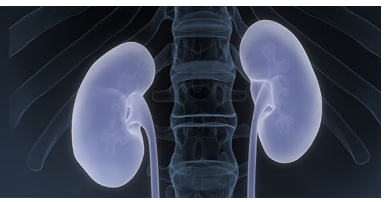
BETTER EDUCATION ON GLOMERULONEPHRITIS: IMPROVING KNOWLEDGE OF IgA NEPHROPATHY



Editor's Note: This is a transcript of a presentation on June 14, 2022.It has been edited and condensed for clarity.

Introduction to IgAN

Dana Rizk, MD: What is IgA nephropathy? IgA nephropathy is a disease that is characterized by an elevated level of galactose-deficient IgA1 that we commonly refer to as Gd-IgA1. This serves as an autoantigen that ultimately is bound by an IgA or IgG autoantibody. We think the IgG autoantibody plays the major role in the pathogenesis of the disease.

The disease is diagnosed by kidney biopsy that allows us to identify the deposition of immune complexes formed by these IgA antibodies in the mesangium of the glomeruli, resulting, ultimately, in glomerular inflammation and injury.

IgAN is the most common primary glomerular disease. Its incidence is estimated at about 2.5 cases per 100,000 globally, however this incidence varies substantially across the world, being highest in East Asia and, as you move towards Europe, the incidence goes down and is rarely there in Central Africa, and somewhere in between in North America.

The difference in this global incidence is, in part, related to the threshold that we have in practice for performing kidney biopsies, specifically in patients that have only hematuria and no evidence of proteinuria. It may also differ across the globe based on our ability and practices in screening patients for urinary abnormalities.

Twenty to 30 percent of patients with IgA nephropathy will progress to end-stage kidney disease within 25 years of their disease diagnosis which is defined as the time of kidney biopsy. And, in fact, 20% to 25% of patients who have end-stage kidney disease and are getting some form of renal replacement therapy are thought to have an underlying glomerular disease, with IgA nephropathy being the most common of these disorders.

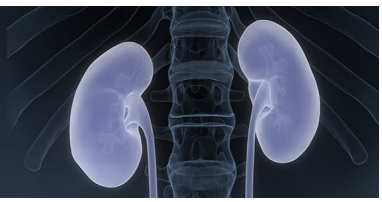
IgA diagnosis is based on a kidney biopsy. It is not unusual to know that access to kidney biopsy is very different across socioeconomic classes, countries, and populations. It is often associated with higher socioeconomic classes and countries in which patients have access to healthcare. The prevalence can certainly be under-represented in developing countries and among populations that have less access to healthcare. The incidence is often higher in children and young adults and in the elderly, but that may, again, be due to screening urine analyses that are carried out most commonly in these 2 extremes of age populations.

Any kidney disease that leads to end-stage kidney disease and ultimately the need for renal replacement therapy, specifically dialysis, can affect the patient's quality of life. In fact, studies have shown that patients that are on dialysis have decreased health-related quality of life. Those include physical limitations, poor sleep, feelings of social isolation, and depression. Higher proteinuria, when present, can also be associated with decreased well-being and that has been shown among adolescent patients. Edema and kidney disease and symptoms related to kidney dysfunction can impair both physical and mental health, but sometimes the treatment that we give to patients to address these underlying glomerular diseases can affect the patients as well. That includes steroids, for example, and side effects that are related to corticosteroid use, such as weight gain, Cushingoid features, and that can lead also to mood swings.

IgA nephropathy is now thought of as an autoimmune disease and what is known as a multihit disorder. The first step in the disease development starts with what we refer to as Hit 1, this increased circulating level of the galactose-deficient IgA1. Where this galactose-deficient IgA1 comes from is thought to be the mucosal surface and, in fact, B-cells at the mucosal surface produce galactose-deficient IgA1, but at some point in time in patients, these B-cells mistraffic, or miss home, and become present in the systemic circulation, releasing galactose-deficient IgA1 in high quantities. How this mistrafficking happens is still not quite clear, but, regardless, it leads to an elevated level of galactose-deficient IgA1. This is then recognized as an autoantigen against which the body starts producing autoantibodies of the IgA or IgG subtype. And again, as mentioned earlier, the IgG autoantibody subtype seems to play the biggest role in the disease pathogenesis.

