

### Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:

<https://reachmd.com/programs/cme/advancing-igan-care-expert-strategies-for-transformative-patient-outcomes/17824/>

Released: 06/26/2024

Valid until: 06/26/2025

Time needed to complete: 15 minutes

### ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

---

## Advancing IgAN Care: Expert Strategies for Transformative Patient Outcomes

### Announcer:

Welcome to CME on ReachMD. This episode is part of the Global Kidney Academy and is brought to you by Medtelligence.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

### Dr. Floege:

The management of patients with IgA [immunoglobulin A] nephropathy [IgAN] demands more effective treatment options to achieve sustained proteinuria remission. Join us as we discuss how novel therapies can help advance clinical care for patients with IgA nephropathy and improve patient outcomes.

This is CME on ReachMD, and I'm Dr. Jürgen Floege.

### Dr. Huynh-Do:

And I'm Dr. Uyen Huynh-Do from Switzerland.

### Dr. Floege:

So we have a lot of discussion today, and let's get started. We will start with a very interesting patient case from Uyen.

### Dr. Huynh-Do:

Well, okay, so let me present a very interesting case of, actually, a young woman, a 29-year-old, as I first saw her in September 2020. She presented with edema and 1 episode of macrohematuria, and the blood pressure was also quite high. Luckily, she still had a normal eGFR [estimated glomerular filtration rate] above 90 mL, but her serum albumin was already low, and she has definitely a nephrotic range proteinuria of 900 g/mmol creatinine, or between 4 or 5 g protein/day.

So because of her age and because of this high proteinuria, we decided to put her on immunosuppression with steroids just to have a look whether she could react. But after 6 months, because there was not much of a difference, we stopped immunosuppression. In February '22, we added dapagliflozin 10 mg/day. And in August, we repeated kidney biopsy. And so the definitive pathological likely diagnosis at that time was IgA nephropathy M1, E1, S1, T0, C1. Now, luckily, in September '23, we could have her on early access program with sparsentan, starting with 200 and going up to 400 mg/day. And it was quite impressive how the residual proteinuria decreased from 350, 400 to 200 g/mmol creatinine after 3 months.

And so I think the case illustrated very nicely that proteinuria is a strong predictor of the rate of IgA progression, but it is not always possible to tackle it with the standard of care, and therefore new treatment strategies are highly needed.

Can you tell us a little bit what kind of new treatment considerations you can take into consideration in this special case that we had just presented?

### Dr. Floege:

Yeah, thank you, Uyen. So first of all, we have learned that there is no safe proteinuria. And that is a very relevant insight, because the

old KDIGO [Kidney Disease: Improving Global Outcomes] guidelines, old, 2021, said lower proteinuria below 1 g/day, and we now realize that that is inadequate. We have learned from the British RaDaR cohort that, essentially, you should target zero proteinuria and not just smoldering disease.

So we need better treatment options in addition to what was already said, to have sparsentan in here. And one option, of course, would be Nefecon. Nefecon is a particularly encapsulated targeted-release formulation of budesonide.

So in the phase 3 NeflgArd trial, we have tested patients on RAS [renin-angiotensin system] blockade with IgA nephropathy being randomized to either receive 16 mg of Nefecon daily or to go on placebo and to continue that for 9 months, after which time this was briefly tapered, and then there was an observational phase of 15 months with no specific added therapy.

And what the Nefecon trial showed us is that the 9 months of treatment led to a complete stabilization of kidney function. In fact, GFR increased early on. And then as you stop the treatment, GFR starts to fall in parallel to placebo.

And more remarkable was the effect of proteinuria, which almost was a 50% drop in proteinuria with Nefecon. And once we stopped the treatment, there was a 3-month carryover phase where proteinuria still dropped, but then, no surprise, it did increase again as we had stopped the treatment.

So in terms of safety, what we observed in the Nefecon study was that there are steroid-related side effects, as to be expected, yes. Budesonide has a high first-pass effect, but a little bit does reach the systemic circulation. And not unexpectedly, we saw acne, mood changes, sleep disturbances, some weight gain. But what we didn't see, and that's essential, and that's the big, big, big difference to high-dose systemic steroids, we didn't see serious infections. We had no mortality, and there was no de novo induction of diabetes. So in terms of safety, yes, a little bit, but certainly one order of magnitude below what we used to see with intense steroid therapy.

**Dr. Huynh-Do:**

So, Jürgen, what are the insights from other recent trials that can reshape our treatment strategy for IgA nephropathy?

**Dr. Floege:**

Yes, in addition to the NeflgArd trial, the, I believe, most important trial of recent years is the PROTECT trial. And PROTECT is a landmark trial because it's one of the very few with an active control. Whereas most other trials in recent times had a placebo control, PROTECT had irbesartan as an active control. And I think that is the big distinction.

In PROTECT, patients with IgA nephropathy and proteinuria above 1 g were randomized to receive either irbesartan or sparsentan. And sparsentan, of course, is a dual endothelin A receptor blocker plus angiotensin receptor blocker. And the natural choice for comparator was irbesartan, because irbesartan has a molecular structure which is very similar to that of sparsentan, except it only blocks the angiotensin system, whereas the sparsentan is a dual action blocker. And these were rapidly up-titrated.

