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Updates in Glomerular Disease

Announcer:
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CHAPTER 1: IgAN Case Presentation

Dr. Floege:
What are the underlying mechanisms of glomerulonephritis and sclerosis in patient populations with kidney disease, and what about clinical presentation, diagnosis, and risk stratification? Can clinical trial data provide insights on the challenges with current standards of care?

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

Dr. Barratt:
And I'm Dr. Jonathan Barratt.

Dr. Jayne:
And I'm Dr. David Jayne.

Dr. Floege:
In this first chapter, we'll look at immunoglobulin A nephropathy, also known as IgA nephropathy or IgAN, with a very interesting patient case of mine.

So here's Mrs. XY. She first presented to me about 2 years ago, with a GFR around 50-60. We did a kidney biopsy, found IgA nephropathy. Remarkably little activity here, so M0 and E0 imply there was very little proliferative change. S1 saw this was some glomerular sclerosis, and almost nothing in the tubulointerstitium and no presence. And what you see down there is the course that she took at the time of the kidney biopsy. Her GFR was 47. And then right under my eyes, she dropped to 35 within half a year. In terms of supportive care, she has well-controlled blood pressure, she follows a pretty reasonable diet. She has a diuretic. She's not obese, and she doesn't smoke. So in terms of optimizing her supportive therapy, there's pretty little room for improvement.

The guidelines say we recommend that all patients with a proteinuria above half a gram per day, irrespective of hypertension, receive a RAAS [renin-angiotensin-aldosterone system] blocker – a 1B recommendation – and clearly we've done that. Here comes the tricky part. We suggest that patients who remain at high risk – and she clearly does with her proteinuria of 1-2 grams – are considered a 6-month course of steroids. But you need to discuss the important risk of treatment-emergent toxicity with a GFR below 50. And you shouldn't even consider this at a GFR below 30 in a diabetic, obese, et cetera.

Why am I so skeptic about steroids? Well, this is the German study that we did some time ago. But this is the long-term outcome, and you can see that adding immunosuppression to a comprehensive, supportive regimen did not increase the chances to stay free of

death, dialysis, or 40% GFR loss. It just added adverse events. This data has been challenged recently by the TESTING trial. TESTING used the same primary endpoint – 40% GFR loss, dialysis, or renal death and we clearly retarded the primary endpoint. However, this came at the price of 6-fold increase in serious adverse events. So we were forced to halve the dose of the methylprednisolone. We still had 2.5 times as many SAEs, but this, too, worked and it retarded the onset of the primary endpoint. But there are 2 notable things here. First of all, this is an almost purely Southeast Asian population. We know IgA nephropathy is more severe in Southeast Asians. And the other notable thing here is that the event rate starts to become parallel after about 2.5 years. And the bad implication is that, in theory, you would have to re-treat every 2.5 years, excepting that you create adverse events.

So we were very thrilled when this study came out, the phase 2 study of target released budesonide and encapsulated budesonide, where much to our surprise, the 9-month treatment period resulted in a totally stable GFR, whereas GFR dropped significantly in the placebo group.

At the same time, SGLT2 inhibitors made it into nondiabetic glomerular disease, and this recent meta-analysis concludes that in IgA nephropathy, being on an SGLT2 inhibitor reduces your likelihood of the primary renal endpoint by 50%. So what did I do to my patient? I did both. And look at what happened. She went into complete remission proteinuria-wise, and quite remarkably, her GFR stabilized out at a very low level, and you can see that she has maintained a stable GFR for half a year, which she never had before I saw her. But then, she developed a deep vein thrombosis and pulmonary embolism, and I've now started to taper off her budesonide.

Dr. Barratt:
So Jürgen, in terms of therapies that are currently being evaluated or perhaps are potentially going to be approved in the next 2 or 3 years, what kind of approach might you have wanted to take?

Dr. Floege:
Very clearly, if I were to see this patient today, I would put her on combination therapy right away.

Dr. Barratt:
And with the only other drug, really, that's close to approval is bosentan, which is an endothelium receptor antagonist. Do you think an endothelium receptor antagonist would add value in this lady's case, bearing in mind the data showing that that may have a significant antiproteinuric effect as well?

Dr. Floege:
Yes, I would clearly consider sparsentan or any other endothelin receptor antagonist because, one, they seem to be very safe, and, B, there's reasonable evidence already now from phase 2 studies that if you add them on top of full-dose RAAS blockade, they have an additive antiproteinuric effect. So clearly this lady calls for combination therapy.

