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Put Your Foot on the Gas: Rethinking CSU Treatment

Announcer:
This is *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. Here's your host, Dr. Steve Jackson.

Dr. Jackson:
Welcome to *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Steve Jackson, and joining us to discuss the newest treatment options for chronic spontaneous urticaria, or CSU for short, is Dr. Neil Bhatia. He's the Director of Clinical Dermatology at Therapeutics Clinical Research in San Diego, California. Dr. Bhatia, we appreciate you being here today.

Dr. Bhatia:
Well, thank you Dr. Jackson—Steve. It's a joy to be here to reach out to the listeners and talk about urticaria.

Dr. Jackson:
So to begin, we know that many patients with CSU are still symptomatic despite up-dosed antihistamines, and some still struggle after trying omalizumab. How have the newer therapies like remimutinib and dupilumab changed what you can offer those patients?

Dr. Bhatia:
We now have an era where we can actually stop the process before it starts. I like to use the example of turning off the faucet rather than mopping up the mess and chasing it. Antihistamines are helpful for symptomatic relief: reducing itch and mitigating the flares. But the era of omalizumab is now rising into what we've seen with the dupilumab approval and the approval of remibrutinib as a pill, something that's also very safe and proven effective in the recent trials. And then we have the development of barzolvolimab and several others that are in trials. I think we have a new approach, where systemic treatments and targeted treatments can really help patients get their quality of life back.

Dr. Jackson:
So these two agents, remi and dupilumab, work very differently from antihistamines and omalizumab, and from each other. Can you walk us through what makes each mechanism of action unique?

Dr. Bhatia:
Obviously, we're talking about mast cells. So in terms of the mast cell, if you think of where histamine lives, it's granules that live throughout the entire cell. They're not being pocketed or isolated anywhere else. It's the immediate release of histamine that causes the flare, as well as several other granules like bradykinins, serotonins, and other basal motor active peptides.

When you look at the periphery of the cell, there are multiple receptors that are triggered to start that process. They go by the names of IgE—which is the most common; that's the target for omalizumab—interleukins four and 13, which are the targets for dupilumab, and multiple other receptors, like TSLP. There are other interleukins, and several others that work with other cell lines, such as dendritic cells, which start the process, like the radar of the immune system. And there's some crosstalk receptors with eosinophils and several others.

So without getting too scientific, the point is that, when you have a target that blocks only the receptor, there's a thought that this may be an incomplete way of stopping the process, even though it's still very effective. But when you process the receptor binding of those proteins, they have to go inside the cell to go through a process of conversion, and that conversion protein is called Bruton tyrosine kinase, or BTK for short. And what BTK is trying to do is convert these active process compounds with phosphorus to make them active,

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so that they can create the granule release of histamine and keep the process rolling. So by going after the source, which is BTK, what drugs like remibrutinib and several others that are being looked at in trials can do is actually stop the phosphorylation from happening, which means that those compounded receptor-bound proteins cannot work. They basically cannot work to deliver histamine out into the skin, where granules induce the urticarial flare.

So my analogy of stopping the faucet or turning it off is actually where you see BTK being stopped from doing its job, and therefore, we could stop the flare or and perhaps keep it at bay.

Dr. Jackson:
Alright. Let's talk about the evidence for these therapies now. What stood out to you in the pivotal trial data for each, particularly in terms of how quickly patients responded and whether those responses were durable?

Dr. Bhatia:
Dupilumab came several years ago. The study was called LIBERTY, and there were three programs, one of which was a comparison of patients who had been on omalizumab and failed, and two others that were not, one involving six-year-olds and up. The one trial did not make its numbers. That was the one that was the omalizumab-exposed group. The other two actually did do well.

The nice thing about dupilumab is dermatologists have dupilumab in their office pretty typically for atopic dermatitis. So it's an easy reach to get patients started. For me, the mechanism is a little bit incomplete, because it only goes after the receptors of interleukins four and 13, and it might be a little bit of an incomplete approach. Some would say it works well. There are others who say they've had patients who flared. But it is a viable option and definitely FDA-approved for us.

The use of remibrutinib has some very rich data. The REMIX-1 and 2 trials, which is what they were called, were performed worldwide. The demographics actually showed that there were more females than males. Most of them were in their upper 40s. And there was an independent response whether they had been on omalizumab or not. So these are very important highlights to the demographics.