So in terms of proteinuria, it fell a little bit with irbesartan. But it fell much more with sparsentan, and within a few weeks, it fell by 40%, whereas the irbesartan arm led to a 5% to 10% decrease in proteinuria.

And that is why I consider PROTECT an absolute landmark trial, because the control arm, and let's focus on that one first, received irbesartan at the maximum dose; 97% of the patients had the maximum dose of 300 mg irbesartan. And despite the fact that all these patients had been on a RAS blocker prior to the trial, you still see a little dip in GFR with the start of irbesartan, suggesting that RAS blockade was not maximized; despite the assumption they were all on there, it wasn't maximized.

And PROTECT is notable for one of the slowest losses of GFR per year in any of the recent trials, minus 3.7 mL/min/year, whereas most other trials have seen in the control arm 5 mL/min/year or more. However, if you replace irbesartan with sparsentan, then the GFR drop was even less, and it went from 3.7 with irbesartan to 2.7 with sparsentan.

The safety was good. There was no increase in diuretic use. There was no change in body weight. The most common side effect, which was a little more in the sparsentan arm compared to the irbesartan, was dizziness and hypotension.

Despite the adverse events of a little more dizziness and a little more hypotension, the actual blood pressure data of the trial suggested there was a small change in diastolic pressure, and systolic pressure was essentially identical.

But overall, this is a landmark study because it sets a new standard in treatment, and the GFR loss in IgA nephropathy patients can be lowered so much that future trials will indeed have somewhat of a difficult stand in improving this even further, but very clearly, minus 2.7 mL/min/year is still not what we would consider physiologic. Don't you agree?

**Dr. Huynh-Do:**

Yes, so definitely. So I think we really still have to remember RaDaR study, which will say you have to have a loss of 1 mL/min if you

want really to preserve the nephron. And I think this is what we aim at. We are very close to that. And I really believe this is a really nice study because the irbesartan, instead of placebo, really sets us very high.

**Dr. Floege:**

So, Uyen, what other investigational therapies should we be aware of?

**Dr. Huynh-Do:**

Okay, so you mentioned the PROTECT study, which is the dual RAS blockade and endothelin antagonist, but we also have a pure endothelin antagonist, which is called atrasentan, where the data has been presented in the late-breaking trials and where you also have a substantial significant reduction of proteinuria.

On the other hand, we know that what is driving the production of Gd-IgA1 is the APRIL pathway, and here I can mention 2 molecules. The one is a monoclonal antibody, the sibeprenlimab, a phase 2 study, with about 155 patients, placebo compared with 3 different doses, and at the end of the 1-year period, there could be observed a substantial reduction of about a 50% reduction of proteinuria in the 2 higher doses of sibeprenlimab compared to placebo.

And the second is a fusion protein called atacicept. This one is a dual inhibitor of BAFF and APRIL, and again, a placebo against 3 doses. And what could be observed is that also with atacicept, the proteinuria could be reduced. But on the other hand, we also have interesting data about eGFR, which at the beginning already of the treatment was increased. And this is an interesting hint. It could say that when you tackle that way, you could also decrease inflammation. And I think this is something we have to pursue and look at in the phase 3 study.

Okay, the third pathway and the third molecule I would like to mention is, what else, complement. Because nowadays we feel a complement everywhere. And in this case, one of the molecules, which is iptacopan, this is a molecule which is inhibiting factor B, has been shown in a phase 3 study to be able to reduce significantly proteinuria. We don't have the data yet, but we know from preliminary communications that proteinuria could be reduced by about 35% in patients receiving iptacopan compared to placebo.

So in conclusion, we can say that, apart from the standard of care, the non-immunosuppressive treatment, we have now 3 different molecules tackling different pathways leading to inflammation and to the loss of the eGFR.

**Dr. Floege:**

So the challenge of the future will be, once you optimize your therapy, how do I combine? And what is the best therapy to reduce proteinuria? And as I said earlier, ideally to induce full remission of the disease, that is no proteinuria, below 0.3 g/day, no microhematuria, and a stable eGFR.

And as Uyen had already indicated, I tell my patients, you have 2 diseases. We tackle the CKD, which you have lifelong, and this will require persistent treatment with RAS blockers, sparsentan, SGLT2 inhibitor, whatever. And you have an immune disease, which may require intermittent therapy, possibly low-dose continuous therapy. Those are all questions we need to find out, and we will find out.

So I think that has really been a fascinating conversation. But before we wrap up, Uyen, what is your final take-home message?

**Dr. Huynh-Do:**

So I really believe that we have a new era for treatment of IgA. We can treat the causes of IgA, tackling inflammation, and treat the consequences, which is CKD. So in addition to RAS blockade and SGLT2 inhibitor, we have now the dual angiotensin and endothelin antagonist sparsentan.

**Dr. Floege:**

And I'm afraid that's all the time we have today. So I want to thank our audience for listening in. And thank Dr. Uyen Huynh-Do for joining me and for sharing all your valuable insights and expertise. It was great speaking to you today.

**Dr. Huynh-Do:**

Thank you very much.

**Announcer:**

You have been listening to CME on ReachMD. This activity is provided by Medtelligence.

To receive your free CME credit, or to download this activity, go to [ReachMD.com/Medtelligence](https://ReachMD.com/Medtelligence). Thank you for listening.