Dr. Jayne:
I note that the ACR reduced down, but it was still quite abnormal, and I would be interested in your comment on what a target should be.

Dr. Floege:
Good question. Her lowest proteinuria was 0.25. In a woman almost close to normal, given that proteinuria is such a strong predictor of progression, we should aim to have proteinuria go down to the normal range and not just below 1 g/day.

Now, in Chapter 2, we'll have a look at a case of FSGS. Stay tuned.

CHAPTER 2: FSGS Case Presentation

Dr. Floege:
So welcome back. Let's continue onto our second chapter. Jon, please tell us about the patient case you have on focal segmental glomerulosclerosis, or FSGS.

Dr. Barratt:
So this is a 47-year-old Caucasian man, first presented with quite an abrupt 6-week history of increasing leg swelling that was associated with worsening tiredness, reduced exercise tolerance, and breathlessness on exertion. He was obese with a BMI of 34. He had type 2 diabetes, hypertension, and dyslipidemia. And he was taking the usual drugs we might expect. There was no family history of kidney disease. He was a nonsmoker, drank occasional alcohol, and had quite a sedentary job. Urine analysis showed 4 pluses of protein, 1 plus of blood, and 1 plus of glucose. And he had pitting edema to both mid-thighs. But there were no other stigmata of systemic disease. His autoantibody screen was negative, including a PLA2R. His spot urine protein-to-creatinine ratio was 507, which roughly approximates to over 5 g/day of proteinuria. His ultrasound scan showed 2 normal-sized kidneys, and his renal biopsy was a good biopsy with 28 glomeruli, 3 of which showed segmental scars, but the remaining glomeruli were all normal by light microscopy.

There was some modest acute tubular injury that you might expect with that degree of proteinuria, but there was really no established interstitial fibrosis. Immunofluorescent studies were negative, and electron microscopy demonstrated widespread foot process effacement with microvillus formation, but no electron density posits and a normal GBM morphology and thickness.

So if we think about this presentation, Jürgen, what would be going through your mind in terms of what you think the diagnosis is likely to be, and what potential type of cause might there be?

Dr. Floege:
The obvious first thought here would be diabetic nephropathy, but then you have the electron microscopy, which clearly argues against this. And maybe, Jon, you can explain why this is evidence of FSGS and not diabetic nephropathy.

Dr. Barratt:
If this was an advanced case of diabetic nephropathy, you would see nodule formation, unlike microscopy, but importantly, you would see thickening of the glomerular basement membrane. And that would be quite striking.

What would your thought process be about how you would categorize this patient, Jürgen?

Dr. Floege:
Well, I'm a KDIGO guy, so I go to the categories of primary FSGS, secondary FSGS, which is a possibility in this obese gentleman. Genetic, he's too old. He could have the type of FSGS where we simply don't know the cause.

Dr. Barratt:
Absolutely. The case really resembles very much more a primary case of FSGS. It's really important to understand, when you see a case of FSGS – which we must remind ourselves is a pattern of morphological changes on a kidney biopsy – you start thinking what could be the underlying cause. And so this abrupt presentation, the kidney biopsy features – particularly the electron microscopy – made me think much more about this being a case of primary FSGS than any of the other causes.

If we now look at the algorithm that was generated as part of the KDIGO 2021 guideline, you can see that if patients have primary FSGS, where we believe this is due to the presence of a circulating factor that damages podocytes – so it's a podocytopathy – that results in increased proteinuria and the development of nephrotic syndrome, we need to be considering immunomodulatory therapy.

And so, David, in view of this gentleman's background history, what treatment options would you be thinking about, and how would you weigh up one over the other?

Dr. Jayne:
Important factors, that the man's nephrotic, with a high proteinuria, and he has impaired kidney function. And we've agreed that immunosuppression is indicated, and glucocorticoids would usually be the first place to go when considering immunosuppression. However, in this case, the presence of diabetes, the presence of obesity, hypertension, and dyslipidemia are all contraindications for steroids. And you need to use reasonably high-dose steroids to get an effective response in a steroid-responsive case of FSGS. So I've been looking at alternative drugs to glucocorticoids, and in particular, at the calcineurin inhibitors cyclosporin or tacrolimus.

