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A New Paradigm in IgAN Management—Advancing Clinical Practice in the Era of Therapeutic Expansion

Announcer:
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Dr. Geetha:
IgAN is the most common glomerular disease worldwide, with a global incidence of 2.5 per 100,000. There are marked geographic differences in disease prevalence. It is most common in East Asia, followed by Europe, and it is really rare in Africa.

Coming to the US, IgAN is identified in about 8.7% of kidney biopsies. The annual incidence is 2.1 to 2.2 per 100,000. The prevalence rate is 59.9 to 62.7 per 100,000. The prevalence in racial and ethnic groups is unclear. Even though IgAN is a common glomerular disease, it meets the criteria or definition for a rare disease affecting less than 200,000 people.

Clinical Manifestations

Coming to the clinical manifestations, the clinical presentation is heterogeneous and varies widely among different age groups. The classic phenotype is synpharyngitic hematuria. Gross hematuria is most common in younger individuals, whereas microscopic hematuria and varying degrees of proteinuria are seen in older patients. Nephrotic syndrome can occur in about 5% of patients, and other rare clinical phenotypes include RPGN and IgA vasculitis.

Infection and Genetics May Contribute to Development of IgAN

Now, we know infection and genetics may contribute to the development of IgAN. As mentioned before, IgAN presents as a synpharyngitic hematuria, so infections are common triggers, especially mucosal infections, either upper respiratory or GI infections. Bacteria with surface expression of GalNAc or N-acetylgalactosamine might stimulate the production of autoantibodies that can cross-react with galactose-deficient IgA1.

Now, coming to genetics, there are several studies which have reported on the familial aggregation of IgA nephropathy. GWAS has identified 31 risk alleles that explain 11% of the disease risk, and several loci in the pathways have been identified. The most prominent signals are the MHC or the HLA region. The other important signal is the complement factor H loci.

They also identified genes encoding the loci for APRIL and TACI, which is the receptor for APRIL, as playing a major role in IgAN. The CHIVAS studies have actually provided strong support for targeting the mucosal immunity than the alternative complement pathway and the APRIL and BAFF signaling.

Burden of IgA Nephropathy

IgAN is associated with substantial humanistic and economic burden. It affects younger individuals. It is a chronic disease. The symptom burden is really variable and can vary from pain, fatigue, anxiety, and depression. With the onset of CKD and end-stage kidney disease, the quality of life is worse. There is loss of productivity, increased medical expenses and higher mortality. It is a significant economic burden.

IgA Nephropathy Care Costs and Utilization

Now, this study looked at the economic burden in IgAN. What you see here is the unadjusted mean cost by CKD stage, and it shows that with advanced stages of CKD, there is a significantly higher number of outpatient visits and pharmacy claims.

The Multihit Model

The pathogenesis of IgAN is complex and multifactorial, and it involves 4 sequential processes, which is also called as the 4-hit hypothesis. Hit 1, what you see is the generation of the galactose-deficient IgA, which then comes to the systemic circulation mostly from a mucosal source.

Now, hit 2 is the formation of autoreactive autoantibodies against the galactose-deficient IgA. Hit 3 is formation of immune complexes. Hit 4 is where the immune complexes get deposited in the mesangium, which then triggers an inflammatory cascade, which results in mesangial cell proliferation, activation of the alternative and lectin pathway, and also recruits macrophages and monocytes, and all of these lead to kidney injury.

Therapeutic Mechanisms: Targeted-Release Formulation (TRF) Budesonide

Now, coming to the basis of some of the newer therapies. The mucosal-associated lymphoid tissue, particularly the Peyer's patches, are abundant in the distal ileum and are an important source of the galactose-deficient IgA.

Targeted Steroid Delivery to Stabilize the Gut–Renal Axis in IgAN

Now, the targeted-release budesonide is an oral-targeted release formulation of corticosteroids, which delays the release of the active drug until it reaches the distal ileum. This improves the efficacy of the drug, and also because of the first-pass metabolism, there is less systemic effect. Since it acts at the Peyer's patches, it decreases the production of the pathogenic galactose-deficient IgA.

Therapeutic Mechanisms: Reno-Protective Agents

The other agents that I want to focus is the reno-protective agents, which is the RAS inhibitors, SGLT2 inhibitors, and the Endothelin-1 Receptor Antagonist, all of which act on the hit 4.

Therapeutic Mechanism: Emerging Agents

The other emerging agents act on hit 1 and 2, which include the BAFF and APRIL inhibitors, and then the hit 4, which include the complement blockers.

Why Are There Guidelines for Proteinuria and GFR Goals?

We know now we have new guidelines or goals for proteinuria and GFR. I just wanted to go over some of the basis for forming the guidelines. Retrospective registry studies both from UK, US, and China have shown that there is a significant association between the level of proteinuria and adverse kidney outcomes.

