Transcript Details

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Advances in IgAN: New Frontiers in Biomarkers and Treatment

Announcer:
You're listening to *On the Frontlines of IgA Nephropathy* on ReachMD. And now, here's your host, Dr. Gates Colbert.

Dr. Colbert:
Welcome to *On the Frontlines of IgA Nephropathy* on ReachMD. I'm Dr. Gates Colbert, and joining me to discuss our current understanding, research, and treatment of IgA nephropathy, or IgAN for short, is Dr. Edward Filippone, who is a nephrologist and Professor of Medicine at Thomas Jefferson University in Philadelphia. Dr. Filippone, thank you for being here today.

Dr. Filippone:
Thank you for asking.

Dr. Colbert:
So to give us some background, Dr. Filippone, can you tell us about the pathogenesis of IgAN?

Dr. Filippone:
IgAN is one of the most common glomerulopathies, and the exact pathogenesis is incompletely understood. The current view involves four distinct steps, which have been termed hits, against which specific therapies may be directed, and this is an active area of research.

The first hit is increased production of IgA1 that's deficient in galactose residues on the hinge region. This galactose-deficient IgA, or Gd-IgA1, is produced by plasma cells that have matured from naive B-cells and have class-switched to IgA production under the influence of survival factors BAFF and APRIL. These are potential future targets for therapy. The main source of this galactose-deficient IgA appears to be plasma cells residing in the mucosa associated lymphoid tissue predominantly in the gut and the pharynx, which also represents a target for therapy.

Hit 2 involves the production of antibodies which react to exposed epitopes from the galactose deficiency, predominantly N-Acetylglucosamine. These antibodies are predominantly of the IgG subclass, but also to some extent, IgA1 itself may be an autoantibody. They may represent autoantibodies or actually simply cross-reacting antibodies with microbial antibodies. Normal people also make these antibodies but at a lower level than patients with IgA nephropathy.

So Hit 3 involves the formation of immune complexes in the circulation of the Gd-IgA1-associated proteins and the anti-Gd-IgA1 antibodies. These immune complexes are of sufficient size to escape hepatic clearance and deposit in the mesangial region of the glomerulus.

This results in Hit 4, which is activation of the mesangial cells to proliferate and create cytokines that recruit inflammatory cells directly into podocytes.

Dr. Colbert:
Now IgA nephropathy presents in a variety of ways, from asymptomatic microscopic hematuria to rapidly progressive glomerulonephritis, so how can clinicians better identify the signs that indicate severe disease progression?

Dr. Filippone:
The signs of severe progression would most importantly include reduction of the GFR. They would also include persisting or increasing proteinuria and hypertension. It's unclear now, but it is being studied as to whether persisting hematuria is also a sign, but those would be the most important clinical signs.

Dr. Colbert:
And as a quick follow-up to that, what role do biomarkers play in predicting disease progression?

Dr. Filippone:
Well, biomarkers can be used to predict who is most likely to progress in a rapid fashion. This disease normally evolves over decades, and we'd like to determine upfront who is likely to progress most rapidly so they could be appropriately treated. Biomarkers can be assessed at baseline when you make a diagnosis, or they can be followed over time. By far, the most studied biomarker is probably proteinuria, especially time-averaged proteinuria. The Toronto Registry demonstrated that declining GFR will be 25 times faster if you maintain greater than 3 grams per day of proteinuria compared to less than 1 gram per day. The Kidney Health Initiative evaluated 13 randomized trials and 7 observational studies and established that proteinuria reduction is not only a biomarker, but is a reasonably likely surrogate endpoint that is a target for therapy in randomized controlled trials for which now it is used, so that is the most important biomarker. Similarly, reduced estimated GFR at baseline is a biomarker, which intuitively makes sense, and similar to proteinuria, it is also a reasonably likely surrogate endpoint for therapeutic trials. Hypertension is a biomarker for progression, as I stated previously. Hematuria at baseline does not appear to be a valid biomarker but time-averaged hematuria may be. There is research suggesting that.