This leads to formation of immune complexes in the circulation that ultimately deposit complexes, specifically in the mesangial area initially and through a cascade of events leading to local immune activation and injury can ultimately lead to mesangial proliferation, glomerular sclerosis and tubular interstitial fibrosis, all of which culminate in a decline of kidney function and, in severe cases, in end-stage kidney disease. Of course all of this happens on a background of a genetically-susceptible host and, in the right environmental conditions, there's some data to suggest that the disease can be triggered by infectious processes or even things in our diet and changes in our microbiomes.

It's important to distinguish primary IgA nephropathy from secondary cases. IgA nephropathy, or at least IgA deposition in the kidneys, have been described in patients with chronic liver disease, for example, inflammatory bowel diseases, several autoimmune disorders, including rheumatoid arthritis, psoriasis, ankylosing spondylitis. Patients with chronic viral infections, such as hep-B and hep-C, can have secondary IgA nephropathy. Chronic infections, including parasitic infections, neoplasm and chronic respiratory problems. In all of these cases, the thought is that treating the underlying disease will result in halting—or perhaps the resolution of—the secondary IgA nephropathy. For the rest of this activity, we will be primarily referring to primary IgA nephropathy, so cases that do not have an underlying systemic cause.



Diagnosis & Prognosis of IgAN

Dana Rizk, MD: How do we diagnose IgA nephropathy and what do we know about the disease prognosis? Clinically, patients with IgA nephropathy often present with hematuria, proteinuria, sometimes they have hypertension, certainly early onset of hypertension should make you concerned for an underlying kidney disease, including IgA nephropathy. And, in adults, they often present with plain old chronic kidney disease, so an elevated creatinine that then prompts the primary care physician or provider to look for urinary abnormalities and ultimately to refer the patient to a nephrologist.

In about 30% to 40% of patients, the disease is asymptomatic and can only be identified based on an abnormal urine test that includes proteinuria or microscopic hematuria. Again, to go back to this original idea that if we don't look for the disease, we can certainly miss cases, which is why the incidence of the disorder may be underestimated.

Once the patient is suspected of having a glomerular disease and, in particular, IgA nephropathy, we do need to have a kidney biopsy done to establish the diagnosis. And the characteristic or hallmark finding in IgA nephropathy is the presence of IgA deposition on immunofluorescent staining in the glomerulus, particularly in the mesangial area, and the immunoglobulin A or IgA deposition has to be the dominant, or at least codominant, immunoglobulin on immunofluorescent staining. On your right-hand panel here, you can see a very nice, bright immunofluorescent staining of the mesangial area in a patient that has IgA nephropathy.

Some histopathologic features have been used to predict long-term outcomes of the disease and that is referred to as the MEST-C score, again a pathologic score that refers to the presence of mesangial proliferation, endocapillary proliferation, segmental scarring, tubule interstitial atrophy as well as the presence or absence of crescents. And these features, pathologic features, carry prognostic information as well. To this day, there are no validated biomarkers available for diagnosis and so, again, we have to have a kidney biopsy to establish the disease diagnosis.

What prognostic markers have been associated with worse outcomes? Here's a summary of all these markers. Some are demographics, so they're easily available, but unfortunately not modifiable. Male sex, older age at diagnosis, age of 60 years or beyond, and the presence of obesity, which I would put under clinical parameters perhaps, are associated with worse outcomes.
Some of the clinical features associated with a worse outcome include the persistent hypertension, an elevated serum creatinine at the time of presentation, persistent microscopic hematuria, interestingly a history of macroscopic hematuria or visible hematuria has a better prognosis, perhaps because these patients are brought to their physician's attention at the much earlier stage of their disease.

On the laboratory side, hematuria and abnormal serum creatinine carry worse prognosis. Other important features include persistent proteinuria, particularly if the patient has more than 1 gram of proteinuria per day. Other things that can affect or are associated with worse outcomes include hyperuricemia and hyperlipidemia, and these need to be addressed and treated, as necessary.