The first data to come out was the UK RaDaR data, which evaluated more than 2,300 adult and pediatric patients with IgAN with proteinuria greater than 500 milligrams and eGFR less than 60 milliliters per minute. What you see here is the time-averaged proteinuria. Even with the time-averaged proteinuria of less than 0.44, 20% of the patients progressed to end-stage kidney disease at 10 years, and with proteinuria between 0.44 to 0.88, a third of the patients progressed to end-stage kidney disease at about 10 years.

What you see here at the bottom is the annual decline in GFR. If you have an annual decline in GFR of 3 milliliters per minute, 100% of the patients under the age of 40 will progress to end-stage kidney disease in their lifetime.

Then, on this side, you see that data from the Kaiser Permanente from the US. The difference is the UK was predominantly Caucasian population, the Kaiser Permanente is ethically and racially diverse population. What they also showed is adverse kidney outcomes with proteinuria less than 0.5 grams.

Why Are There Guidelines for Proteinuria and GFR Goals? (cont'd)

Similarly, the prospective study from China, which evaluated over 2,000 patients with greater than 12 months of follow-up, looked at kidney survival. Kidney failure occurred in about 24% of the patients, and they also showed that adverse kidney outcomes occurred in

patients with proteinuria greater than 0.5 grams.

Risk Assessment: Kidney Biopsy

We know that patients with IgAN have a progressive decline in kidney function, but it is at a highly variable rate. The MEST-C classification is an evidence-based prognostication scoring system using histologic variables. It uses 5 histologic variables which have been independently associated with prognostication. M stands for the mesangial hypercellularity, E endocapillary hypercellularity, S for segmental glomerulosclerosis, T for tubular atrophy and interstitial fibrosis, and C for cellular or fibro-cellular crescents. Please remember this is a prognostication tool. It does not help you to guide therapy.

IgAN Disease Progression and Risk Assessment

The last prediction tool that I want to focus is the IgAN prediction tool, which uses clinical and histologic variables at the time of biopsy and also at 1 or 2 years to predict the risk of disease progression defined as a GFR decline of greater than 50% or end-stage kidney disease after biopsy.

Now this is available online. As I said, you can do it at the time of biopsy or at 1 or 2 years, once again, to prognosticate and not to guide treatment.

Thank you for listening.

Redefining IgAN Treatment: From Supportive Care to Targeted Therapies

Dr. Bomback:
I am going to take over talking about redefining IgA nephropathy treatment as we move from supportive care to targeted therapies.

2025 KDIGO Guidelines: IgAN Treatment Goal for Patients at Risk of Progressive Kidney Function Loss

We have new guidelines from KDIGO, talking about treatment goals for patients with IgA nephropathy. These are very notable in that the new recommended goal for getting our patients' proteinuria is to 500 milligrams a day or less as the goal, and actually ideally to getting patients to 300 milligrams a day or less, in terms of their proteinuria.

That is all based on the natural history data that Dr Geetha just showed, where we now recognize that lower levels of proteinuria that were previously considered to not be higher risk for progression clearly do show higher risk.

The key thing from these guidelines in terms of treatment goals is get your patients to as low of a proteinuria as possible, at least less than 500 milligrams a day, and ideally to less than 300 milligrams a day.

Changing Treatment Landscape:
Targeting Pathophysiology to Treat IgAN

How are we going to get there? There is a changing treatment landscape where we actually are targeting the pathophysiology of IgA nephropathy to actually treat the disease along its pathophysiologic model. You heard about the multi-hit model from Dr Geetha, and you are going to be seeing how many of these trials are using therapies that go after different parts of the multi-hit model. At the same time, we have gotten much better at using standard CKD therapies in the management of IgA nephropathy.

2025 KDIGO Guidelines: IgAN Treatment Algorithm

You will see from the KDIGO guidelines, they actually break it down into 2 classes of therapy that should be used essentially simultaneously. There are the CKD type therapies, which they call managing the generic responses to IgA nephropathy-induced nephron loss. Another way to phrase this is conservative therapies. Another way to phrase this, which I really like, is to call this foundational therapies.

But these are medicines like renin angiotensin aldosterone system inhibitors, SGLT2 inhibitors, which are really staples of treating all forms of chronic kidney disease and should be staples of treating IgA nephropathy.

What is so exciting about IgA nephropathy is that we have other foundational non-immunomodulatory nephron-sparing therapies we can use, which are endothelin receptor antagonists.

We have a dual-acting endothelin angiotensin receptor antagonist in the form of sparsentan. We have endothelin receptor antagonist on its own, atrasentan, which can be added to an ACE inhibitor or an angiotensin receptor blocker.

While you are doing your best with the conservative foundational therapies to prevent nephron loss, you also, for many of your IgA nephropathy patients, want to be going at the IgA specific drivers for nephron loss. This is what most of us would call

immunomodulatory therapy. The immunomodulatory therapy is really directed at breaking that multi-hit model of IgA nephropathy pathogenesis.

