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How Advances in Immunology Are Shaping CSU Care

Announcer:
You're listening to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. Here's your host, Dr. Steve Jackson.

Dr. Jackson:
This is *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Steve Jackson, and joining me to discuss how recent advances in inflammatory skin disease are translating to chronic spontaneous urticaria, or CSU for short, is Dr. Christopher Bunick. He's a board-certified dermatologist and an Associate Professor of Dermatology at Yale School of Medicine in Middlebury, Connecticut.

Dr. Bunick, welcome to the program.

Dr. Bunick:
Thank you, Steve. It's a pleasure to be here.

Dr. Jackson:
To start us off, Dr. Bunick, how would you describe the underlying mechanisms driving CSU, and how do they differ from other inflammatory skin diseases?

Dr. Bunick:
So CSU is primarily driven by mast cell activation, and this involves the release of mediators including interleukin four, interleukin 13, interleukin 31—not just histamine. Certainly, histamine is part of that too. And this distinguishes CSU from other inflammatory skin diseases, which are largely T-cell mediated, like psoriasis and atopic dermatitis.

CSU does involve immune dysregulation. It has both auto-allergic, or type 1, and autoimmune, or type 2B, subtypes. The auto-allergic subtype has IgE autoantibodies to self-antigens. The autoimmune subtype is driven by mast-cell directed activating IgG autoantibodies, and that can target either IgE or the high -affinity IgE receptor known as FC epsilon receptor 1.

Given the differences in the inflammatory pathways involved, CSU exhibits differences in triggers and chronicity compared to other conditions, like atopic dermatitis.

Dr. Jackson:
And building on that, what have we learned from advances in other inflammatory skin diseases that's helped to deepen our understanding of CSU?

Dr. Bunick:
Importantly, insights into cytokine signaling and immune pathways have informed how we think about inflammation across diseases. These insights have helped identify commonalities between pathways that were not previously known, as well as unique aspects.

And as for CSU, one of these unique aspects is the importance of a particular kinase called Bruton's tyrosine kinase, or BTK for short. And this BTK is very important to mast cell activation. It's also important in other cell types beyond mast cells that do impact CSU treatment, and that's basophils and B cells. The innovation and uptake of advanced targeted therapies in other inflammatory skin diseases has helped identify physiologically relevant pathways in CSU and has largely reassured providers that it is safe to use. So, for example, biologics like dupilumab in CSU. Growing comfort with the use of JAK inhibitors in dermatology also helps encourage providers to use another type of kinase—in this case, a highly selective BTK inhibitor, remibrutinib, for the treatment of CSU.

I believe, ultimately, our experience with advanced targeted therapies across the dermatology disease landscape has really allowed us

to recognize the shared inflammatory mechanisms of these diseases and how to leverage them, even though these diseases can present differently morphologically in the clinic.

Dr. Jackson:
With those mechanistic insights in mind, can you tell us how they've influenced the development of targeted therapies for CSU?

Dr. Bunick:
Well, for starters, there's been a very significant shift from broad immunosuppression—for example, from the use of short or long-term corticosteroids. There's been a lot of initiative in dermatology to move away from overuse of corticosteroids. So this shift has occurred in CSU from this broad immunosuppression to a very targeted, both small-molecule and biologic approach.

And these are truly pathway-specific treatments. There's been a leveraging of the experience from other dermatologic therapies to really inform CSU drug development. So, for example, we're understanding the role of Th2 cytokines—not just histamine, but beyond histamine—and how these Th2 cytokines play a role in the pathophysiology of CSU, actually connecting the production of these cytokines and their release for mast cells to the upstream activity of the BTK kinase; hence, why inhibiting it can be a very effective therapy for CSU.

Dr. Jackson:
For those just tuning in, you're listening to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Christopher Bunick about our evolving understanding of CSU mechanisms and therapies based on advances in other inflammatory skin diseases.

So, Dr. Bunick, when you think about the current and emerging treatment landscape, what stands out to you as most promising for improving outcomes?

Dr. Bunick:
In 2025, we had two new therapies that were approved for CSU: the biologic dupilumab and the oral small molecule BTK inhibitor remibrutinib. Both of these therapies represent key advances in our ability to improve patient symptoms such as itch and reduce the disease burden of hives. They also are more convenient for patients to take than omalizumab, which was the third approved therapy in our CSU space. And omalizumab targets IgE.

When we indirectly compare the CUPID clinical trials for dupilumab in CSU and the REMIX trials for remibrutinib in CSU, we do see a quicker onset of action and a deeper overall UAS7 response—which is the Urticaria Activity Score—with the BTK inhibitor remibrutinib. So while dermatologists and allergists are just adopting and adapting to these new therapies, there are actually many more in development, such as an anti-KIT antibody called barzolvolimab, as well as other therapies.

Dr. Jackson:
And given those advances, how might they change the way we approach treatment selection or sequencing for patients with CSU?

Dr. Bunick:
More than ever, we now have the ability to take a more personalized or mechanism-driven approach to treating CSU, with three available advanced therapies. The speed of onset and depth of response seen with remibrutinib makes it an attractive first-line option. The oral pill, which is twice daily, is also very attractive to patients.

Similarly, there's a familiarity and comfort with dupilumab, because of its number of indications. It has a good safety profile, and the every-two-week dosing can make it a very effective, convenient first-line therapy for many CSU patients as well.

Lastly, omalizumab is there for those CSU patients where targeting IgE is essential to disease control.

Dr. Jackson:
And before we close, Dr. Bunick, let's look ahead for a moment. What's one key takeaway or area of ongoing research we should keep an eye on as the field continues to evolve?

Dr. Bunick:
I'd like to highlight two points. So the first is, with these advanced therapies, we now have less reliance on antihistamines, which are historically ineffective for a lot of patients with CSU. And we also have less reliance on corticosteroids, which is a good thing given the side effect trial profile of chronic steroids.

But while there have been all these advances in CSU, where the trigger of the hives is not known, I'd like to highlight that clinical trials are ongoing in chronic inducible urticaria—which is called CIndU for short—for several drugs. This includes remibrutinib and dupilumab, which we've talked about for CSU. They're also being investigated in CIndU, as well as the anti-KIT antibody barzolvolimab. There's

also another molecule, EVO756.

One of the areas to watch in parallel to using these therapies in CSU patients is actually this chronic inducible urticaria space, where there's a number of investigations ongoing.

Dr. Jackson:
With those forward-looking comments in mind, I want to thank my guest, Dr. Christopher Bunick, for joining me to discuss how advances in inflammatory skin disease shape our understanding and treatment of CSU. Dr. Bunick, it was great having you on the program.

Dr. Bunick:
Thank you for having me and letting me talk about CSU.

Announcer:
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