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Advances in Biomarkers and Targeted Therapies for CSU

Announcer:
This is *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. Now, here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Charles Turck, and today, we'll be exploring biomarkers and advanced therapeutics for chronic spontaneous urticaria, or CSU for short, with Dr. Jonathan Bernstein. He's a board-certified allergist and immunologist, and a Professor of Medicine at the University of Cincinnati. Dr. Bernstein, thanks so much for being here today.

Dr. Bernstein:
It's a pleasure.

Dr. Turck:
So Dr. Bernstein, we know that biomarkers have become an important area of investigation in CSU. From your perspective, what role do biomarkers play in our current understanding of the disease?

Dr. Bernstein:
Well, the reason we started looking at biomarkers was because we were interested in understanding why some patients respond to a drug and others don't. As you know, only maybe 45 percent or so of patients have complete responses to a therapy for chronic spontaneous urticaria, depending on the therapy and so forth.

But if we could have more precision medicine and have better ways of selecting one treatment for one patient that might work better versus another treatment, that would be ideal. So we started looking at this in the context of omalizumab, which was the first biologic approved for chronic spontaneous urticaria. And this is, I think, where a lot of interest occurred, because we found there were some correlations with some biomarkers and response to omalizumab.

Dr. Turck:
With that in mind, would you walk us through what some of the other biomarkers currently being studied in CSU are, how they're being used, and what their limitations are?

Dr. Bernstein:
For instance, for H1 antihistamines, we looked at certain biomarkers like CRP—C-reactive protein—as well as D-dimer. And we found that patients who had elevated levels might not respond as well to H1 antihistamines. We found that low IgE, high thyroid peroxidase antibody, low eosinophils, and low basophil counts, as well as a test called CU Index—which is a marker for basophil activation in patients with chronic spontaneous urticaria—were, potentially, other predictors of response or decreased response to omalizumab.

So these were some of the markers that emerged and that have subsequently been looked at in terms of drug development for some of the newer therapies that are coming out. So we found that patients who had high thyroid peroxidase antibodies—TPO levels—did not respond as well to omalizumab. We found patients who had very low IgE—and what the cut point is is subject to discussion—were not as responsive or might have had a slower response to treatment. Patients who had no or low eosinophils base—low basophils also—may not have responded as well to omalizumab.

And then CU index is a limited test, because it hasn't yet been validated. That process is ongoing, but it seemed to correlate with, autoantibodies against IgE receptors. And so patients who have autoimmune urticaria, where there's IgG antibodies, targeting IgE

receptors or binding to IgE receptors doesn't often respond as well to some therapies versus others. So that's what that test is designed to do: to look at a marker for autoimmune urticaria. But there's still work ongoing.

So that's basically what has been looked at. So that is the standard now for novel therapies, to be able to say, "Yay or nay—we work regardless of whether patients have these biomarkers or not."

Dr. Turck:
For those just tuning in, you're listening to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Jonathan Bernstein about advances in CSU management.

So, Dr. Bernstein, as the treatment landscape continues to expand, what factors guide your decision-making when considering advanced therapies for patients with CSU?

Dr. Bernstein:
Well, it's a difficult situation, because there's a lot of factors that have to be considered.

Subsequently, new therapies have emerged after omalizumab. Dupilumab, which has been around for many years and has been approved for other indications, is now approved for chronic spontaneous urticaria. And the most recent therapy, remibrutinib, was also approved, and this targets B-cells, which are important for producing IgE and regulating IgE receptors on mast cells.

So again, how the studies were done and, subsequently, what's emerged from this, is that some of these markers that we looked at from omalizumab don't seem to be as relevant for these agents. For instance, dupilumab was able to be effective in patients who had higher IgE over 50 versus under 50 international units per AML. It doesn't seem to be affected by BMI, body mass index, or the presence or absence of angioedema, which is potentially a factor associated with more severe hives.

So those are some of the things that have been looked at. I don't believe they've really looked at other markers, like TPO, to determine if they would be as responsive or not. And then of course, remibrutinib has also been looked at with these markers, and they found that regardless of the level of IgE and whether or not patients have other autoantibody markers, these patients will respond.

Now for some of these agents, in the presence of autoantibodies, the drugs may work, but they just may not work as fast, or they may take longer. And there's some studies showing that in the presence of some of these markers, omalizumab may work, but it may take up to six months to work. And it may be more effective if you up-dose: if you go to every two weeks instead of every four weeks, or even double the dose and go to 600 milligrams every four weeks.

So those have been other proposals for interpreting responders and non-responders based on these biomarkers. So when we look at the patient who presents with hives, we're trying to characterize them. We want to make sure they have hives. We want to make sure, and we look at a few tests. It's not recommended to do extensive testing in patients with chronic spontaneous urticaria. We don't need to test for foods or for aeroallergens. We don't need to do skin testing on these individuals. And it's not recommended to do excessive testing for underlying causes. A CBC with differential, a TSH, or a CRP might be appropriate initially.