Now, these guidelines, even though they just came out this year, are already a little bit out of date when it comes to the immunomodulatory therapies, because they are recommending systemic glucocorticoids and targeted-release formulation of budesonide, because these were developed before the FDA did an expedited approval of iptacopan and now most recently sibeprenlimab. That is not reflected in the immunomodulatory therapy.

There really are 4 therapies now for immunomodulatory therapy. You can choose between not just the 2 that are pictured here. We will talk about some of the other therapies listed on the bottom, because those are really only for select populations.

2025 KDIGO Guidelines: IgAN Treatment Goal for Patients Without a Variant Form

Going back to the guidelines, what they are recommending for most patients is that the focus of therapy should be to prevent or reduce the immune complex formation of galactose-deficient IgA1 and anti-gliadin antibodies to prevent or reduce glomerular injury that is mediated by those immune complexes, all the while managing the consequences of IgA nephropathy-induced nephron loss, which will be a lifelong need.

To put it into a different phraseology, think about immunomodulatory therapy early in the disease course to basically turn off the IgA pathogenesis, get your foundational therapy on board early in the disease course to prevent nephron loss, and long term, you will continue the foundational therapy to prevent any further nephron loss and preserve the kidney that you have hopefully been able to save with the immunomodulatory therapy early in the disease course.

Contributors to Pathogenic "Hits"

When we think about the medications and where they are hitting in the model, it is again very helpful to think about the pathogenesis. If you think about some of the newer therapies that are in development. We already have an anti-APRIL monoclonal antibody sibeprenlimab approved, and that is working at the levels of hit 1, hit 2, and hit 3, not just the production of galactose-deficient IgA, but the production of the anti-glycan antibodies and the formation of the pathogenic immune complexes.

There is combined APRIL/BAFF targeting therapies, atacicept, povetacicept. We expect at least one of them to be approved within the next year. Then once the immune complex is deposited at the level of the glomerulus, the inflammatory response and the fibrotic response, that is where we start pulling in complement inhibitors, endothelin receptor antagonists, and renin angiotensin aldosterone system inhibitors.

Therapies Targeting Pathophysiologic Drivers of IgAN

Again, all of the therapies that we are using are really driven by pathophysiology. They go after different parts of that multi-hit model.

To just round it out with the actual drugs themselves that are available and we could add very recently, sibeprenlimab has been approved. What goes after hit 1, we know that targeted release formulation of budesonide clearly goes after the production of circulating galactose-deficient IgA1 because it acts at the Peyer's patches, which are where those IgA are produced.

Sibeprenlimab, the monoclonal antibody to APRIL, which was just approved, as we just said on the previous slide, is targeting both hits 1, 2, and hit 3. Then the factor B inhibitor, which targets the alternative complement pathway, iptacopan, that is working more at the level of hit 4 once the immune complexes deposit to prevent the further inflammatory response that those immune complexes elicit, and then the endothelin receptor antagonist, sparsentan and atrasentan, these are all the new drugs are boldfaced. Those, along with renin angiotensin aldosterone system inhibitors and SGLT2 inhibitors, are really renal protective effects.

In my mind, they are working by reducing the work the kidney has to do and eventually having an anti-fibrotic anti-chronicity effect in the disease.

2025 KDIGO Guidelines: Use Reduced-Dose Systemic Glucocorticoids + Antimicrobial Prophylaxis if TRF-Budesonide Is Not Available (2B)

Let us go through each of these therapies individually. We will start with corticosteroids. The KDIGO guidelines say if you are going to use systemic corticosteroids, they recommend using a reduced dose. This comes from the study that all of us called the low-dose TESTING study. The low-dose TESTING study was a follow-up on the original TESTING study, which showed good results with steroids in terms of efficacy, but too much toxicity. They then did a subsequent study called the low-dose TESTING, where they basically used about half the amount of steroids that had previously been used in the original TESTING study, and they saw similar efficacy with far less toxicity.

Basically, if you are going to be using systemic corticosteroids, which for many people will still be an option, the newer drugs are very expensive. They are not always easy to get for some patients. They may not be able to be obtained quickly. There are some patients who need to treat right away, make sure they can get drug that day. That is where corticosteroids may still be an option.

If you are going to use it, you are generally going to be using about half the amount that we use 5 or 10 years ago, and that is based on the low-dose TESTING study.

2025 KDIGO Guidelines: Supportive/Conservative Treatment

In terms of supportive care beyond drugs, there is lifestyle modifications, but the biggest thing is that in addition to renin angiotensin system blockade, which has always been a staple of IgA nephropathy treatment, we now recommend SGLT2 inhibitors for most patients with IgA nephropathy. There are some exceptions. Most patients will qualify for SGLT2 inhibitor.

For me, when proteinuria is above 500 milligrams a day, I am very eager to add an endothelin receptor antagonist, whether it is alone as atrasentan on top of an ACE or an ARB, or it is part of a dual endothelin and angiotensin receptor antagonist, sparsentan.