Pathologically, again we talked about the MEST-C score, and we're going to go through some of those details in a minute. The mesangial IgG or immunoglobulin-G costaining also seems to carry a worse prognosis. And I should point out that IgG is not a universal finding in IgA nephropathy. When it *is* present, it does tend to associate with a worse prognosis. And in a subset of patients, you can see thrombotic microangiopathic changes on the kidney biopsy and those, again, tend to carry a worse prognosis.

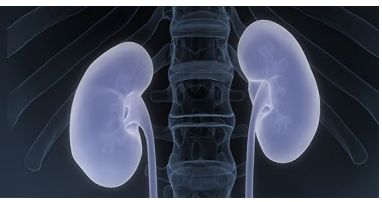
What is the MEST-C score? Each one of these letters stands for a particular pathologic finding. M stands for mesangial hypercellularity. By definition, this is when you have more than 4 mesangial cells in the mesangial area of the glomerulus. And it can be subdivided into either M0 or M1 score, and with M0 referring to less than 50% of glomeruli showing mesangial hypercellularity. E is endocapillary hypercellularity. Hypercellularity due to an increased number of cells within the glomerular capillary lumen. Again, here, E0 is when you don't have hypercellularity, E1 when you do have hypercellularity.

S stands for segmental glomerulosclerosis, with S0 referring to the absence of glomerulosclerosis, and S1 is when you do have any glomerulus with segmental sclerosis. T stands for tubular interstitial fibrosis and the scores are divided into 2, T0, T1 and T2. And cellular or fibrocellular crescents, again C0 is when you have no crescents, C1 less than 25% of your glomeruli have crescents, and C2 at least 25% of the glomeruli, or more, have crescents.

Importantly, the higher the MEST-C score, the worse the prognosis, and there are particular lesions—for example the segmental glomerulosclerosis and tubular interstitial fibrosis—that tend to carry quite severe prognostic value, the higher the S or the T score, the worse the patient's prognosis.

Taking into account all these prognostic markers that are, for the most part, easily available in the clinic, the International Collaboration Group, IgAN Collaboration Group, led by Sean Barbour, developed an International IgAN Prediction Tool that takes into account the patient's GFR at the time of biopsy, the blood pressure, the presence or absence of proteinuria and the quantification of proteinuria, the age at the time of biopsy, whether the patient has hypertension, what's their blood pressure, the MEST-C score and the use of ACE inhibitor and/or immunosuppression at the time of the biopsy. And putting all these information values together, the International IgAN Prediction Tool can predict the progression to end-stage kidney disease or a 50% decline in GFR in the foreseeable future, up to 5 years from the time of biopsy.

This gives you a good sense of how severe this disease is in the patient you're looking at in clinic. Importantly, the KDIGO guidelines certainly recommend using the prediction tool to risk-stratify this



patient, but this tool has not been validated and should not be used to make treatment decisions. Again, keep that in mind.

The other important note is that the prediction tool, at this point in time at least, can only be applied at the time of the kidney biopsy or diagnosis. A patient that had the diagnosis or biopsy 10 years ago, you cannot come into clinic today and use the prediction tool to determine their prognosis.

Proteinuria in IgAN

Dana Rizk, MD: Proteinuria has clearly emerged not only as a negative prognostic factor for IgAN patients, the higher the proteinuria, the worse the outcome, importantly it is a modifiable risk factor. We should use proteinuria reduction as a treatment goal and it can be used as a meaningful surrogate marker of improved outcome, meaning if you reduce proteinuria in a patient using available therapies, you will likely reduce their progression to end-stage kidney disease, or at least the decline in their GFR, which is quite important.

Keeping that in mind, you want to treat the patient's blood pressure aggressively, again with the intent to change their prognosis. And you need to change their proteinuria, again treating them to try to reduce the proteinuria to at least less than 1 g/day and preferably closer to .5 g/day which seems to be even more protective.