Dr. Colbert:
For those just tuning in, you're listening to *On the Frontlines of IgA Nephropathy* on ReachMD. I'm Dr. Gates Colbert, and I'm speaking with Dr. Edward Filippone about the latest strategies for IgA nephropathy management.

So, Dr. Filippone, if we continue looking at the patient journey, why is a biopsy essential for diagnosing IgA nephropathy?

Dr. Filippone:
A biopsy is absolutely necessary to diagnose IgA nephropathy because there is no sufficient noninvasive way—no biomarker is sufficient in terms to diagnose IgAN.

In general, in the context of higher proteinuria and falling GFR, a more inflamed biopsy, positive M score, positive E score, and cellular or fibrocellular crescents would push the needle towards immunosuppression.

Dr. Colbert:
Now when it comes to treatment, what are the key challenges clinicians face when deciding on immunosuppressive therapy? And how might future research address these challenges?

Dr. Filippone:
The key challenge facing nephrologists is who to immunosuppress, how to immunosuppress them, and how long to immunosuppress them. Certain patients with IgAN deserve immediate immunosuppression. That would include patients who have frank nephrotic syndrome with only minimal changes found on biopsy. These patients should be treated as adult minimal change disease. Another group that would require immediate therapy are patients with a rapidly progressive course who have significant crescents on biopsy. Such patients should be treated immediately with cyclophosphamide and steroids as per KDIGO recommendations. Other patients remain questionable. All patients with IgAN deserve supportive therapy. This would include lifestyle modifications, like strict BP control, RAS inhibition if proteinuria, and SGLT2 inhibition if proteinuria or declining GFR. Sparsentan, which is a dual angiotensin type II receptor and endothelin A receptor blocker, is approved for use in patients with proteinuria who have failed these other lifestyle modifications. So all these therapies should be offered as required to patients with IgAN.

Now if they're on these therapies and they have persisting proteinuria, declining GFR, or hematuria or some combination, you may have to consider immunosuppression. Options for immunosuppression include oral steroids, targeted-release budesonide, which affects plasma cells in the mucosa-associated lymphoid tissue of the small intestine directly with more limited systemic effects, and complement inhibition with the one approved complement inhibitor for IgA nephropathy, which is iptacopan, an oral factor B inhibitor. Other immunosuppressives have been used, such as MMF, and more nonspecific ones, such as hydroxychloroquine and leflunomide. The data really in support of these is somewhat questionable.

Other agents are currently being studied that may be useful. Since B-cell maturation in the plasma cells is dependent on the survival factors BAFF and APRIL, they have been targeted, and phase II data indicate positive effects of inhibitors BAFF and APRIL. Complement, obviously, is involved. A complement factor B inhibitor is approved. Factor D inhibitor is being studied.

The currently approved medications include oral steroids, targeted-release budesonide and the factor B inhibitor iptacopan. I suspect over time the other drugs which have shown benefit in phase II studies will be approved, and a combination of therapies will probably be most effective, combining inhibition of B-cell development and complement activation or complement effects.

Dr. Colbert:
And before we close, is there anything else you'd like to leave with our audience today?

Dr. Filippone:
Well, I think this is a fascinating disease because there's a lot involved in the pathogenesis, as we discussed. There's a lot of possibilities to inhibit various steps in the progression. And I think the real issue is going to be what combination of therapy should be used? How long should they be used for? How about sequential therapies? The landscape is changing. I think a lot will be learned over the next few years. Right now, the therapies are limited to corticosteroids and other immunosuppressives and possibly complement inhibition on top of supportive therapy, but I suspect this landscape will change.

Dr. Colbert:
And with those key takeaways in mind, I want to thank my guest, Dr. Edward Filippone, for joining me to summarize the latest knowledge, studies, and treatment approaches for IgA nephropathy. Dr. Filippone, it was great having you on the program today.

Dr. Filippone:
Thank you.

Announcer:
You've been listening to *On the Frontlines of IgA Nephropathy* on ReachMD. To access this and other episodes in our series, visit On the Frontlines of IgA Nephropathy on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!