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Targeting BAFF and APRIL in IgA Nephropathy

Announcer:
You're listening to *On the Frontlines of IgA Nephropathy* on ReachMD. 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 the rationale of dual BAFF and APRIL inhibition in IgA nephropathy, or IgAN for short, is Dr. Edgar Lerma. Dr. Lerma is a Clinical Professor of Medicine in the Section of Nephrology at the University of Illinois at Chicago. He also serves as the Educational Coordinator for Nephrology with UIC Advocate Christ Medical Center. Dr. Lerma, we're so glad that you're here today.

Dr. Lerma:
Thank you, Gates.

Dr. Colbert:
So let's start with the big picture, Dr. Lerma. Can you walk us through the immunological processes that drive IgA nephropathy, and where BAFF and APRIL fit into that picture?

Dr. Lerma:
When we talk about IgAN, or IgA nephropathy, you really have to talk about the multi-hit hypothesis, right? This is sometimes called the four-hit hypothesis, which really links mucosal immunity and kidney injury.

And we talk about these four hits. So hit number one is the production of Gd-IgA1, or galactose-deficient IgA1. So this IgA1 is produced by the plasma cells, especially these plasma cells located in the mucosal tissues like the gut and the tonsils. And this aberrant IgA1 has deformed glycosylation. Specifically, there's a deficient galactose in the hinge region of the IgA, and this abnormal IgA1 is actually more immunogenic as compared to normal.

So hit number two is when the autoantibodies form. As you know, the immune system recognizes this Gd-IgA1 as foreign, and so the body starts generating IgG and IgA autoantibodies against it.

Hit number three comes in, which is immune complex formation. So the Gd-IgA1 binds these autoantibodies, thereby forming what we call circulating immune complexes.

And of course, this leads us to hit number four, which is mesangial deposition and injury. So the formed circulating immune complexes start depositing in the mesangium of the glomerulus, and during this time, it activates several things, like the complement pathways, and this includes your alternative and lectin pathways. It leads to mesangial cell proliferation and finally, cytokine and extracellular matrix production. Ultimately, this progressive inflammation leads to fibrosis and then chronic kidney disease.

Now, where do BAFF and APRIL fit in here? Well, BAFF—which is short for B-cell activating factor—and APRIL—which is short for a proliferation-inducing ligand—are cytokines in the TNF super family, and these cytokines regulate B-cell biology. These cytokines actually act upstream—that is, before the formation of the immune complexes. That is what I referred to earlier as hit number three. And they act upstream by shaping the B-cell and the plasma cell compartments that produce IgA.

So if you think about it, the key functions of BAFF and APRIL are, number one, they promote B-cell survival and maturation. Number two, they drive class switching to IgA. And number three, they support plasma cell differentiation and longevity. And of course, lastly, they do enhance mucosal immune responses.

Now, in IgAN, both BAFF and APRIL are often elevated, and these contribute to, number one, overproduction of IgA, especially those galactosylated-deficient IgA1, or Gd-IgA1, and of course, the persistence of the autoreactive B-cell clones.

Dr. Colbert:
Now, although BAFF and APRIL are closely related, what unique roles does each pathway play in the process?

Dr. Lerma:
So, although BAFF and APRIL overlap, the biology is not exactly redundant. So when we talk about BAFF, its effects are more upstream—broader B-cell effects—while APRIL is more downstream and really focused on IgA and plasma cells.

The receptors are the same for both cytokines: the TACI as well as the BCMA. The functions, however, are kind of where it differs, because of their effects. BAFF is more upstream. So they're critical for naive B-cell survival, supporting B-cell maturation and selection, and again, helping maintain the peripheral B-cell pools.

Now, with APRIL, the function really centers on promoting class switching to IgA and supporting long-lived plasma cells. And again, APRIL is important in mucosal immunity.

Now, if you take this in the context of IgAN, or IgA nephropathy, BAFF allows autoreactive B cells to escape deletion, thereby expanding the pool of cells capable of producing the pathogenic IgA, which is the Gd-IgA1. And when we talk about APRIL in IgAN, APRIL is directly linked to the increased IgA production. Again, that is the Gd-IgA1, and of course, it also sustains the plasma cells that continuously secrete the pathogenic antibodies.

So, in short, the way I remember it: with BAFF, we're talking about B-cell survival and expansion. That's upstream fuel. With APRIL, we're talking about IgA production and plasma cell persistence, so more downstream output.

Dr. Colbert:
With all of this being said, what's the scientific rationale behind investigating dual BAFF and APRIL inhibition rather than targeting either pathway alone?

Dr. Lerma:
So targeting only one pathway may actually leave the other pathway to compensate. In a way, dual inhibition makes sense, right? One, there's redundancy and overlap. Both cytokines, as I said, share the same receptors: TACI and BCMA. So if you block one, it can lead to compensatory signaling via the other.