Hypertension and proteinuria represent risk factors for the progression of IgA nephropathy, but can also be modifiable. It's important that we address hypertension and treat it aggressively in patients with IgA nephropathy. Fortunately, a lot of them are young and can tolerate lower goals of blood pressure. And for proteinuria, there's significant data showing that if you're able to reduce the proteinuria to less than 1 g/day at least and perhaps closer to .5 g/day, you can also change the long-term outcome of your patient. There has been consistent evidence that link sustained proteinuria reduction with lower risk of disease progression. Lowering proteinuria also protects that patient from cardiovascular events in patients with chronic kidney disease, including IgA nephropathy.

Is there a minimum duration of proteinuria remission that's associated with an improved outcome in IgA nephropathy, meaning how long do I have to keep my patient in proteinuria remission to make a difference in their outcomes? This is an important study that looked at 7 international cohorts, so looking at patients from all over the world. They were able to identify 1,864 adult patients with biopsy-proven IgA nephropathy who were treated and achieved proteinuria remission and they wanted to see, the authors wanted to see, if they sustained this remission, how long of a remission translated into improved outcomes.

First, by definition, they determined proteinuria remission to be at least a 25% reduction in proteinuria and achieving an absolute proteinuria level of less than 1 g/day. The primary outcomes they were trying to reduce or mitigate were, of course, end-stage kidney disease or a 50% drop in eGFR. You can see the cohort was quite diverse, 47% of the patients included were Chinese, 16% were Japanese, 35% were Caucasian. Patients had an average follow-up of about 3.9 years and, at the time of first remission, the average proteinuria was .55 g/day, so again achieving guidelines or goals. And the eGFR was quite preserved at 78 mL/minute.

Importantly, for every 3 months that the patient was in remission, for the first 4 years of the remission, there was a 9% reduction in the occurrence of the primary outcome. It really didn't take much to change outcomes if you're able to achieve proteinuria remission. After 4 years, that benefit seems to flatten out and you only gain about a 1% reduction in outcomes for every 3 months you continue to be in remission past 4 years. Again, there seems to be a strong dose-response relationship between longer durations of proteinuria remission and the lower risk of disease progression in IgA nephropathy.

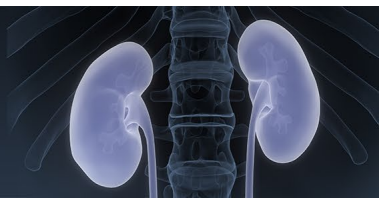
We've known for quite some time, for a lot of diseases, that proteinuria is not a good thing to have and is associated with end-stage kidney disease progression. This is not peculiar for IgA nephropathy, but again has been highlighted in IgA nephropathy in multiple studies. Any renal injury that leads to reduced nephron mass will lead to increased glomerular capillary pressure, ultimately podocyte dysfunction and loss, which subsequently leads to increased glomerular permeability to macromolecules, leading to increased filtration of plasma protein that exceeds the tubular reabsorption capacity. This, in turn, causes an increase in vasoactive and inflammatory cytokine release, tubular cell apoptosis, inflammatory cell infiltration and, ultimately, scarring and decline in GFR, leading to end-stage kidney disease.
The National Kidney Foundation, the FDA and the European Medicines Agency organized a scientific workshop in 2018 and determined that early change in albuminuria, proteinuria in

general, and GFR slope, fulfill criteria for surrogacy to be used as endpoints in clinical trials for chronic kidney disease progression, in general. The Kidney Health Initiative, which was a public-private partnership between the American Society of Nephrology and the FDA, subsequently decided that there was sufficient evidence in IgA nephropathy to use proteinuria as a surrogate outcome for any treatment trial. This, of course, will allow clinical trials to be planned, developed in a relatively shorter period of time, however this will only provide conditional approval for a therapeutic intervention for IgA nephropathy and ultimately, this—any therapeutic that's being tested—will have to prove that it does, in fact, reduce the progression of kidney disease. So the reduction in proteinuria has to translate into slowing down of GFR loss and reduction of ultimately end-stage kidney disease development.

IgAN Treatment Strategies

Dana Rizk, MD: With that in mind, the KDIGO treatment algorithm that, the guidelines being updated in 2021, support aggressive care for patients addressing blood pressure with the blood pressure goal being as low as 120 mmHg for the systolic blood pressure.

