittent episodes of gross hematuria following an upper respiratory tract infection, since his early 20s, but otherwise feels well.

Kidney biopsy confirms IgA nephropathy with mesangial hypercellularity and segmental glomerulosclerosis, Oxford classification M1 and S1, without crescent. At diagnosis, his estimated glomerular filtration rate, eGFR, is 92. Blood pressure is well controlled at 122 diastolic over 76, remarkably. So he's started optimized supportive care, including renin-angiotensin system blockers and dietary sodium restriction.

Over the next 18 months, his proteinuria decreased but stabilized between 0.5 and 0.8 g/day, confirmed on repeated measurement. But his eGFR gradually declined to 78. So in Japan, so we often see patient with early-stage IgA nephropathy presenting mild to moderate proteinuria.

Professor Lafayette, what do you think about the treatment for such patients?

Dr. Lafayette:

Yeah, thanks. And I agree, I think this is a very common scenario where patients come in not at our very highest risk, with more proteinuria than we would like, but not such a bad pathological presentation. Good blood pressure control, normal kidney function, and the patient's treated, I think, appropriately with just a little supportive care up front. But their proteinuria comes down, but it's still in a range where we now know, after many collaborative studies have been done looking at data from England, Scandinavia, Germany, California, and even some treatment trials, that patients who have persistent proteinuria still between 0.5 and 0.8 g/day can be at a pretty substantial risk of progressing over the next 5 to 10 years, where as many as a third of them come into renal failure in that time point.

So I think clearly, in this case, and maybe even in earlier time points, we have to really consider more aggressive therapy, because with conservative interventions, I think you really need to achieve well under 0.5 g/day early and keep it there, or there really is a call to get to

more targeted therapies. And in a case like this, I think some people would consider a repeat biopsy. I'm not a big advocate of that, but I think you can move further with this therapy.

Right now, our best class of therapy in the United States are starting to look like B-cell modifier agents because they really flatten GFR progression, at least in phase 2 and in phase 3 for the telitacicept study. But we have sibeprenlimab available in the United States, and that would be a strong consideration. But the main goal would be to do more to really drive that proteinuria to well under 0.5 g/day, watch the GFR and make sure it really stabilizes.

So, again, I think we want the proteinuria to go as low as possible, or to use drugs that are more targeted, such as we're finding with the B-cell modifiers.

So, Dr. Suzuki, what do you think about that approach?

Dr. Suzuki:

Yes, thank you very much. So it's indicated in many recent reports that mild proteinuria carries a non-negligible risk of progressing to kidney failure over the long term. So consequently, indeed, the recently revised KDIGO guideline recommended aggressive therapeutic intervention, particularly in the younger patient with new candidate of drugs, right? So this approach involved aiming for the urinary protein levels below 0.3 g/day as much as possible with eGFR slope also serving as a reference point. So I understand that the treatment approach is shifting toward a more aggressive approach.

Dr. Lafayette:

Yeah, and again, I agree with everything that you said. I think it's really important for people to understand that the treatment, the goal posts, are really shifting. We want to get aggressive control. We want to think about a lifetime without kidney failure. And the easiest thing to focus on is the proteinuria. If you can get it nice and low, then you're doing really, really well.

But it may be also important how you get there. And it's starting to look like the exact mechanism of the drugs are also going to be really important.

Dr. Suzuki:

Thank you very much for a nice discussion.

Announcer:

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