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Beyond Antihistamines: Targeted Options for CSU

Announcer:

You're listening to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. Here's your host, Dr. Charles Turck.

Dr. Turck:

You're listening to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss advances in targeted treatment for 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. Dr. Bunick, thanks for taking the time to be with us today.

Dr. Bunick:

My pleasure to be here.

Dr. Turck:

Well, to get us started, Dr. Bunick, what do we understand about what drives CSU today that we didn't a decade ago?

Dr. Bunick:

I think the biggest thing is that we no longer consider CSU idiopathic. It's really recognized as an autoimmune mast cell disease, and the mast cell is really at the center. It's the orchestrator of CSU. And all of the effective therapies that have been developed now converge around mast cells. This could be upstream of mast cells—IgE or IL-4/-13—or within the mast cell itself, which is BTK. And then, even now, we're targeting the mast cell through the KIT receptor and being able to deplete mast cells. We have all these effective therapies because we now recognize the central role of the mast cell in this autoimmune disease.

Dr. Turck:

At EADV 2026, you discussed some of the latest advances in targeted therapies for inflammatory skin diseases. Looking more broadly at the field, how is the shift toward pathway-specific therapy changing the way dermatologists approach treatment decisions?

Dr. Bunick:

Well, I think, in the big scheme of things, pathway specific means disease specific. And when you have disease-specific or targeted therapies, there's the promise of higher efficacy, better safety, and even the potential for disease modification.

And what this means for the clinician when they're thinking in the clinic and face-to-face with a patient is they're no longer really focused on, how do I treat this disease. They're actually now focused on, which pathway does this patient likely have as the dominant form of their CSU or the driver of the CSU, and how do I treat the patient with one of my targeted therapies?

Now, where we have a gap is some of the bedside diagnostics to understand which endotype or pathway is active in a CSU patient. That's still lagging behind. One of the things that we do know about CSU now is there are two dominant endotypes, what are known as the autoallergic, or type 1, and then the autoimmune, or type 2B. And one of the differences between those is that the autoallergic is predominantly IgE autoantibodies, and the autoimmune or type 2B is largely IgG autoantibodies. And what's really interesting about these pathways is many patients have overlapping endotypes, and this can make it very difficult for identifying and treating them.

What we now know is that these pathways largely converge through a receptor, the FCER1, which is a major player in CSU. And a lot of our therapies—whether they're targeting IgE, IL-4/-13, or BTK—are really focused on how you limit the aberrant signaling from FCER1 or the high-affinity IgE receptor.

Dr. Turck:

I'd like to take a closer look at a couple of CSU therapies. We know that the efficacy of dupilumab was first established in atopic dermatitis, and it's now approved for CSU. What does that crossover tell us about how biology might be shared across inflammatory skin diseases?

Dr. Bunick:

You can't talk about dupilumab without first starting with the cytokines IL-4 and IL-13. What we now know about IL-4 and IL-13 is they're involved in a few key processes that are important to mast cells and CSU. That's IgE class switching, Th2 differentiation, mast cell sensitization, and sensory nerve itch signaling. And therefore, a drug like dupilumab, by targeting the IL-4 receptor alpha, can decrease IL-4 and IL-13 signaling and affect all of these different aspects of the pathology that underlies CSU.

Now, one of the things that we do know is that Th2 diseases are not just limited to CSU. There's atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, prurigo nodularis, and bullous pemphigoid. These are all areas where dupilumab has made a huge impact in treating patients' lives. But one of the other interesting aspects of research into diseases, particularly inflammatory skin diseases, is that they're not always purely Th2. This has been true for atopic dermatitis, and it's also true for CSU, where patients may have Th1 or Th17 signaling, complement signaling, or even MRGPRX2 signaling, which is a IgE-independent receptor signaling pathway that mast cells can use.

Therefore, there are two key points here. One, there's a need for therapies that can address some of the non-Th2 components of the disease. But also, second, understanding Th2 biology has really led to major advances across numerous diseases because of the overlap of a lot of the Th2 signaling pathology. And I think that's where dupilumab has really shined in a lot of these Th2 diseases, including CSU. It's really about how central IL-4 and IL-13 are to so many different pathologies.

Dr. Turck:

Oral targeted therapies have become a bigger part of dermatologic care, and remibrutinib is an oral BTK inhibitor approved for CSU. What sort of impact does having an oral option like that have on patients?

Dr. Bunick:

Well, it is really exciting that we now have an oral option. I think that this is where, when you're deciding upon therapies, having a mechanistic approach... We have oral BTK inhibitors. We have the IL-4 receptor alpha injectable biologic dupilumab, and we have the IgE-targeted therapy omalizumab. But what makes BTK unique is it's not just targeting mast cells. So we now know that the SYK—so S-Y-K, SYK—to BTK pathway—and then BTK stands for Bruton's tyrosine kinase—this signaling pathway is important in mast cells and basophils, and it's downstream of the FCER1, which we talked about.