Patients have to be on maximally-tolerated ACE inhibitor or angiotensin receptor blockers as a first-line management for blood



pressure, but they also should be prescribed in patients that don't necessarily have hypertension, but have proteinuria. If the proteinuria is more than .5 g/day, regardless of hypertension diagnosis, you should be prescribing a RAS inhibitor, renin-angiotensin aldosterone system inhibitor. Patients have to be counseled about lifestyle modifications, so weight loss, exercise, anything to reduce their cardiovascular risk. That includes screening them for hyperlipidemia and treating the hyperlipidemia, if needed. If, on the other hand, despite your best effort, they continue to be at high risk of progression, meaning they continue to have high levels of proteinuria, you should counsel them about clinical trial enrollment. And this change in the guideline, putting clinical trial ahead of systemic steroid use, was a significant change and a significant update, highlighting the importance and the availability of clinical trials addressing the disease pathogenesis.

If the patient has a GFR that's quite advanced in the order of less than 30 mL/minute, it may be too late for them to go into a clinical trial, certainly one that includes an immunomodulator, and those patients should be just on maximally-supportive care. If their GFR is preserved and either they don't qualify for a clinical trial or they refuse to be in a clinical trial, you can then consider the use of systemic steroids while taking into account the risk/benefit ratio for that particular patient. You have to look at your patient's risk for metabolic complications, obesity, bone complications, so on and so forth, before you prescribe, and weigh this against the potential benefit of a treatment before you decide about prescribing systemic steroids.

The KDIGO also recommended against the use of antiplatelet agents, anticoagulants, azathioprine or Imuran, cyclophosphamide which is usually reserved for patients that have the rapidly progressive and crescentic version of IgA nephropathy, calcineurin inhibitors, rituximab, fish oil, all of which have been tested and have not proven to be beneficial in IgA nephropathy, based on the current literature. Fish oil is fairly benign, but there's also no benefit that has been proven.

Mycophenolate may have a role in the Chinese population. It has certainly shown some benefit in small Chinese study on a background of steroids. It can be used as perhaps steroid-sparing therapy. And hydroxychloroquine is an emerging therapy. There's, again, limited data in the Chinese population that suggests that it may be of benefit, again very preliminary data at this point in time.

With everything we've discussed so far, there is clearly a need for better treatments to be offered to patients with IgA nephropathy. Any kidney disease that can ultimately lead to end-stage kidney disease, proteinuria, so on and so forth, is associated with a detriment to healthcare and quality of life of patients affected. There are, so far, limited benefits and potential adverse events from the currently-available standards of care and there are limitations to the standard of care. Although ACE inhibitors, for example, and angiotensin receptor blockers, improve outcomes, they have not been shown to cure the disease. There are no alternative approaches when the standard of care fails, at least to date, and there is still a subpopulation of patients that is at high risk of disease progression and should hopefully be offered novel treatments in the foreseeable future.

Jai Radhakrishnan, MD: We'd like to first start with the reduction of the abnormal IgA1 and that's produced, to some extent, in the Payer's patches of the small intestine and, if you can reduce this using a local corticosteroid preparation and there's a specially-formulated budesonide that's available, I'll discuss this, it's been shown to reduce production of this antibody.

Secondly, both the abnormally glycosylated antibody and the auto-antibody against this abnormal Iga1 could be affected by using B-cell therapies, and there are several B-cell therapies that are being investigated. And the idea is to reduce both these components of the immune complexes which can cause damage by deposition. And the third group of therapies center on complement activation. Both the lectin pathway and the alternative pathway intergroup to the pathogenesis of IgA nephropathy. Interrupting these pathways might reduce inflammation and prevent progression of IgA nephropathy.

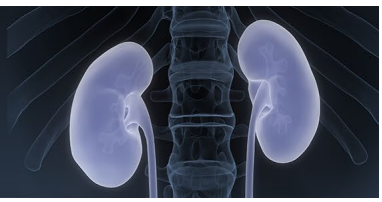
Then finally, there are medications like ACEs and ARBs which may reduce fibrosis and inflammatory effects within the kidney and this is the distal-most area in the pathogenic pathway that is amenable to therapy.

