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Examining Key Factors in IgAN: The Role of B Cells and BAFF/APRIL

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is brought to you by Vera Therapeutics. Here's your host, Dr. Charles Turck.

Dr. Turck:
IgA nephropathy, or IgAN for short, is increasingly understood as a systemic immune disorder driven by B-cell dysregulation. B-cell activating factor and a proliferation inducing ligand, otherwise known as BAFF and APRIL respectively, are central to this process, and uncovering their role in IgAN may help us transform our understanding and management of this complex disease.

Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss these key players and the pathogenesis of IgAN is Dr. Jonathan Barratt. He's the Mayor Professor of Renal Medicine at the University of Leicester in the United Kingdom, where he also leads the Renal Research Group. Dr. Barratt, thanks for being here today.

Dr. Barratt:
Thank you. And it's really a great pleasure to join you today.

Dr. Turck:
So, let's start, Dr. Barratt, by taking a look at how our understanding of IgAN's pathogenesis has shifted in recent years. What do we currently know about the role of B cells in IgAN?

Dr. Barratt:
So, over the past few years, it has become very apparent that the primary driver for IgA nephropathy is the formation of immune complexes that deposit within the glomeruli and trigger inflammation and scarring. And of course, those immune complexes are driven by the particular form of IgA that we know aggregates together and is associated with circulating antibodies. And of course, antibodies and IgA are produced by plasma cells, which are a B-cell lineage cell line, and these cells have a number of different specific controlling mechanisms. And a number of studies, including genetic studies, have shown that the controlling mechanisms for antibody production are dysregulated in IgA nephropathy—in particular, the signaling of BAFF and APRIL that drive B cell survival, IgA class switch recombination, and antibody production.

Dr. Turck:
And how does the production of galactose deficient IgA-1 initiate the pathogenic cascade of IgAN?

Dr. Barratt:
So, as I said, we believe this disorder is a disorder of immune complex formation, and immune complexes have to start somewhere. And we think the main driver for this immune complex formation is a particular type of IgA that appears in the circulation in excess quantities in patients with IgA nephropathy. And this IgA carries very specific changes to the sugars that are attached to the hinge region of the IgA1 molecule. And there are lots of different types of IgA1 molecules with different patterns of sugars on their hinge region, and collectively, those changes that are associated with forming immune complexes are called Gd-IgA1. And so Gd-IgA1 is a collective term for all of these different IgA antibodies that have specific changes in the sugars on the hinge region that makes them prone to form immune complexes.

Dr. Turck:
Now if we zero in on the BAFF/APRIL pathway, what impact does it have on B cell survival and antibody production?

Dr. Barratt:
So BAFF and APRIL are two cytokines that are critical to the survival and function of B cells and antibody secreting plasma cells. These two cytokines act through at least three different cell surface receptors: the BAFF receptor, TACI, and BCMA. And by acting through those receptors, they promote B cell and plasma cell survival, IgA class switch recombination, and proliferation of B cells, and as I say, survival and longevity of plasma cells. So these two factors are critical both in the immune system within the central lymphoid sites like lymph nodes and bone marrow, but are particularly important in the mucosal immune system where they can drive T-cell independent IgA class switch recombination which is believed to be pivotal in the formation of the Gd-IgA1 I've mentioned that ultimately is responsible for their formation of circulating immune complexes.

Dr. Turck:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Jonathan Barratt about how B cells and the BAFF/APRIL pathway play a role in the pathogenesis of IgA nephropathy, or IgAN.

So if we look at this at the cellular level, Dr. Barratt, what do we know about the downstream effects of these immune complexes on kidney function?

Dr. Barratt:
So the immune complexes are formed in the circulation, and they are trapped within the glomerular mesangium. And here, they interact predominantly with mesangial cells which recognize this deposited IgA, become activated, proliferate, and generate proinflammatory and profibrotic factors that drive kidney injury, both within the glomerulus but also within the rest of the kidney. These fractures can lead to the recruitment into glomeruli of inflammatory cells. These are predominantly monocyte macrophages which can worsen inflammation. They can promote the generation of profibrotic factor, so the laying down of extracellular matrix and the generation of scarring within the glomerulus.

But in addition, these factors that are generated by activated mesangial cells can cross the glomerular basement membrane, where they then can directly impact the function and integrity of podocytes and of tubular epithelial cells. And so this activation within the mesangial cells ultimately spills over to impact on podocytes, promoting podocyte loss, segmental sclerosis, and activation of tubular epithelial cells, which in turn drive tubular interstitial inflammation and fibrosis.

Dr. Turck:
Now, given all these mechanistic insights, how are therapeutic strategies evolving to specifically target the BAFF/APRIL pathway?

Dr. Barratt:
So coming back to the critical role of BAFF and APRIL in driving the production of this Gd-IgA1 that ultimately forms immune complexes, there's been a great deal of interest in blocking BAFF and APRIL signaling for obvious reasons. And at the moment, we have a number of Phase 3 clinical trials looking at the impact of new therapies in blocking either BAFF and/or APRIL signaling to prevent the production of IgA immune complexes and the downstream effects of those immune complexes in the kidney tissue.

And so we have two monoclonal antibodies that currently target APRIL exclusively, and these are zigakibart and sibeprenlimab. We have three drugs that specifically target both BAFF and APRIL, and these drugs are povetacicept, telitacicept, and atacicept. And all of the five drugs I've mentioned are currently in Phase 3 clinical trials in IgA nephropathy. We don't have any published results yet from these studies, but we hope to have data starting to come out over the next six months or so in terms of looking at the safety and effectiveness of this approach in patients with IgA nephropathy from global clinical trial populations.

Dr. Turck:
Before we end our program, Dr. Barratt, how do you see this growing understanding of B cell biology shifting our approach to managing IgAN in the future?

Dr. Barratt:
I think our aspiration has always been, in the treatment of IgA nephropathy, to switch off IgA deposition in the kidneys. After all, that is what drives kidney failure in our patients. But we've never had the drugs that can safely and effectively achieve that. What drugs that target both BAFF and/or APRIL appear to be delivering with the data we have at the moment is a real ability to switch off the production of pathogenic IgA in a safe way, and in turn, switch off the formation of immune complexes and stop IgA deposition in the kidney and all of the downstream consequences. So I think for me, the way we will approach IgA nephropathy in the coming years will be first and foremost to use a treatment that is both safe and effective at turning off the production of pathogenic IgA. And the early data we have from drugs that target BAFF and/or APRIL suggests that these may well be a highly effective way of doing that.

Dr. Turck:

Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Jonathan Barratt, for joining me to discuss IgA nephropathy and the influence of B cells in the BAFF/APRIL pathway. Dr. Barratt, it was great having you on the program.

Dr. Barratt:
Thank you very much. I've really enjoyed our discussion today.

Announcer:
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