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Identifying Unmet Needs in the Management of Glomerular Diseases

Announcer:
Welcome to *Clinician's Roundtable* on ReachMD. On this episode, sponsored by Novartis Pharmaceuticals Corporation, we'll discuss common challenges in the management of glomerular diseases like complement 3 glomerulopathy and IgA nephropathy with Dr. Frank Cortazar. Dr. Cortazar is the Director of the New York Nephrology Vasculitis and Glomerular Center and is Chief of the Division of Nephrology at St. Peter's Hospital. Here he is now.

Dr. Cortazar:
The prevalence of all primary glomerular diseases is low as they are rare diseases. They're often considered orphan diseases, but in terms of glomerular disease, IgA nephropathy and C3 glomerulopathy are on opposite ends of the spectrum. IgA is the most common glomerular disease worldwide, with an incidence of about 2.5 per 100,000 patients. There are a lot of undiagnosed cases because patients are often not biopsied if they have microscopic hematuria and only mild proteinuria. Conversely, C3 glomerulopathy is significantly more rare, with an incidence of about 1-3 per million. C3 glomerulopathy is divided into dense deposit disease and C3 glomerular nephritis based on the findings on electron microscopy. Dense deposit disease tends to present more in the pediatric population, while patients with C3GN on average are often slightly older.

The challenges in managing patients with IgA are numerous. One is the heterogeneity of the disease. It can range from microscopic hematuria all the way to RPGN, so appropriately classifying patients and tailoring treatment to the different subpopulations can be a challenge. Late diagnosis in IgA nephropathy is a challenge. Often patients are not diagnosed until significant, irreversible fibrosis has occurred. And in retrospect, you can often see patients had preexisting hematuria and proteinuria, sometimes for years before diagnosis. So increasing awareness and diagnosing patients earlier is of paramount importance in the management of this disease. And finally, lack of effective and safe therapies. There is broad agreement that patients with proteinuria above about 0.5 gram should be on a maximally tolerated ACE inhibitor or angiotensin receptor blocker, but for high-risk patients, the only therapy available in the last few decades has really been prednisone. Clinical trials in recent time have yielded conflicting results over the benefit of steroids. In particular, the STOP-IgA trial did not show a major benefit in terms of slowing the progression of kidney disease, whereas the TESTING trial, which was done more recently, did show some benefit but also highlighted the inherent risk of treating patients with steroids. And so there's a tension for each patient in terms of balancing the risk and benefits of steroid therapy.

In terms of C3GN, it's really, I would say, a poor understanding of the pathogenesis in any particular patient. There are a number of hypothesized causes of C3GN. One of them is an autoantibody against the C3 convertase, which stabilizes it and perpetuates its activity. This is often called the C3 nephritic factor. There can be autoantibodies directed against complement regulatory components, such as Factor H. There can be genetic mutations that lead to inappropriate activation of the alternative pathway. And in older patients, monoclonal proteins can be involved in the pathogenesis of the disease. However, these mutations and antibodies often do not correlate well with disease activities, and you can also find these mutations in some healthy controls, so how they're actually driving the disease activity is unclear, and this has led to a lack of targeted therapies up to this point.

Announcer:
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