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IgAN Management Into Practice: Evolving Guidelines & Targeted Therapies

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Dr. Latus:
After much anticipation, we now have the updated KDIGO 2025 clinical practice guideline for the management of IGA nephropathy. Joining me today is one of the co-chairs in the KDIGO Working Group, and today we will review important changes in the guideline including diagnostic criteria, proteinuria-based treatment thresholds, and revised therapeutic goals and discuss how these changes will impact your clinical practice.

This is CMD on ReachMD and I'm Dr. Jörg Latus.

Dr. Floege:
And I'm Dr. Floege.

Dr. Latus:
So let's begin by reviewing the important changes to the guideline, and who better to give us the highlights than you, Jürgen?

Dr. Floege:
Yes. so there are quite dramatic changes in the guideline. And if I summarize them, there are 3 major topics. First of all, get more aggressive in your diagnosis and your treatment goals. Biopsy early. Now that we do have drugs, we need a biopsy to confirm the diagnosis. Second of all, no longer aim for proteinuria below a gram per day as we advised in the 2021 version, but now we advise that you aim for full remission, no proteinuria, so below 0.5 g/day, ideally below 0.3, and a stable GFR, which of course is what I'm interested in at the end of the day. We have many more drugs and we now separate formally box with treatments for the immune disease targeting the immunologic dysfunction, inflammation, fibrosis.

And on the other side we have a box targeting, let's say, generic CKD mechanisms. Realizing that this, if you look really hard, it's not exactly 100%, but it helps you sort your brain in how to approach these patients. So in the immune box we have, of course, still systemic steroids, but we have Nefecon, and there will be more to come. In the CKD box, we have good old RAS blockers up-titrated, lifestyle, SGLT2 inhibitors, and most recently sparsentan and maybe, in the future, selective endothelium blockers and maybe even mineralocorticoid receptor antagonists. Big change number 3, no longer start these therapies sequentially as we have done in the past where first we optimized supportive care and then we thought about steroids. And in the course of doing so, patients did lose eGFR irreversibly. We now advocate that you target both processes simultaneously. So quite fundamental changes.

Dr. Latus:
Thank you very much. I'm really pleased and I have to say that I truly like this guideline in this way especially because it sets very clear

goal and does hopefully improve patient care. And what I would like to point out again is that when we give talks about IgAN, the same question always comes up: Should I now apply immunosuppressive therapy like Nefecon, or should I intensify CKD therapy? And with that there's always the question about certain biomarkers. And I think here, too, KDIGO makes it very clear the only true established risk factor is proteinuria.

Could you perhaps briefly comment on that, Jürgen?

Dr. Floege:
Proteinuria is not perfect. We have several examples where treatment lowered proteinuria. In the STOP- IgAN trial, this was significantly more common with the steroid, but 10 years later there was no benefit GFR-wise and dialysis-wise. So clearly whatever you do, you want something that lowers proteinuria but then keeps it low and doesn't bounce back up. And that's an important consideration for how we are going to structure our treatment in the future.

Dr. Latus:
Thank you very much for the clear comment. I'm really pleased, and I have to say when I saw the guideline, I really liked the guideline, especially because it sets very clear goals and does hopefully improve patient care. I hope so.

What I would like to point out again is the point when we talk about IgAN, the same question always comes up, should I now apply a immunosuppressive therapy like nefecon or should I intensify CKD therapy? And with that there's always the question about certain biomarkers. And I think here too, KDIGO makes it very clear the only true established risk factor is proteinuria.

So, Jürgen, why are we targeting the gut instead of depletion?

Dr. Floege:
Well, there's a lot of evidence for gut-kidney axis. and at one point I was even afraid that IgAN would become a GI disease. Nobody wants that. So there's genetic evidence that there are links to mucosal genes or mechanisms in IgA nephropathy. There's the observation that mucosal infections can trigger activity in IgA nephropathy, and there's a very clear link between several inflammatory bowel diseases and secondary IgA nephropathy, celiac disease, chronic inflammatory bowel diseases as well. So I think the rationale is really there. And finally, Nefeon is probably the best evidence we have. If you treat the gut unit, you can do something good for the kidney.

Dr. Latus:
You're listening to CME on ReachMD. I'm Dr. Latus and he with me today is Dr. Floege. We are discussing the updated KDIGO guidelines and their application in clinical practice.

Just an additional comment, what KDIGO also clearly states is that we need to address both pathways of the disease. We need of course optimal CKD therapy, but of course also treatment of the disease itself. So Nefecon is a disease-modifying therapy. Of course there are systemic steroid effects, but as Jürgen also described, as a nephrologist, we are used to treating patients with long-term steroid therapy from transplantation. For me it's also very clear that combination therapy is the way forward here. Clearly SGLT2 inhibition and later on, of course, endothelium antagonists. We are of course looking forward to further treatment options in the future, but if we are talking about what we can already do for our patients starting tomorrow, then Nefecon clearly has to be mentioned.

