Exploring the APRIL Pathways in IgA Nephropathy

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You're listening to *Clinicians Roundtable* on ReachMD. On this episode, sponsored by Chinook Therapeutics, we'll explore the role of the APRIL pathway in IgA nephropathy with Dr. Jonathan Barratt. He's the Mayer Professor of Renal Medicine at the University of Leicester in the United Kingdom. Here's Dr. Barratt now.

Dr. Barratt:

So in IgA nephropathy, we know that there are high levels of immune complexes within the circulation of patients and these are what deposit in the kidneys. We think the main substrate for this immune complex formation is a particular form of IgA that is produced within the mucosal immune system. And the mucosal immune system is that immune system that lines our respiratory tract, our gastrointestinal tract, and our genitourinary tract. And what we know about the biology of the mucosal immune system is that there are two cytokines, called APRIL and BAFF, that are very important in B cell maturation, differentiation, and survival.

And in particular, APRIL is important because it's the level of APRIL that determines whether an activated B cell becomes a plasma cell that produces IgA or produces IgG. And we believe that APRIL is very important in driving the production of IgA in the mucosal immune system. And certainly, we think that that has some role to play in the generation of pathogenic IgA. And that formation of those immune complexes that ultimately deposit in the kidneys and cause inflammation and scarring.

So there have been lots of studies of the role of APRIL in IgA nephropathy. There have been genetic studies that have identified that changes in the gene for APRIL are associated with an increased risk of developing IgA nephropathy. There have been studies of lymphoid organs, such as the tonsils, that have shown there is a great increase in the amount of APRIL being expressed within those tonsils in patients with IgA nephropathy. And that APRIL can drive the production of the abnormal form of IgA that forms immune complexes from cells derived from tonsils. And equally, when we look at B cells, that we can find an isolate in the bloodstream, a similar effect is seen. So we know that APRIL is increased in the mucosal immune system, which is where we think the IgA is derived from. We know APRIL levels are higher in the circulation in IgA nephropathy than in healthy subjects. And we know that there are changes in the genetics of the APRIL system that are related to an increased risk of developing IgA nephropathy.

So having identified a significant role for APRIL in IgA nephropathy in driving the production of that pathogenic form of IgA, targeting APRIL signaling is an obvious therapeutic choice. And so we have a number of drugs that have been developed and are currently in clinical studies looking at inhibiting APRIL signaling in patients with IgA nephropathy. And what we've seen from these early studies are these agents are very good at reducing the abnormal form of IgA in IgA nephropathy patients that form these immune complexes. And we're starting to see that that reduction in this abnormal form of IgA is associated with early reductions in proteinuria, suggesting less inflammation within the glomeruli. And now we're waiting to see how that translates to long-term kidney function. And those trials are ongoing. And it's going to be really exciting to see the results at the end of these studies to see the impact of these agents on long-term kidney function.

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