Dr. Barratt:
Absolutely. We need to provide a treatment that does not carry significant toxicity for the individual patient in front of us. And if we do look at the KDIGO guidelines, glucocorticoids would be usually the first choice of therapy in this case, but actually for this particular gentleman – who is already obese, already has type 2 diabetes, is hypertensive and dyslipidemic – I felt the risk of giving glucocorticoids, particularly the dose and for the duration that is recommended in FSGS, was just too great. And so what I did was to start him on a calcineurin inhibitor, tacrolimus, and we managed to achieve a reasonable response. He became non-nephrotic, and after 6 months of treatment, he had no edema. His GFR was 57. He had a normal serum albumin. His cholesterol was much better. And he still had significant proteinuria, but not nephrotic-range proteinuria.

And in FSGS, high levels of proteinuria are a risk factor for progressive kidney disease, and we need to think about maneuvers that would allow us to reduce that proteinuria even more and therefore protect against future kidney function decline. I'm very much of the opinion that we need to offer our patients the opportunity to be involved in clinical research studies. And so that is what we actually did, and he's now currently in a clinical trial.

So what clinical trials are there out there at the moment in FSGS? We have a compound that's specifically being evaluated in those patients who carry the APOL1 mutation. We have other drugs targeting different aspects of podocyte biology and glomerular signaling in terms of the SLIT2, protein antagonists; we've got a chemokine receptor 2 antagonist that is being evaluated, and we have a TRPC5 inhibitor that's being evaluated.

But actually, most of the data we have are new therapies concerning sparsentan, a dual angiotensin receptor blocker and endothelium receptor antagonist. And this has been evaluated in a phase 2 study, the DUET trial, which has evaluated the drug in both children and adults, and it's shown a very clear anti-proteinuric effect and preservation of GFR effect in a small phase 2 study with reasonable-length follow-up now. And actually, sparsentan is currently being evaluated in the DUPLEX study in FSGS and in the PROTECT trial in IgA nephropathy. And early data from both of those studies have shown that sparsentan has a significant anti-proteinuric effect in FSGS but also in IgA nephropathy.

Dr. Floege:
We have a similar discussion as in IgA nephropathy, whether or not to use combination therapy right away. Clearly to me, sparsentan sounds like little risk to this patient, and if he stays proteinuric and has partial remission only, I would certainly consider that next, if it were available.

Dr. Barratt:
I think that speaks really to some of the generic mechanisms of progressive kidney disease that are involved in generating glomerular sclerosis, but also tubular interstitial fibrosis and inflammation. And the mode of action of RAAS inhibitors, which we know very well in terms of altering glomerular hemodynamics, but also now combined with endothelium receptor antagonism really offers us an opportunity to target those generic mechanisms that drive glomerular hyperfiltration and glomerular scarring, but at the same time drive proteinuria and that tubular interstitial response.

I wonder whether endothelium receptor antagonist combined with renin-angiotensin system inhibitors might be something that we might want to think about for all causes of generic kidney scarring and progressive kidney disease. What are your thoughts on that?

Dr. Floege:
Absolutely. Absolutely.

Dr. Barratt:
I'm looking forward to your presentation, David, because the avacopan trial is a very interesting trial in terms of trying to show efficacy but also reduce the toxicity associated with steroids.

Dr. Floege:
Thanks, Jon. I think that's a perfect introduction to Chapter 3, where we'll have a look at a case of ANCA-associated vasculitis. Stay tuned.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jürgen Floege, and here with me today are Drs. Jonathan Barratt and David Jayne. We are evaluating the underlying mechanisms of glomerular nephritis and sclerosis in patient populations with kidney disease, specifically those with IgA nephropathy, focal segmental glomerular sclerosis, and ANCA-associated vasculitis.

CHAPTER 3: AAV Case Presentation

Dr. Floege:
Welcome back. In our third chapter, we're looking at a case of ANCA-associated vasculitis, or AAV. I'll turn to you, David.

Dr. Jayne:
This is a 67-year-old female. She had an elevated serum creatinine at 358, which equated to a GFR of 15, and a historic serum creatinine from last year of 81. In terms of the history, she gave these symptoms of flitting polyarthritis, particularly of large joints, of a 3-kg weight loss, and drenching night sweats. More recently, she had developed a cough with hemoptysis, nasal congestion, and epistaxis or nose bleeds, profound malaise, and fatigue. So here, we're exploring a patient with acute kidney injury, but with a background of progressive, multisystem features and prominent lung involvement recently.