KDIGO was developed when only sparsentan was available, so it does not really reflect the use of atrasentan.

2025 KDIGO Guidelines: Suggest Treating Patients at Risk for Progressive Kidney Function Loss With an SGLT2 Inhibitor (2B)

As I mentioned previously, SGLT2 inhibitors are being used for most patients with IgA nephropathy, and the data from this is very encouraging. Both the DAPA-CKD study and the EMPA-KIDNEY study enrolled a number of patients with IgA nephropathy.

If you do the subgroup analysis in the patients with IgA nephropathy, number 1, these turn out to be pretty big trials for IgA nephropathy. Over 100 patients with IgA nephropathy randomized to each arm. It is a good study for IgA nephropathy, but it is more of a chronic kidney disease version of IgA nephropathy. You can see that there is a huge reduction in progression to hard kidney endpoints using SGLT2 inhibitors.

The patients that I use SGLT2 inhibitors for IgA nephropathy, pretty much anybody with proteinuric IgA nephropathy, I am going to use SGLT2 inhibitors. Anybody with IgA nephropathy with a GFR below 60, even if they do not have heavy proteinuria, I am going to throw an SGLT2 inhibitor on board.

Alternative Pharmacotherapies Evaluated for IgAN

Other therapies that have been evaluated for IgA nephropathy, which do not get the KDIGO stamp of approval, which we used to use pretty frequently in the past before we had all these new IgA therapies, I do not really think there is much use for them anymore.

There still is a use of cyclophosphamide, but that is pretty much only in an RPGN version of IgA nephropathy, where there is a heavy crescentic burden on the biopsy.

I would say if the glomerular compartment is more than a third of the glomeruli have crescents, you should start thinking about should I use a course of IV cyclophosphamide in the care of this patient, but otherwise, cyclophosphamide really does not have a common role.

Calcineurin inhibitors, rituximab, these drugs are no longer routinely used in IgA nephropathy. Fish oil, it has always been some studies say yes. Some studies say no. The evidence has been pretty equivocal. I think in terms of reducing pill burden, there is not a real need to throw fish oil on, given we have so many other better therapies that are non-immunomodulatory. I would much rather use an SGLT2 inhibitor and endothelin receptor antagonist than to use fish oil.

Mycophenolate. This is still an option according to KDIGO, in patients of Chinese ancestry you can use it as a glucocorticoid sparing agent. There are a number of patients I have seen mycophenolate used almost like a maintenance long-term therapy. In general, it is not routinely used outside of that population. Likewise, for hydroxychloroquine. There is really only been one study that showed a nice response to hydroxychloroquine. Again, it was done in China. It is used as mostly reserved for patients of Chinese ancestry who would be considered at high risk. Again, special subpopulations.

Phase III NeflgArd Trial: Composite Kidney Endpoint

Let us move on to targeted-release formulation of budesonide. This is one of the first IgA nephropathy drugs to be approved. It has been used very frequently since its approval. The approval came initially on proteinuria reductions, eventually on GFR stabilization at a 2-year mark. You can see when you look at a composite endpoint of kidney failure or GFR reduction of 30% or more, you can see that budesonide clearly reduces that risk compared to placebo, with maybe a little bit of a more profound response in those patients who have heavier proteinuria.

NeflgArd: Proteinuria

The long-term data on the use of budesonide, and this is looking at a 9-month course of budesonide. Some folks have wondered is there a rebound effect occurring the further away you get from the use of budesonide. That is actually something that is going to be tested now in an ongoing study where the use of budesonide is extended beyond 9 months. We will keep our eyes out for the results of that trial.

NeflgArd: eGFR (Primary Endpoint)

What is clear, even if you stop the drug at 9 months, you can see that those who were treated with the drug for 9 months, compared to those who were on placebo, clearly had better GFR slopes over a 2-year period, which is why the drug got its full approval.

The safety profile was pretty good when you compare it to placebo. The rates of adverse events were pretty much what you saw in both the placebo and the active arm.

NeflgArd: Safety

Notably, there was not a high amount of steroid-like side effects.

NeflgArd: Safety (cont'd)

There is a slightly increased risk of steroid-like side effects in those who got budesonide compared to placebo. In practice, I would say even in my own patients, I have seen some rare cases where people get a corticosteroid-like effect, but that is really the exception. The expectation is that patients will not get systemic corticosteroid-like effects when they use targeted-release formulation of budesonide.

Phase III PROTECT Trial: Primary Efficacy Endpoint

We are going through these trials pretty much in order of how they were done. Now we are switching over to endothelin receptor antagonists, looking at sparsentan. This is not an immunomodulatory therapy. I would put this more along the lines of a conservative or a foundational therapy.