And then obviously, starting with high-dose, non-second generation, low-sedating or non-sedating antihistamines would be the first step, dosing up to four times the recommended dose. If those patients have a high CRP, then you could say, oh, interesting, that correlates with not responding. But if they have other markers like high autoantibodies, TPO, or even if you order a CU index, that's sort of how I've looked at this. I've ordered a few tests, like an IgE level, a TPO, and sometimes a CU index. But certainly, the CBC will tell you what the eosinophils and basophils are doing.

So you can kind of get a sense of, do these patients have autoallergic urticaria, where they're making maybe IgE antibodies, targeting IgE receptors that are causing activation of mast cells, or do they have IgG antibodies, which tend to be more interfering with the response to treatments?

So I think this is where real-world evidence will emerge and provide us some direction over time. But the most important thing is that patients need to know they have options, and they need to know safety about these drugs and what they potentially could expect based on clinical trials.

And then, based on their clinical profile, there would be shared decision-making to determine what would be the best treatment for this patient: up-dosing omalizumab, switching to dupilumab, switching to remibrutinib. There's a lot of options now for patients with chronic spontaneous urticaria.

Dr. Turck:
Now, continuing to get at when patients don't respond as expected to therapy, what else can you tell us about how you approach reassessing the diagnosis or treatment strategy?

Dr. Bernstein:
So when patients don't respond, I want to make sure they have hives. There are a lot of mimickers. There are a lot of rashes and things that may patients relate to hives, and certainly, there's a lot of things that can cause itching. So hives are certainly evanescent. They come and go in less than twenty-four hours. They don't leave bruising or scarring. They travel over the body. They are polymorphic. They have different shapes and different sizes, and sometimes they can be very small, pinpoint-type welts. Or they can be larger.

I think that the other thing you have to know is, do they have a inducible component? Do they have other inducible triggers like heat, cold, exercise, sunlight, scratching, which we refer to as symptomatic dermatographia? All of these features can actually complicate the treatment of hives. In fact, patients who have chronic inducible hives are thought to have a more protracted course and can be more difficult to manage.

So I think these are the kinds of things you think about. Other underlying conditions—we know that this is not caused by an infection. We know that it's not caused by parasites or something like that. And this is what I think people are always thinking, that it's from a viral infection or it's from this or that, but this is why we call it chronic spontaneous urticaria. These things come on. It's not entirely clear what causes them to pop up. And certainly, we know what triggers them in some cases, but there are still some areas that need to be further investigated. But that's what we do, and then we have to decide what the next steps are for treatment, which I think we've discussed.

Dr. Turck:
So, speaking of areas that continue to need investigation, what unanswered questions remain about biomarkers or treatment selection in CSU, and where is additional research most needed?

Dr. Bernstein:
In our current guidelines, which will be released in the next month—the Joint Task Force guidelines for the American Academy of Allergy, Asthma, and Immunology, and the American College of Asthma, Allergy, and Immunology—we don't really insert biomarkers into our algorithmic approach for treatment or management, because we don't feel that we have very strong data yet to make firm recommendations to use one drug over another.

I think that I personally am biased towards biomarkers. I think they have value. I don't know if we have the right biomarkers yet that we're looking at, but I think the real-world evidence will determine that. Real-world use of these therapies, when individuals don't respond, perhaps, inquisitive physicians will look to to see if some of these biomarkers exist, hopefully before they start the therapy, so we can learn from this.

On the other hand, people might argue, is it cost-effective to do biomarkers if they're not predictive of response to treatments? And again, those are both good points. I feel that we learn a lot about patient management from managing patients, and this is real-world data that. We're all scientists. Our patients are our laboratory. We look at them and try to understand how we can improve their care, and we're getting some limited testing that is hypothesis-generated—but supported by the existing literature—that it is not unreasonable to determine why someone responds and doesn't respond.

But that's an ongoing area of research, and there's a lot of ways of activating mast cells. There are over three hundred receptors on mast cells—different types of receptors—and we're only starting to target a few of them to block mast cell activation responses. So there's a lot of opportunity for investigation, research, and drug development.

Dr. Turck:
And finally, Dr. Bernstein, continuing to look ahead, are there any other developments you think are likely to influence the future management of CSU?

Dr. Bernstein:
Well, there are a lot of therapies that are currently being developed. There's, therapies that are targeting c-Kit receptors on mast cells. Those are like the master switches of mast cells. There's other BTK—Bruton tyrosine kinase—inhibitors that are being looked at. There are bispecific antibodies that are being looked at. There's even thoughts of vaccines and so forth.

So there's a lot of interesting targeted therapies. I didn't mention MERTK PyR2 receptors, which are receptors on mast cells that are activated by neuropeptides. Unfortunately, one of the companies investigating this molecule did not meet its primary endpoint in Phase II studies. That doesn't mean they're not relevant. There are other reasons that need to be explored as to why it wasn't effective.

But there is a lot of work going on right now beyond targeting IgE receptors on mast cells that might be very relevant in understanding not only mast cell activation, but also how we can better treat patients who present with chronic spontaneous urticaria and chronic inducible urticaria.

Dr. Turck:
Great way to round out our discussion. And I want to thank my guest, Dr. Jonathan Bernstein, for joining me to discuss developments in CSU care. Dr. Bernstein, it was great speaking with you today

Dr. Bernstein:
Thank you very much. It was great to be here.

Announcer:
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