And then also, a lot of people may not realize that B cells, particularly B cell receptor signals through BTK, are responsible for a lot of autoantibody production. And we know that both type one, the autoallergic, and type 2B, the autoimmune, endotypes of CSU have autoantibody production, whether it's IgE or IgG. And therefore, BTK is really at the center of these different pathways in these different cells.

And I think that explains a lot of the clinical trial data that we saw, where remibrutinib, as an oral BTK inhibitor, had some of the fastest onset in the clinical trials and some of the deepest responses when you're looking at the UAS7, so urticaria activity score seven, where you're looking at completely clear results at week 12. Remibrutinib's hitting that mark in almost a third of patients at week twelve, and it grows to around 50 percent of patients at week 52. This is, I think, really important. That fast onset and that deep clinical response is what patients are looking for.

Now I'll throw in the caveat that there's no head-to-head trials amongst any of these three major therapies that we're now using for CSU. But one caveat to all of this is that we do know, from the clinical trial data of dupilumab in the LIBERTY/CUPID trial, that omalizumab-naïve patients tended to do really well. But dupilumab in the omalizumab-refractory patients didn't meet the primary endpoint.

And I think that what this tells us is how complicated treating CSU patients can be. We still don't fully understand the endotypes and how to target the right therapy to the right CSU patient all the time, and we do have to pay attention to patients that have failed one therapy and how we're going to sequence future therapies. And without head-to-head trials, that is a little complicated. Without good biomarkers, it's still a little bit complicated. But the reality is, the patients with CSU have more options than ever, and one of the key take-home points is, if you do fail one therapy, don't give up. We have three really good targeted therapies.

Dr. Turck:

For those just joining us, this is *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Christopher Bunick about emerging mechanisms and treatment options in CSU.

So let's look to the future for a moment, Dr. Bunick. Beyond IgE, interleukin-4 receptor alpha, and BTK, which pathways are currently under investigation as targets in CSU, and what do we know about them?

Bunick:

What I say is that there's been many pathways that have been looked at in CSU. A lot of them are not panning out. But one pathway—and the major one that everyone should know about, because the top-line phase 3 data was just released a month ago—is barzolvolimab. This is a monoclonal antibody that targets the KIT receptor on mast cells, and it actually depletes mast cells. And the KIT receptor is really responsible. It's that big receptor that regulates the activation of mast cells. And if you can inhibit this KIT receptor and the signaling and activation of mast cells, you don't get mast cell degranulation, and the clinical outcome is that you can control CSU.

And in this top-line phase 3 data of barzolvolimab—this KIT-targeted monoclonal antibody—we saw really, really good results. At week 12, upwards of 40 to 46 percent of patients were having complete clearance of their skin—UAS7 complete response. And this grew upwards around 70 percent at year one. This is really outstanding data.

Now, when we think about depleting mast cells, some of the side effects that were observed were dyspigmentation, so hyperpigmentation or hypopigmentation of both the hair and the skin. But when you look at the clinical pictures, while that might scare a provider or a patient at first, the reality is, this dyspigmentation tends to be, for many of these patients, very mild and something that I think is very tolerable for this degree of response.

So I'm very excited about barzolvolimab. I think it's going to add an incredible fourth option to our CSU targeted therapy portfolio. The one caveat to everything continues to be, again, that there's no head-to-head trials. And how do you sequence them? I do think that future research on the biomarkers and specific endotypes could help identify a little bit better how to choose among them. But nonetheless, this is a huge step forward for CSU patients to have these different therapies.

Dr. Turck:

Now, before we wrap up our discussion, Dr. Bunick, what's the main message you want clinicians to walk away with today?

Dr. Bunick:

Well, I'll end with three key points. The first: CSU is a treatable autoimmune mast cell disease. This is reassuring patients that we know what it is, we can treat it, and we do have effective targeted treatments.

Secondly, in the second line, behind oral antihistamines, we now have a choice of multiple mechanisms of action. We can now match therapies to the best of our current knowledge, to patient phenotype, to comorbidities, and to patient preferences. And I think that this is really the big advance for the provider. Do you want an oral BTK inhibitor? Do you want to target IL-4 receptor alpha and IL-4/-13 signaling with dupilumab? Or do you have a patient with high IgE and you're going to use omalizumab to target IgE?

And lastly, the third and perhaps maybe even the most important point, is don't give up. If you have a patient that's failed one therapy, don't give up. Try another targeted therapy, because, at least in my own clinic, I've seen patients respond to therapies from different mechanisms or different pathways. And that's why having this mechanistic and pathway-targeted approach to CSU is proving to be so helpful to patients.

Dr. Turck:

Such valuable reflections to end on. And many thanks to our guest, Dr. Christopher Bunick, for sharing his insights on the evolving treatment landscape of chronic spontaneous urticaria. Dr. Bunick, it's been a pleasure speaking with you.

Dr. Bunick:

Well, thank you so much for having me.

Announcer:

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