Emerging Therapies: Efficacy and Safety Data From Phase 3 Trials

Jai Radhakrishnan, MD: There are several that are undergoing and, in fact, 1 is completed and we have an FDA-approved drug. And that drug is Nefecon. Nefecon is a specially-formulated preparation of budesonide that's released near the Peyer's patches in the small intestine, so it's responsible for the production of the abnormal IgA1.

The trial is called the NefIgArd trial, the phase 3 has been completed. It's not yet published, but the data were shown at a recent nephrology conference. This is a 9-month trial where the active drug, Nefecon, is compared to placebo and, at the end of the 9 months, the patients are tapered off the drug over 2 weeks, and then there's another 10 weeks of follow-up, and that's followed by a 1-year blinded period to see what happens with these patients.

The outcomes are as follows. If you look at the primary outcome at 9 months, which is the degree of urine protein to creatinine ratio reduction, this was 5% in the placebo group and it was 31% in the treatment group, which is a reduction, a difference in 27% of treated vs placebo. And importantly, a key secondary outcome was the effect on the estimated glomerular filtration rate. There was no change in the eGFR in the Nefecon group vs a 7% reduction in the placebo group. And, by and large, the medication was well tolerated. There were no major serious adverse events, but importantly we're waiting for the trial to be published to examine the complete data. This drug is available for use in the United States.



The other medication that is being investigated, and it's in a phase 3 trial that's currently ongoing, is sparsentan. Now, the mechanism of action is quite interesting. This is a dual endothelin/angiotensin receptor antagonist, so 2 effects in 1 molecule. And if you see the graphic on the left, you can see both angiotensin II on the left and endothelin on the right have very similar effects in the pathogenesis of IgA nephropathy. They have effect on the blood vessels, they cause vasoconstriction and endothelial dysfunction. They can cause the mesangial cells to proliferate and lay down extracellular matrix, leading to glomerulosclerosis, thus direct effect on the podocyte. And then finally, the final common part in most glomerular disease is inflammation and fibrosis and you can see both these cytokines do affect this aspect of pathogenesis as well.

Blocking both these pathways with 1 drug might be beneficial and, in fact, the phase 3 trial, called PROTECT, is ongoing and hopefully will be completed by next year. But there are interesting interim analysis findings in that the level of proteinuria reduction was significant in an interim analysis, but we'll wait for the change of estimated GFR slopes in the 2 groups, placebo vs the active drug. And the comparator group is actually irbesartan which is an ARB, and this is compared to the dual-action ETA and ARB sparsentan.

The other drug which is a pure endothelin receptor antagonist is atrasentan and this is also in a phase 2 and phase 3 trials. This is a selective endothelin receptor antagonist and the endpoints are eGFR, serum creatinine, blood pressure and proteinuria. It turns out that the side effects, again, are mild and there are 2 studies that are ongoing.

The ALIGN study is a phase 3 trial. It's looking at 320 patients and this is comparing atrasentan vs placebo and in a group of patients with IgA nephropathy.

The AFFINITY study is a clinical trial where a number of diverse glomerular diseases are being investigated, including IgA nephropathy. And this is a smaller study looking at 80 patients who are being treated with atrasentan with the same endpoints at week 12 being looked at to see if there's a change.

What is very exciting also is a fair number of agents which are effective against complement pathway components are also being investigated. Iptacopan is a factor B antagonist, and factor B is integral to the formation of the C3 convertase. Inhibiting factor B puts a brake on the alternative pathway of complement and subsequent events in the complement cascade, and without which the inflammatory process gets down-regulated, with the hope that it will reduce proteinuria and maintain eGFR in patients with IgA nephropathy.

The trial's name is called the APPLAUSE-IgAN trial. There are 450 patients. And again, the evaluation's ongoing in this pivotal phase 3 trial.

The lectin pathway is also very important in IgA nephropathy. Narsolimab is a drug that inhibits MASP-2 which is an important enzyme in the pathway that leads to activation of the lectin pathway and, again, this is being investigated in IgA nephropathy patients in the trial that is named ARTEMIS-IGAN trial, 450 patients.

It's a multinational study and it's a phase 3 study that's ongoing.