There's also coverage of the full B-cell life cycle. So BAFF inhibition reduces B-cell survival. APRIL inhibition reduces IgA production and maintenance of plasma cells. If you block both BAFF and APRIL, it impacts not only the precursor cells, but also the effector cells.

Now, there's also suggestion that a stronger suppression of pathogenic IgA may be another effect of dual inhibition, and this is particularly important in IgAN, where continuous production of Gd-IgA1 is of prime importance and is central to the disease. So there's also the potential for deeper disease modification, not just decreasing the inflammation. But it's also interrupting the source of immune complexes.

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. Edgar Lerma about advancing IgAN management through BAFF and APRIL pathway inhibition.

So, Dr. Lerma, we've been talking about the biology of BAFF and APRIL, but let's now put this in the larger context of care. From your perspective, how can dual inhibition fit into the evolving treatment landscape for IgA nephropathy?

Dr. Lerma:
We know that the IgAN treatment paradigm is now shifting from non-specific to targeted therapy. Several years ago, we would treat patients with IgAN with RAS inhibition, plus/minus corticosteroids. Now, with the advent of these novel therapies, we can look at the treatment of IgAN as a pillared approach with four pillars. So supportive care: that's what we've been doing before, right? RAS inhibition and blood pressure control. The second pillar is the SGLT2 inhibitors, like kidney protection. The third pillar is the targeted release steroids. This affects mucosal immune modulation.

And finally, the fourth pillar—which is what we're talking about—is the emerging pillar. This includes complement inhibitors as well as endothelium receptor antagonists. Where does dual BAFF and APRIL inhibition fit in here? As I said, it's the upstream immune modulation and disease-modifying effects. And the combination of this is really something that we probably have to look more into, particularly as to how it affects our patients and how it translates into long-term outcomes eventually.

Dr. Colbert:
And then on the flip side, what are the biggest challenges or questions that still need to be answered about this therapeutic avenue?

Dr. Lerma:
Just like any novel therapies, the first thing you always have to test is safety and efficacy, right? So despite our earlier discussion about the rationale, about how these medications work, and about why they work, there remain uncertainties.

Number one, when it comes to safety and immunosuppression, one can think that long-term dual inhibition may actually increase the risk of infection. It can affect normal mucosal immunity, particularly in patients with IgA-dependent defense. We have to choose the right patient population. Who benefits the most? You have to ask, "Should I treat patients early or should I wait until later? Do I look at Gd-IgA1 levels? How do I interpret that? Should I treat patients who have high levels or low levels, or how do I approach those differently?" And of course, we're still trying to define the biomarkers. How do the biomarkers fit into identifying the patient phenotype?

Then there's also the question of depth versus necessity of suppression. Do we need complete suppression of BAFF and APRIL activity, or is partial modulation sufficient? Maybe it's even safer.

Then you go into the durability of the response. You ask yourself, "If I do reduce the galactose-deficient IgA, is this effect sustained after I stop treatment? How does this translate into long-term kidney protection?"

I mentioned about biomarkers. We do need reliable biomarkers to track Gd-IgA1. We have to track the autoantibodies and immune complex activity. And of course, these biomarkers will hopefully help guide treatment and monitor the response of the patients with treatment.

And of course, how do you position this in therapy sequence? Are we looking at first-line targeted therapy? Are we looking at add-on after supportive care, or is this reserved for patients who are at very high risk? And how do we identify those patients?

So, Gates, there are a lot of uncertainties still. While the trials inform us that there's safety and there's efficacy, I think the real-world evidence will eventually inform us as to, how does this move forward?

Dr. Colbert:
As we start to wrap up, Dr. Lerma, do you have any final thoughts you'd like to share with our audience?

Dr. Lerma:
As I mentioned earlier, we started off with just treating patients with IgAN with RAS inhibition and corticosteroids. Now we have a deluge of different agents with various mechanisms.

Now, what's exciting for me about BAFF and APRIL biology in IgAN is that this represents a shift from treating the consequences of the disease to targeting the cause. Dual inhibition is particularly compelling because, number one, it reflects the complexity and the redundancy of the immune system. It also attempts to shut down the pathogenic cascade at its source. So some people refer to this BAFF and APRIL inhibition as the pre-four-hit effect, because it happens before the four hits of IgAN. And of course, dual inhibition really aligns with a broader trend toward precision immunology in kidney disease.

Again, there's a lot of optimism and there's a lot of excitement. But that said, the field still needs clear clinical outcome data. We still need better biomarker-guided patient selection and, of course, a careful balance between efficacy and immune safety.

Dr. Colbert:
With those takeaways in mind, I want to thank my guest, Dr. Edgar Lerma, for helping us better understand the role of BAFF and APRIL in IgA nephropathy. Dr. Lerma, it was great having you on the program.

Dr. Lerma:
Thank you so much, Gates. It was my pleasure.

Announcer:
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