This is looking at sparsentan, which is a combined angiotensin receptor and endothelin receptor antagonist. The comparison is against an ARB alone, irbesartan. You can see that the ARB with endothelin receptor antagonist, sparsentan, clearly outperforms an ARB alone in terms of proteinuria reduction, a 50% proteinuria drop compared to a 15% proteinuria drop. That is at 9 months, which is what got the drug its accelerated approval.

PROTECT: 2-Yr Proteinuria Outcomes

The full approval came after the 2-year data was released, and you can see at 2 years, again, sparsentan, the endothelin receptor antagonist, with angiotensin receptor antagonist clearly outperforming the ARB alone, and that translated to better control of GFR declines.

PROTECT: 2-Yr GFR Outcomes

The group that was on sparsentan lost less GFR over a 2-year period compared to the group that got just an ARB alone. Again, if you have the ability for your chronic IgA patients, you should try to get them on an endothelin receptor antagonist on top of an angiotensin receptor blocker, either as a combined drug with sparsentan, or as we will get to, with atrasentan, which can be added on top of any ACE or ARB.

PROTECT: Safety

The safety data from the sparsentan study was very comparable to what you would see with a use of an ARB alone.

Sparsentan Boxed Warnings and REMS

There is a boxed warning and a REMs about hepatotoxicity. This has been relaxed a bit. Now you only need to check LFTs every 3 months. Originally, it was every month. Over time, I think we will see more and more data about the safety of this drug. It is not inconceivable that the REMs could eventually be dropped altogether. But right now there is a REMs where you have to check LFTs every 3 months.

Phase III ALIGN Trial: Primary Efficacy Endpoint at Prespecified Interim Analysis

The ALIGN study looked at atrasentan. This is another endothelin receptor antagonist, but now this is an endothelin receptor antagonist on its own that would be added on top of max tolerated dose of an ACE inhibitor or ARB. You can see that atrasentan reduced proteinuria, but now the comparison is against placebo. Atrasentan reduced it by 38% compared to a 3% drop in placebo. Again, a very significant reduction in proteinuria when you add an endothelin receptor antagonist to an ACE inhibitor or an ARB.

ALIGN: Safety

Good safety data on this drug. Specifically, there is a slight increased risk of fluid retention, which is what can be seen with endothelin receptor antagonist, but not to enough of an extent that it is more than just a small difference compared to placebo, something you can monitor on your patients.

Atrasentan Boxed Warning and Contraindication

Here the box warning is not about LFTs, but rather about contraindications in pregnancy, which would also apply to sparsentan as well.

Complement in IgAN

Let us move now to complement inhibition in IgA nephropathy. We know there is a pretty clear role of complement activation in IgA nephropathy, particularly, once the immune complex is deposited on the glomerulus. You see this big influx of inflammatory cells. We think a lot of that is driven by the alternative complement pathway, which is why using an alternative complement pathway inhibitor like iptacopan, which targets factor B, has so much promise in IgA nephropathy.

Phase III APPLAUSE-IgAN Trial: Primary Efficacy Endpoint at Prespecified Interim Analysis

The APPLAUSE study was done comparing iptacopan against placebo in patients with IgA nephropathy who had more than a gram a day of proteinuria, and you can see that iptacopan clearly dropped proteinuria to a significant degree compared to placebo.

APPLAUSE-IgAN: Safety

The 9-month data of that proteinuria reduction is what got the drug an accelerated approval. It does not have full approval yet. As with all these drugs, you need to show 2-year data and particularly 2-year GFR data to get the full approval.

What we know with most IgA nephropathy studies is that early proteinuria reduction has been consistently shown to lead to long-term GFR stabilization, which is why the FDA has accepted early proteinuria reduction at 9 months as a surrogate outcome for expedited approval.

The safety data from the iptacopan study is, again, quite good. Not surprising, I always call this drug a designer drug. It is really only hitting 1 target, which is factor B, so we really do not expect patients to experience any real side effects other than the fact that they are more susceptible to infections because of the alternative complement pathway inhibition.

Iptacopan Boxed Warnings and REMS

Because of that, there is a boxed warning about the risk of encapsulated bacterial infection and the need for vaccination against Neisseria meningitidis, streptococcus pneumoniae, and Haemophilus influenzae B, and boosters for patients who have already been vaccinated but are not updated on their vaccination.

In many instances in my practice, we give the vaccines, but we do not want to wait to start the drug. We give the vaccines and we use prophylactic penicillin for the first 6 months until they complete their vaccine series.

Remaining Questions

Some remaining questions. Which agent would you use first, because we have already talked about a number of agents. What is the duration for each agent? What is the long-term safety data going to show? What about patients who have relapses? Are they going to need repeat courses? Can you repeat course the same of these drugs, or do you want to repeat a course of immunomodulatory therapy with a different drug? How do you combine these therapies and what patient characteristics should you consider as you are choosing between each of these therapies? These are some of the key remaining questions to choose from.