Case Presentations

Jai Radhakrishnan, MD: This was a 54-year-old woman who was referred to us with an elevated creatinine. She had a 20-year history of microhematuria, punctuated with episodes of gross hematuria every 2 to 3 years.

Six years prior to admission, she had developed hypertension, for which she is on treatment. She was also noted to be anemic and had a negative urological examination 6 months prior to her presentation. She was referred to nephrology when her serum creatinine rose to 1.6 mg/dL, at which time she was on multiple antihypertensive medicines, including amlodipine/olmesartan, clonidine and furosemide. She was also receiving erythropoietin for anemia.

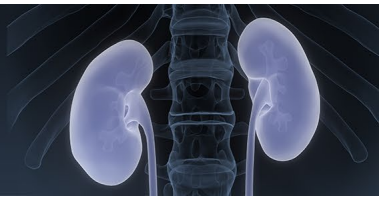
On examination, her blood pressure was 190/90 mmHg. Her BMI was 35 kg/m^2 and she had 2-3+ pedal edema.
Her laboratory examination showed a serum creatinine of 1.9 mg/dL and a 24-hour urine protein was 6.9 grams. Her urine sediment was notable for red cells, but no red cell casts and she had a completely negative or normal serologic exam, including ANA, complements, ANCA, anti-GBM, cryoglobulin, hepatitis profile and she had also a bone marrow biopsy prior to her presentation, which was completely normal. Her kidney sonogram showed normal-sized kidneys.

She received a kidney biopsy and the biopsy was notable for IgA nephropathy and the pathologist reported the fused mesangial and focal segmental endocapillary and extracapillary proliferative lesions with sclerosis, and she had tubule atrophy, interstitial inflammation which is patchy at about 30% and she also had mild arterio- and arteriolosclerosis, which is again mild.

Looking at the scores, she had an M1, E1, S0, T1 and C1 which included crescents.

Several choices we have discussed. Conservative management alone. Is she a candidate for oral corticosteroids? Can she be given targeted enteric corticosteroids? Could we consider mycophenolic acid analogs along with corticosteroids? Because of crescents, would we consider cyclophosphamide or enroll in a clinical trial?

Interestingly, a few weeks prior to this presentation, the results of the TESTING trial which randomized patients into corticosteroids vs placebo was just published. And in this international trial, about 400 patients were randomized to either methylprednisolone with a tapering course of oral methylprednisolone compared to placebo, and the primary outcome was the composite of the first occurrence of sustained 40% decrease in estimated GFR, kidney failure or death from kidney disease.



What is important is that the group that received corticosteroids had a much lower rate of the composite primary outcome, 28.8% compared to 43.1% in the placebo, which led to a hazard ratio of 0.53. Less events in the group that received methylprednisolone. One caveat of this study is that halfway into the enrollment of the study, the patients that received the corticosteroids had a higher rate of adverse events, including death, and the trial was temporarily put on hold after which the dosage of the methylprednisolone was reduced and prophylaxis with antibiotics was also given to these patients, after which the adverse event rates were no different in the 2 groups.

It is important to note that corticosteroids do still have a role and this was not discussed in the last KDIGO guideline, but which will be updated, I'm sure, in the coming months to a year or two.

What happened to this patient? Remember she's the patient who had a creatinine that's elevated, she was heavily nephrotic with high MEST scores. After optimizing blood pressure, she was given a course of prednisone 60 mg daily over a period of 6 months, with a tapering schedule. And you can see her creatinine, which had risen to 2.42 mg/dL, improved, and the urine proteinuria progressively diminished until she reached complete remission by the end of 1 year. It is important to note that corticosteroids do still have a role, but we have other options as well.

Conclusion

Jai Radhakrishnan, MD: We are in exciting times looking at potentially valuable therapies for IgA nephropathy. One has already reached FDA approval and can be prescribed, and a number of them are going to be completed in the next 2 to 3 years. Beyond steroids, there's really not much we can offer patients, but that clearly is going to change in the next 3 to 5 years where a number of therapies with varying mechanisms of action are going to be available for clinical use and will hopefully improve the outcomes of our patients with IgA nephropathy who are many in number around the world, and are clearly in need for therapies with low side effects and high efficacy.