Our investigations demonstrated 3+ proteinuria, 3+ hematuria, suggesting glomerular nephritis, and she had normal kidney size on ultrasound. Her hemoglobin was reduced at 87; she had an elevated white count. Her proteinase 3 ANCA was negative, and her myeloperoxidase ANCA was strongly positive at 130. Her anti-GBM was negative, ANA was negative, and complements were normal. And her chest CT on the right showed widespread, scattered infiltrates compatible with alveolar hemorrhage, but she had normal oxygenation on room air. The kidney biopsy showed that over 50% of glomeruli had crescents, and these were a mix of cellular and fibrous crescents, suggesting that this disease process had been going on for some time. There were foci of acute glomerular necrosis with neutrophil debris. She had quite extensive tubular interstitial atrophy and inflammation. And in the classification that we currently use, ANCA-associated vasculitis, this was a burden class of mixed.

A diagnosis of microscopic polyangiitis was made, and if you have a presentation of rapidly progressing nephritis with crescentic nephritis on biopsy, which is largely pauci-immune, in the presence of an ANCA, the diagnosis is pretty easy to make.

Moving on to the KDIGO 2019 recommendations, following a diagnosis, there is broad assessment of the disease, which really means looking at other organs and then the importance of inducing remission. This is a rapidly progressive process, where patients are losing kidney function over weeks and months. And this particular patient really has a high risk of progressing to end-stage renal failure. In terms of treatment, the vast majority of patients will fall into the central category, where they're treated either with cyclophosphamide and steroids, or rituximab and steroids, and there remains a considerable debate as to which one to choose.

So discussing the preference of rituximab or cyclophosphamide, various points are summarized on this table, particularly use rituximab when you want to avoid cyclophosphamide, such as for ovarian toxicity perhaps in frail, older adults where there may be less bone marrow reserve, and also because rituximab is steroid-sparing. You can reliably stop steroids within 6 months if you use rituximab induction. The evidence also suggests that rituximab is more effective in relapsing disease and in proteinase 3 ANCA disease.

So just to summarize discussion points at this stage, there's a lack of data for rituximab plus steroids in acute kidney injury with a serum creatinine greater than 350 and also less data for rituximab in myeloperoxidase ANCA-positive patients. And, in fact, the definitive trials were largely trials for patients with proteinase 3 ANCA. The rituximab cyclophosphamide combination was assessed in the RITUXVAS trial, which demonstrated cyclophosphamide sparing. Namely, you could stop cyclophosphamide after 2 or 3 doses.

A key trial, PEXIVAS, examined the dose of steroids that should be used and tested the so-called standard or reduced steroid regimen, such that the reduced regimen had around a 50% reduction in steroid exposure, compared to a standard regimen. Why was this so important? Patients with ANCA vasculitis have very high rates of serious adverse events, particularly infection, and these are the major drives of death within the first year, and we think steroids are the biggest modifiable factor in our current treatment regimens. So PEXIVAS found no difference in terms of efficacy between the standard and reduced-dose regimens, but found a lower frequency of serious infection with the reduced-dose regimen. So that has now become the recommended regimen for the use in ANCA-associated vasculitis, particularly if it's glomerular nephritis.

So this patient's current status, we treated her with a combination of rituximab and cyclophosphamide and PEXIVAS reduced-dose steroid. She has no ongoing inflammatory respiratory symptoms. She remains tired, and that's fairly characteristic of this patient population. The constitutional symptoms can continue for many months or years. There's some residual scarring on her CT, but in general, the lungs have healed up well. She has 1+ of residual proteinuria, without hematuria, and her serum creatinine has stabilized at 185. And this is often what you see in myeloperoxidase ANCA, where there's usually more extensive chronicity on the diagnostic biopsy, which translates into a reduced capacity for the kidneys to recover. So you expect to get some recovery, but it's usually limited. The patient continues to be myeloperoxidase ANCA positive, and around 50% of patients remain positive at 6 months after treatment.

So what is remission, and how is it defined? This patient continued to have a little bit of proteinuria. That is a bad thing prognostically, but does it represent damage or grumbling activity? But perhaps the most important change that is occurring in ANCA vasculitis management, is what is the role for avacopan? Avacopan is an oral inhibitor of the complement C5a receptor 1, and it's been shown in a randomized trial to have several benefits for patients with ANCA vasculitis. In relevance to this particular case is the impact that avacopan had, compared to steroids, on GFR recovery.

Dr. Floege:
Thank you, David. This was a really interesting case, and it really nicely illustrates the dilemma of a patient coming in, in very advanced kidney failure, and then the question do you treat him or her and at what cost? Steroids – high-dose steroids versus rituximab versus cyclophosphamide? I know there are no good studies on this, but what is your gut feeling?