So we have steroids available for many years. What's the difference between, let's say, the systemic steroids and Nefecon ?

Dr. Floege:
It's huge. Yes, Nefecon is still a steroid, but it has this huge first-pass effect in the liver. So that little steroid does reach the systemic circulation. And that is the major difference in safety. We have learned from both the STOP-IgAN but in particular the testing trial, both of who tested large doses of systemic steroids, that we kill patients. We kill patients from infections, not even talking about all the other steroids side effects like weight gain, like hypertension, like osteonecrosis, et cetera, et cetera. So yes, Nefecon does have some stereotypical side effects. You can see roundish faces. You may have a little bit of weight gain, you may have a little bit of edema, but by no means does it cause systemic serious infections or even cause mortality.

In terms of efficacy, steroids, in particular in Europe, are controversial. We have the STOP-IgAN study and 3 retrospective European studies showing all consistently that steroids don't prevent kidney failure and that the benefit that you may see on proteinuria winds off and there's no long-term benefit. The GFR testing showed a benefit at the cost of severe side effects, but testing was almost exclusively in Southeast Asia. So that's a different population. Having said that, what do we know about Nefecon? It's efficacious and there's no population which doesn't respond Nefecon. And again, that's a major difference. I'm much more convinced that Nefecon works in my patients than I'm convinced that systemic steroids work.

Dr. Floege:

So now that we've heard about the guideline update, let's take a deep dive into a patient case and see how this can be applied to clinical practice. Jörg?

Dr. Latus:
Yeah, so I would like to present you a case of a patient, 40-year-old who was diagnosed with an IgA nephropathy in 2020. So again, it's very important; you need that diagnosis. You need a biopsy to perform to do the diagnosis of IgAN. So in 2020 the patient was diagnosed and the eGFR was 61 mL/min and the proteinuria was 0.8 g/g and blood pressure was 140 over 80. So of course we started ramipril in the patient and later on we had the excellent studies showing that the SGLT2 inhibition is favorable in these patients. So we started dapagliflozin in the patient in 2021. In January 2024, the patient presented to our outpatient clinic and the eGFR was 41. So we started with 61 in 2020. Now GFR was only 41 mL/min and proteinuria increased to 1.4 g/g; blood pressure was well controlled and the BMI was 20.

So at this time when we decided of course to treat the patient with Nefecon for 9 months, and when you can see in September 2nd, 2024, when we stopped the therapy after 9 months, the eGFR was preserved. It was 42 mL/min and proteinuria went down to 0.5 g/g . When we saw the patient again in March this year, the eGFR was still 40 mL/min, but proteinuria increased again to 0.9 g/g. So the question was, of course, can we do a second cycle of Nefecon in our patient? And we were very happy last year at the kidney week, the data represented that you can do a second cycle of Nefecon in your patient and you'll still see the same reduction of proteinuria and an eGFR preservation. Again, we have to keep in mind that we talk about evidence, of course, with Nefecon, but of course you have to be in label, so near proteinuria of 0.8 g/g or a proteinuria of more than 1 g/day to start Nefecon. At the same time point we started Nefecon for a second cycle. We decided to address the other pathway of the disease and added a therapy of sparsentan. So I believe in the future now, and this was clearly stated by by Jürgen, we need a multifactorial, multitargeted therapy to achieve the proteinuria of zero.

Are there any comments?

Dr. Floege:
Yes, I think this is a great example of how we should combine the newer treatments, and for the Europeans, there's a very, very practical argument of doing so. That is if you start one of these treatments, you are likely to lower proteinuria below the threshold where the drugs are approved. Both Nefecon and sparsentan have an approval minimum proteinuria of 0.8 g/g or 1 g/day. So the moment you start one of them, you're likely not going to be able in the future then to start the other one because proteinuria may be too low, but usually you don't need use for remission. So that's a very practical argument, starting both in parallel. And the other comment here, which is important, is that so far Nefecon is used in 9-month treatment cycles and then you quickly taper. There is an ongoing study in the US where an Nefecon, instead of tapering it and stopping it, is simply reduced by half in dose and then maintained. And I think this is the really interesting study. Maybe we come to a concept of induction and maintenance therapy with Nefeon as we do in so many other diseases. I would not expect that after 9 months of Nefeon the IgA nephropathy has disappeared. So we probably need some kind of maintenance.

Dr. Latus:
Before we wrap up, let's each offer a final take-home message. Look, what do you hope our listeners will leave with today?

Dr. Floege:
We have much better and much safer therapies already and more will come. It's a great time to work in IgA nephropathy. Life will become more difficult because of these many combinations, but in terms of patients, I think we can hopefully soon offer them that we can stabilize their disease or ideally keep it in remission. And that is totally new for IGA nephropathy.

Dr. Latus:
So I do it very quickly. I think the ultimate goal is zero proteinuria and for this, multitargeted therapy is necessary, and I believe Nefecon is part of that. And I should say let's make it happen.

So I want to thank our audience for listening in and thank you, Jürgen, for joining me today.

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