Emerging Therapeutic Agents in Phase III Trials

To add to this is that we have more therapies that are on their way. One that was just approved last week, which is sibeprenlimab, a monoclonal antibody that targets APRIL, but we expect that a dual BAFF/APRIL inhibitor, atacicept, based on its favorable interim analysis, will likely be approved in 2026.

And all the other drugs in these classes, because they have shown similar responses in phase II and are starting to show data from phase III, we think these have a very good chance of becoming approved for IgA nephropathy as well. We are going to have a wealth of new drugs to choose from.

VISIONARY: Sibeprenlimab in Patients With IgAN

Let us talk about sibeprenlimab because this is one that is now approved, just approved last week. Its 9-month proteinuria data that got it approved, so it is an expedited approval. We will, of course, wait for the full 2-year data for the full approval.

This is a monoclonal antibody to APRIL that is dosed once-monthly at home by the patient in a subcutaneous injection.

VISIONARY Interim Analysis: Efficacy and Safety

The data showed a really nice drop in proteinuria compared to placebo. What I am not showing you here is that the data also showed resolution of hematuria in most of the patients who got the sibeprenlimab, which to me, when we talk about IgA responses, yes, I love to see proteinuria be reduced by this degree. That is what I am first looking at.

If I can see proteinuria get reduced like this and hematuria resolve, that to me is a pretty good sign without having to do a repeat biopsy that we clearly have established control of the IgA nephropathy and the IgA nephropathy is quiet.

If you look at the adverse events with sibeprenlimab, again, they are comparable to placebo, and that includes comparable rates of infections and injection site reactions. I think it is going to be a really well-tolerated drug. I think it is going to be a very helpful drug in the treatment of IgA nephropathy.

I am going to hand it back over to Kelly now as we move into the last part of today's program.

Bridging the Evidence-Practice Gap: From Data to Decisions In IgAN Management

Kelly Chen:
The next section, we are going to use all the knowledge that we just learned from Dr Geetha and Dr Bomback, with the pathophysiology of IgA nephropathy and then going into those therapeutic agents, the ones that have been approved, the ones that are emerging.

Patient Case 1: 28-Yr-Old Man

We have this patient case, a 28-year-old man. He has recurrent episodes of coca cola urine following a upper respiratory infection. Three episodes of gross hematuria in the past year, each after a cold, some mild fatigue. He does not have any edema, rash, joint pain or fever. There is no history of hypertension, diabetes or kidney disease in the family.

On exam, blood pressure was 138/86. No edema and no joint swelling. These are the labs. We see some blood in the urine, microscopic hematuria, 0.8 grams of proteinuria. Creatinine was 1.2, GFR of 90. We also have a serum IgA which is mildly elevated, and complement levels were drawn. There are normal and other serologic tests for other proteinuria. Diseases were also done. Hep B, hep C negative, ANA, anti-dsDNA and ANCA.

Poll 3

For this patient, when should you consider a kidney biopsy?

A. Only if the proteinuria is greater than 1 gram per day;
B. We should just biopsy if hematuria and any proteinuria, regardless of the level;
C. Biopsy, if the protein is greater than 0.5, and in anyone where IgAN is suspected;
D. No biopsy until there is decline in function or nephrotic syndrome.

Take a pick and then we will talk about the results.

Results

Most people chose C, 50% of the group. So yes, the renal biopsy will show light microscopy, mesangial proliferation. In the immunofluorescence, there was granular mesangial deposits of IgA and C3, and then there was also electron dense deposits in the mesangium.

Poll 4

Poll 4. This is the fourth question. What is the updated target? We had talked about this earlier with the new KDIGO guidelines in 2025 for IgA nephropathy.

A. Less than 0.1 grams per day;
B. Less than 0.5 grams, but ideally 0.3;
C. 0.7, so slightly higher but then ideally we would like to get less than 0.5; or
D. Greater than 1 gram.

One of our faculty members talked about the updated target for the new KDIGO guidelines for IgA nephropathy. Take your pick. Most of the group chose less than 0.5 and ideally less than 0.3 grams.

Poll 5

The number fifth question. In this patient, the one we just discussed, assuming no contraindications, which of the following therapies would KDIGO 2025 most strongly support? We have:

A. ACE and ACE inhibitors, ARBs;
B. High dose systemic corticoids;
C. Mycophenolate; and
D. Rituximab.

We started talking about the therapies in the second portion of our session. Take a pick. We have A, ACE inhibitors or ARBs. 80% of our group discuss that.

Poll 6

Number 6. If this patient's proteinuria escalated to 1.5 grams per day, despite optimal supportive therapy, which is the most guideline concordant next step. What will we do after we add all the supportive therapies?

A. Add a dual endothelin angiotensin receptor antagonist;
B. Rituximab;
C. Adding systemic corticosteroids;
D. Adding a targeted-release formulation of budesonide.

