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Curbside Consult: Optimizing IgAN Management

Announcer:
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Dr. El Karoui:
Given that IgA nephropathy is a leading cause of kidney failure, we as clinicians need to know what to do about that. So how can we diagnose early IgA nephropathy, which may have an important role in the prognosis of the lesions and the disease? What are the limitations of current therapy of IgAN, and how can emerging therapy such as new treatment in conservative therapy or new immunomodulatory treatment can help achieve proteinuria remission and shape our treatment decision?

Today we will answer this question by reviewing a real-world clinical case.

This is CME on ReachMD, and I'm Dr. Khalil El Karoui.

Dr. Alberici:
Hi, I'm Dr. Federico Alberici, and it's a pleasure to be here.

Dr. El Karoui:
So, Federico, I'd like to begin by reviewing the current standard of care in IgAN. What are the limitations of current therapies, and is there a safe level of proteinuria?

Dr. Alberici:
The pathogenesis of the disease is relatively complex, and it gives us the opportunity to have several potential therapeutic targets. The treatment at the moment ranges from supportive care to immunomodulation. But independently from the treatment approach we are using, the aim is to reduce proteinuria. Proteinuria has been recognized as the most powerful predictor of long-term kidney outcome and long-term risk of end-stage kidney disease. When we talk about supportive care, we talk about certain aspects that we need to clarify to the patients. Patients need to have a healthy lifestyle, need to have a low blood pressure, need to avoid smoking, need to avoid nephrotoxic drugs. And in terms of drugs, what we suggest in terms of supportive care, we suggest patients to be on inhibitors of the renin-angiotensin-aldosterone system (RAAS) and/or SGLT2 [sodium-glucose cotransporter-2] inhibitors.

These drugs are effective in reducing proteinuria, although there's still a residual risk that is significant despite the use of these drugs. Moreover, these drugs may have side effects. They may cause hypertension, hyperkalemia, mycotic infection, and urinary tract infection. Another option is the employment of immunomodulatory drugs.

Several drugs have been studied or studied at the moment, but the only drugs approved at the moment for treatment for IgA nephropathy are glucocorticoids, both systemic or targeted ones. Glucocorticoids may be effective in reducing proteinuria, although their effect usually is transient, it’s not long lasting, and the duration of treatment is limited by the potential side effects.

So, Khalil, now hopefully we have understood a little bit more about the unmet needs we are facing. So let's review a patient case. What do you have for us?

Dr. El Karoui:
This my case. It was a 35-year-old male patient. This patient had a BMI of 32. He had a history of long-term CKD with no previous exploration, and we found an eGFR of 50 mL/min 5 years earlier in the previous serum creatinine evaluation. So the patient is a smoker and is recently seen at his general practitioner which detected high blood pressure, an eGFR of 36 mL/min, and UPCR of 2.2 g/g with hematuria. The patient had a presentation consistent with a chronic glomerulonephritis with proteinuria – significant proteinuria – and hematuria. So we performed obviously a renal biopsy; we saw IgA nephropathy. When you have this diagnosis, so you have to provide a MEST-C score too, based on the work of the Oxford Group to better define the prognosis of this patient. So in this patient the MEST-C score was M-0, there was no mesangial proliferation; E-0, there was no endocapillary proliferation; S-1, there were some lesions of segmental glomerulosclerosis; and T-1 with some tubulointerstitial fibrosis; and it was C-0 with no extracapillary proliferation.

We first evaluated the prognosis of this patient using the IgAN International Prognostic Tool, which takes into account about the renal lesions, historical lesions, and the clinical and biological presentation at the diagnosis. And the risk in this patient was about 35% of a 50% decline in eGFR, or end-stage renal disease, after 5 years. So it was a very serious disease.

So first, we proposed to optimize the conservative therapy in this patient. We have no active renal lesions but a severe proteinuria, so our aim was first to reduce proteinuria below 0.5 g/g, with effective control of blood pressure, including the use of RAAS blockade and diuretics. We also addressed the cardiovascular and lifestyle risk factors, such as he is overweight and the tobacco use in this patient. However, despite this treatment, the patient keep residual proteinuria and persistent hematuria.

Secondarily, he went back in medical consultation 3 years later. At this time eGFR was 32 mL/min and UPC was persistent proteinuria with 2.1 g/g, and persistent hematuria. Considering the persistent disease we chose to repeat kidney biopsy to evaluate the potential presence of inflammatory lesions.

So we performed the secondary, the repeat renal biopsy, which has shown, obviously, IgAN again, but the evaluation of the MEST-C score, we have M-0 lesions, E-0, S-1 – persistent S-1, and T-2. So the fibroses were more severe than the, you know, in the first biopsy. There was no extracapillary proliferation, so he was C-0. So M-0, E-0, S-1, T-2, and C-0. Given the absence of active lesions and the severity of renal lesions we propose to optimize, again, conservative therapy in this patient with the use of new therapeutics aimed at reducing proteinuria.

Dr. Alberici:
Thanks, Khalil. This is a very interesting case. You highlighted several topics that it may be worth discussing. And in particular, I think the role of the repeat kidney biopsy is indeed a very interesting topic. The data out there are relatively scanty. KDIGO Guidelines, for example, does not address this topic, so this is something that, of course, we perform in our clinical practice. We rely on the results in order to guide our treatment, but still, I think, data need to be collected. But it's very interesting. My feeling is that in case a repeat kidney biopsy would show a high degree of chronicity and no activity, as it was in your case, it's a stronger suggestion for pursuing a supportive treatment as effective as possible and to, you know, employ as many drug available as possible in this context.