Dr. Jayne:
The head-to-head study between rituximab and cyclophosphamide showed no difference in safety, particularly infection, but it's notable this study has sustained quite high-dose steroid. And for that and other reasons, we think steroids are the major driver of infection. We are just completing a large registry study, and over a long period of time, rituximab-treated patients suffer more infections and recurrent infections than patients treated with conventional agents. And we are increasingly concerned about the induction of secondary immunodeficiency with rituximab. So although up front rituximab seems a cleaner and easier drug to use than cyclophosphamide, you have to consider that there may be long-term implications of this treatment in terms of safety. But coming back to your first point about steroids, I think PEXIVAS has, if you like, optimized how we use steroids at the moment, and I think the real future is alternatives, and I think avacopan is going to provide an alternative to steroids, certainly for some patients.

Dr. Floege:
Are there already any biomarkers that we can use to decide whom to treat with avacopan and who not and maybe how long?

Dr. Jayne:
There are no predictive biomarkers that will suggest who you should treat. We were interested in whether avacopan or complement

targeting would just work for the kidney or whether it would work for other manifestations, for example, granulomatous disease and GPA. And the data to date suggests that all manifestations – whether they're respiratory, renal, glomerular, granulomatous, or what we call vasculitic – appear to benefit from avacopan. Around 70% or 80% of patients in the definitive phase 3 trial had kidney disease, but 20%-30% did not, and they still benefited. So I don't think we can select patients in terms of preferential efficacy.

Dr. Floege:
I agree. Thank you, David.

Now, in Chapter 4, we'll have a last look at the 3 cases we've discussed so far and see what we can learn. Stay tuned.

CHAPTER 4: Key Takeaways in Glomerular Disease: The Big Picture

Dr. Floege:
So welcome back. I'd like to know your thoughts on the common comorbidities that we see in patients with IgA nephropathy, FSGS, and ANCA-associated vasculitis.

Dr. Barratt:
We need to look at the baseline comorbidities within our patients and individualize our approach, and particularly individualize the approach of the treatments we want to give and the potential toxicity associated with them. And the common theme is the use of systemic glucocorticoids, which clearly have a place, but they also are associated with significant toxicity. And so in the case I presented of FSGS, we need to be cautious about the presence of obesity, comorbidities such as diabetes, and dyslipidemia because we are always concerned in any patient with kidney disease about long-term cardiovascular risk. But I think even in ANCA-associated vasculitis, cardiovascular disease is a significant burden over the longer term.

Dr. Jayne:
So, I think, 2 things. One is absolutely, cardiovascular disease is placing a primary role in our sort of concerns about comorbidities and how newer drugs such as avacopan might affect cardiovascular risk.

But also, you know, what is remission in these disorders? We've tended to be dominated by the risks of end-stage renal disease. We got the proteinuria down to below a gram or below half a gram. We think that will reduce the risk of end-stage kidney disease, but does remission actually mean we're restoring a patient to health? I don't think we are. And I think we need to take maybe a more holistic approach to really what the goals of treatment are in these patients.

Dr. Floege:
Very important points, and thank you both for commenting on this because I think for a long time, we've rather somewhat neglected cardiovascular disease in these patients. And that applies to all 3 diseases.

So I think the general take-home message here is, as much as we can, reduce these very, let's say, invasive immunosuppressive therapies with their side effects. Increase our armamentarium on safer therapies that apply broadly to all glomerular diseases, such as RAAS blockade, such as an SGLT2 inhibitor, or in the future, hopefully, endothelin receptor antagonist and similar drugs that can dampen the disease so we don't need that much immunosuppression.

So this was certainly a fascinating conversation, and I thank both of you very much for your insights. But before we wrap up, I invite each of you to share a final take-home message with our audience.

David, what do you hope our listeners have learned today and will leave with today?

Dr. Jayne:
This era of nephrology has moved from being evidence-free to now having quite high-quality evidence to drive guidelines, harmonize therapy, and improve the outcome of our patients.

Dr. Floege:
Jon?

Dr. Barratt:
This is a highly complex area of nephrology, and I think we need take a very personalized approach to the patient in front of us. And that approach may need to change over time, but if we have these new drugs available, we will be able to modify therapy to suit the patients.

Dr. Floege:
Absolutely agree, Jon. So, unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you in particular, Jon and David, for joining me and for sharing all these valuable insights and expertise. It was great speaking to you today.

Dr. Jayne:
Thanks very much for the conversation. I've enjoyed it.

Dr. Barratt:
Yes, thank you, very much enjoyed it.

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