We are at 1.5 grams optimal supportive therapy. What should we add next for an IgA nephropathy patient? The group is a little bit split. We have 30% adding a dual endothelin angiotensin, so DEARA; or D, adding a targeted-release budesonide, 46%.

I think adding both options are great in this situation. We definitely want to get that 1.5 grams of proteinuria down to the guidelines that we had discussed earlier.

Summary

In summary, thank you everyone. This is the discussion about the multi-hit model. Dr Geetha talked about the pathophysiology between all of the hits, and then Dr Bomback targeted each of the hit 1, 2, 3, 4 and aligning each of these new therapies that we have FDA-approved, as well as the emerging therapies and how those different mechanism of action target the various pieces of the IgA nephropathy pathophysiology.

At this point, the new and emerging therapies are still being studied and they are not being used in place of optimal supportive care. We do want to reassure and reiterate that optimal supportive care still being used as well. Then we, as part of the guidelines as well, in the KDIGO, also encourage patients to do participate in clinical trials and registries, as the IgA nephropathy treatment landscape is still actively changing.

Posttest Questions

I do want to get to the post-test questions. These are the same questions that we started off with in the beginning with the pretest.

Posttest 1

Again, a 42-year-old male with a biopsy of IgAN, had persistent proteinuria despite optimized RAS, and is being evaluated for targeted therapy. Which of the following novel therapeutic agents, primarily by modulating the complement pathway or rather than the endothelin system or B-cell activation signals?

A. Atrasentan;
B. Iptacopan;
C. Sibeprenlimab; and then
D. Sparsentan.

The group was mostly choosing iptacopan, B.

Posttest 2

Let us get to our second post-test. We have a 32-year-old female with IgAN. It is about 1.3 grams of persistent proteinuria despite max RAS blockade. Stable blood pressures. This is pretty good, 118/74. eGFR of 62. She is interested in the new therapies. She is looking for any of the FDA-approved or emerging agents that would be best for this option. Which do you think? We have:

A. Atrasentan;
B. Obinutuzumab;
C. Povetacicept; and
D. Zigakibart.

We have some FDA-approved agents on this list, as well as emerging agents as well. Actually, just 1 FDA approved. The group answered mostly atrasentan and then pretest. It was a little bit more split towards obinutuzumab. Any comments the faculty want to discuss?

Dr. Bomback:
Many of these things would be potentially used, but this is one of those things. It is like, how do you word the question? Only 1 of these is actually FDA approved, which is atrasentan. I think it is very conceivable that in the future you would use drugs like obinutuzumab, povetacicept or Zigakibart in this setting, but we just do not have FDA approval to use those drugs.

If you are just going by FDA approval, only atrasentan here would work. To be honest, you would use atrasentan and one of B, C, or D ideally because atrasentan more to improve your conservative therapy, and then you probably need something immunomodulatory given just how high the protein is.

Kelly Chen:
For this, the choice was atrasentan alluding to those thoughts that you had, Dr Bomback.

Posttest 3

For number 3, which of the following new or investigational therapies for IgA nephropathy acts as dual BAFF and APRIL, targeting both the BAFF and APRIL to modulate aberrant B cell activity? Which of these are dual BAFF and APRIL?

A. Felzartamab;
B. Sibeprenlimab;
C. Povetacicept;
D. Zigakibart.

This might be a hard question. These names. Take a pick. Answer is C, povetacicept.

Posttest 4

Number 4. We have a 29-year-old female with IgAN. She comes in with persistent proteinuria of 1.2 grams and eGFR of 80, is on maximal RAS inhibition and has excellent blood pressure control. What is interesting is she is doing some family planning. She is planning on a pregnancy within the next year and is concerned about preserving her kidney function. We had talked about earlier. She wishes to avoid teratogenic or immunosuppressive medications. Which of the following strategies best reflect her wishes and her patient-centered approach to slow the disease, as well as optimizing her long-term outcomes?

A. Initiate sparsentan for rapid proteinuria reduction;
B. Begin iptacopan to target the alternative complement pathways;
C. Start a budesonide, the targeted-release formulation to reduce mucosal IgA production;
D. Defer all of these novel therapies until after pregnancy planning and prioritization of supportive care measures in the meantime.

What are your thoughts on this 29-year-old female?

Posttest 4: Rationale

Answer is D, we would want to defer. We love all the novel therapies that Dr Bomback discussed, but we would want to defer them until after pregnancy planning. Any additional thoughts, Dr Bomback?

Dr. Bomback:
No. For this patient, this is the absolute right management. We just do not know the safety data of all these new drugs in pregnancy. This is someone that once they are done with their childbearing years, there is a lot of options now available for someone like this,

young preserved kidney function, but pretty significant amount of proteinuria. If we can get that proteinuria down to the targets, we think they can have a good long-term outcome. I think you are asking for closing thoughts or just on this question?

Kelly Chen:
Just on this question, yes.