So, Khalil, what are the data telling us about emerging agents that maybe help address these issues?

Dr. El Karoui:
And for those just tuning in, you are listening to CME on ReachMD. I'm Dr. Khalil El Karoui, and here with me is Dr. Federico Alberici. We are discussing our clinical approach to identifying and managing patients with IgAN in light of emerging clinical trial data.

Regarding the production of IgA, recently, as you may know, treatment targeting the digestive gut part of the inflammation in IgAN with targeted with budesonide has been provided. This treatment has been shown to reduce the proteinuria in patients with persistent proteinuria with the reduction of about 50% of UPCR in patient treated with targeted with budesonide compared to placebo.

A second option, and another emerging therapy, is to target the cytokine pathway. The action of cytokine is very important in the production of IgA and B cells. And recently a treatment with sibeprenlimab, which targets a specific molecule APRIL, has shown to reduce significantly the proteinuria after 9 months of treatment.

However, in our patients, they were, as you mentioned it, there was no active lesions, no inflammatory lesions. So we first evaluate the possibility to optimize the conservative therapy.

And the better way to do it with new emerging therapy, is in this patient to use sparsentan. So sparsentan is a dual blocker of both endothelin receptor and angiotensin receptor and has been shown that, compared to a long-term treatment with irbesartan in patient

with IgAN, persistent proteinuria more than 1 g/g despite also treatment with irbesartan 300 mg/day, the sparsentan, there was a strong reduction of proteinuria with UPCR reduction of about 50% versus 15% in patients treated with irbesartan. The strong reduction in proteinuria was not associated with an excess in treatment-associated side effects. And there was a similar blood pressure control in both groups, suggesting that there was a diuretic effect of the two treatments, sparsentan, in the glomerular lesion leading to reduction of proteinuria. Moreover, this association with the reduction of proteinuria was also associated with a better eGFR slope in the chronic part of the disease after 114 weeks of follow-up, with the benefit of about 1 mL/min/year in patient treated with sparsentan versus irbesartan.

So to optimize the conservative therapy in patients with chronic lesions and no inflammatory lesions, I think that the best way in patients already treated with ARB blockers and SGLT2 inhibitors is to propose sparsentan.

Dr. Alberici:
Thanks. This data you highlighted are very, very interesting. Since the supportive care is the cornerstone on the management of IgA nephropathy, I think we should focus a little bit more on this new molecule, on sparsentan, which is very attractive from this point of view. This is a single molecule with dual endothelin and angiotensin receptor antagonism activity. And there's a very strong rationale for targeting endothelin 1. Endothelin 1 is produced by several renal cells and it induces several adverse events within the kidney. It causes vasoconstriction; it causes inflammation; it causes fibrosis; it causes extracellular matrix deposition.

There's a strong rationale there, therefore, to targeting this pathway. And what is also very interesting is that the endothelin 1 pathway and angiotensin II pathway are tightly connected, and the stimulation of one of these pathways would stimulate the other one. So there's a strong interconnection there. And the inhibition of one of these pathways would lead to a decreased activity of the other pathway. So there's a strong rationale for targeting both pathways at the same time.

The interest in endothelin receptor antagonism is spreading throughout the medical community. There are other drugs out there that acts on this pathway. For example, atrasentan. Atrasentan has been tested in diabetic kidney disease. It showed an impact in lowering proteinuria and in improving hard outcomes, such as risk of end-stage kidney disease and doubling of serum creatine. And now, it is also explored in IgA nephropathy. This is not approved by the FDA, but is a nice suggestion that there's, therefore, something going on in that pathway and we need to focus on that very, very carefully.

So, Khalil, having discussed this and having discussed the role of sparsentan in the PROTECT study results, do you think that these emerging agents will cause some change in the treatment guidelines soon?

Dr. El Karoui:
Thank you, Federico. As you know there have been recent updates in the other renal diseases of the KDIGO recommendations such as ANCA-associated vasculitis and lupus. And, to date, I don't know if the new KDIGO Guidelines will have clear recommendation for the use of sparsentan. To date, the Committee for Medicinal Products for Human Use recommends approval for the conditional marketing authorization for sparsentan for the treatment of IgAN in Europe. Now, in France, we don't have the possibility to have the treatment to date, but it will be probably possible at the last part of the year.

Well, this has been a fascinating conversation, but before we finish, Federico, what's your own take-home message for our audience?

Dr. Alberici:
Proteinuria is the most powerful predictor of prognosis in patients with IgA nephropathy. So it has been shown that whatever is higher than half a gram, roughly, per day in terms of proteinuria poses patients at high risk of progression. So the lower the proteinuria, the better. This is a very well-established marker for disease control in this context, and the lowest proteinuria possible for each patient is what we should try to achieve.

And if we divide patients with IgA nephropathy in different proteinuria category, we realize that with the increasing of the proteinuria value, the risk of progression increases significantly.

Dr. El Karoui:
I think that we need new therapy to optimize this path because whenever we use immunomodulatory treatment we always will need to have a reduction of proteinuria with the best conservative therapy to be provided to our patient. And I think that the dual blockade of both endothelin receptor and angiotensin receptor is maybe a very, very interesting path to have as the option to optimize the conservative therapy.

And with that, I want to thank our audience for listening in and thank you, Dr. Federico Alberici, for joining me and sharing your clinical experience. It was a pleasure speaking with you today.

Dr. Alberici:
Thanks, Khalil. It's been my pleasure and thanks for this very nice conversation.

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