Poll 7

This is a poll for the audience. After learning everything we have been learning from our faculty today, do you plan to make any changes in your clinical practice based on what you have learned? We have this question, and then the next one, and I do want to address any of our Q&A for our faculty.

Poll 8

The next poll is, take a moment to enter one key change you plan to make in your clinical practice based on today's education?

Q&A

As you type away, I will also bring up our Q&A. We have a couple questions. Would budesonide help a 71-year-old female with IgA nephropathy, eGFR about 24, and interesting history of a liver transplant taking cyclosporin. Dr Geetha, do you want to take a stab at it?

Dr. Geetha:
This is an interesting question. The first question I would have is whether this patient actually has primary or secondary IgA, because someone with liver disease. Secondly, all the trials we have, I think this GFR is actually excluded. You have to have a GFR of greater than 30 milliliters per minute. Personally, I would not be using budesonide in a patient like this until I have more clarification on number 1, whether this is primary or secondary IgA and the trajectory of the disease is important.

Kelly Chen:
I think Dr Geetha is saying that most of the trials were for primary IgA nephropathy, and so there is a possibility that this patient profile perhaps has secondary IgA nephropathy. Dr Bomback any thoughts?

Dr. Bomback:
No, I completely agree. The 2 points that Dr Geetha made not just is it primary, secondary, but also how low the GFR is. All the trials for the immunomodulatory drugs had a cut off of GFR above 30.

Another way to think about it is you can think about if they have a recent biopsy, if the interstitial fibrosis is less than 50%, but there is a point of no return with IgA nephropathy where we expect they are going to go to end-stage kidney disease regardless of what you do. That is typically been a GFR less than 30 and a interstitial fibrosis greater than 50. Especially in someone who has got all these other comorbidities on other immunosuppressants, I would not think about adding more immunosuppression in that setting.

Kelly Chen:
We have a question about primary care providers. There is a lot of folks in the audience who do provide a lot of primary care in their care setting. Do primary care providers treat IgA nephropathy, or should this diagnosis always be referred to a nephrologist?

Dr. Geetha:
Definitely a nephrology referral. I think what I would add from the primary care is early nephrology referral in terms of managing, especially with all the new drugs and hiatus the nephrologist who manages.

Kelly Chen:
This question is, I believe, for Dr Bomback's practice. This is for the iptacopan. There was the black box warning where we are doing the vaccinations. The question is, what if they have a penicillin allergy? I think you had alluded that you use penicillin in your practice, too.

Dr. Bomback:
There alternatives you can use. People used to use fluoroquinolones. We do not love long-term fluoroquinolones because of the potential risk for joint abnormalities, cartilage abnormalities. You can use fluoroquinolones, but most people if you have a penicillin allergy, I think are recommending a low dose of a macrolide antibiotic like azithromycin to take the place of penicillin.

Again, you are doing that while you are waiting for the vaccine. It does not replace the vaccine. You are going to use penicillin prophylaxis, or if they are penicillin allergic, azithromycin while you are giving the vaccine. We generally keep the antibiotic prophylaxis going until about 3 to 4 weeks after the last vaccine is given.

Kelly Chen:
Last question before we run out of time, it is about recurrent IgA nephropathy after kidney transplant, 42-year-old patient showing proteinuria and hematuria after transplant. Is it possible that the IgA nephropathy has returned?

Dr. Geetha:
It is quite possible.

Dr. Bomback:
Yes. But you have to do a biopsy here, because you can get proteinuria and hematuria with rejection as well. You cannot just make an empiric diagnosis of recurrent IgA and start treating. You need to do a biopsy of the transplant. And then you look at what that IgA is showing, if it is back, and most of the times if there is a fair amount of proteinuria and hematuria, we give them immunosuppression on top of the maintenance immunosuppression they are using for the transplant.

There also is some mild recurrent IgA that you see if you do protocol biopsies that we do not have to treat. Someone with proteinuria, hematuria, and recurrent IgA on the transplant, someone we are probably going to treat unless proteinuria is minimal and the hematuria is minimal.

Kelly Chen:
That is all the questions that we have. We might have a little bit more time for one more question. From a primary care perspective, how do we give them the right tools if IgA nephropathy is on the differential, what are those labs that should be drawn and ready, finalized to go before that referral or even during referral?

Dr. Geetha:
I guess serum creatinine, eGFR, UA microscopy and spot urine protein creatinine, right?

Dr. Bomback:
Yes, I agree. They need a biopsy. You probably want to add. I always like when someone's already checked the coags, so like a PT/INR and a PTT because they are going to need a biopsy to make the diagnosis.

The big thing from the primary care doctor that is helpful for us is, as you heard from Dr Geetha, creatinine with the GFR, maybe a cystatin C, UA, urine protein to creatinine ratio. We do not need a 24-hour urine, just a spot protein to creatinine ratio. I think the nephrologist can do more serologies as part of the differential, but those are the basics that would really help us, and then we can take it from there.

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