The data that shows us the most important outcome is the week one data, which was how quickly the patients responded, both with the control of their hives and itch. For me, that's a very significant marker of using a pill in the office and getting patients underway as fast as I can. The 52-week data for the REMIX trials was also very significant, and there was a very low adverse event profile. The only thing that was of measure was a few reported cases of petechiae and some mild bleeding. There was no real significant major bleeding or severe bleeding in the trials. But there was concern that petechiae may have developed, or even some ecchymosis. So there is a little bit of a disclaimer that everyone wants to make, and we talk to our patients about it if you see any bleeding signs. But you'll break down the data. There were patients with hemorrhagic uterine cysts, some with some nosebleeds, some with some very incidental findings. So I personally would just counsel the patients to watch, but it would not stop me from using this.

Dr. Jackson:
Can we tease apart the safety data between the two? Are there any particular monitoring steps or patient factors that clinicians should have on their radar before prescribing either one?

Dr. Bhatia:
When we're thinking about remibrutinib, there really is nothing to monitor. Now, I always make the distinction between lab evaluation and lab monitoring. Lab evaluation is what you're studying for the disease. You're working up your urticaria patients and trying to find the source. Typically, we get a CBC, a liver panel, and a comprehensive metabolic panel. We get a thyroid. We check under the hood to see if there's a source for urticaria, and we often get a chest X-ray to make sure there's no lymphoma or anything else.

Lab monitoring is, let's follow the drug. And what we found in the studies was there is no reason to follow the drug for any kind. There's no box warning on this medication, unlike the Janus kinase inhibitors for eczema. And there's really nothing in the blood counts or coagulation indices that show that they need to be followed. Personally, once I get these patients started, I don't want to see them back in a routine. I just want them to keep taking their medicines and getting better. So I give them that goal in mind. For vaccines, they can still take non-live vaccines, but if they're going to take a live vaccine, I give them a holiday and let them take two weeks, and then we get back on again.

Dr. Jackson:
For those just joining us, this is *On the Frontlines of Chronic Spontaneous Urticaria* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Neil Bhatia about advances in CSU care.

Can you walk us through your decision-making process? When do you reach for remibrutinib versus dupilumab, and where do they fall in your sequencing compared to omalizumab?

Dr. Bhatia:

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I personally do not have any phobias of writing omalizumab. I've successfully managed patients on omalizumab and had some good results with it.

That being said, I think we live in an era now where you just have to ask patients, "Do you want pills or do you want shots?" And you give them that decision tree. There are many who believe that they would rather get a pill going and start fast, especially when you talk about the speed of onset of the data. With dupilumab, there's the phenomenon of the dose every two weeks. And is it going to really hold the urticaria patient like it does the eczema patient? Obviously, the atopic dermatitis data for dupilumab speaks for itself. But for urticaria, it's a little bit different phenomena because of the different immune processes.

So for me, I'd probably lean more towards remibrutinib because of the speed of onset. I'm thinking in terms of daily dose that we can control. Patients could maybe take a holiday if they need to. With dupilumab, it's a little bit of a slower start, and it's a little bit of a slower reach to match the equivalence of what we see with remibrutinib. What I would start with is thinking of the patient experience. How do they do with antihistamines? What have they done? Have they been on omalizumab, and what is their preference?

Dr. Jackson:
And practically speaking, as in third-party payment, what are the hurdles in getting these therapies to patients? Are there any ways we can overcome those challenges?

Dr. Bhatia:
It's an important phenomenon in today's medicine. We grew up in a day where we wrote a prescription, and the patients got what they wanted, or what we wanted them to get. Now, we have hurdles of prior authorizations and a hub for the prescriptions that has to work with benefits and everything else.

I think, given the more emergent nature of urticaria and the quality of life detriment that the patients go through with flares, it's imperative on the clinician of any level and of any specialty to really tell the story as blatantly as you can about how the patient is struggling, how over-the-counter antihistamines are not the solution, and how important the recognition of this disease state is for getting the patient started. So that has to be in the clinic notes. Often, we extend that into the paperwork that goes to get the drugs covered. And the laboratory values or even a biopsy as needed would be helpful.

So that being said, proving the diagnosis helps—showing the lab monitoring and any evaluation that's done, and then just standing up for the patient to get their drug. Fortunately, I work in a place where I can use samples to get started. I show the clinical improvement, and I get on the phone with medical directors of insurance if I have to to tell these stories. But the bludgeoning of paperwork to get these drugs refused has to be matched with that much effort to get the drug started.

Dr. Jackson:
I understand that there are some other therapeutic approaches for CSU currently being investigated. Which ones are you most excited about and why?

Dr. Bhatia:
One of the drugs in motion is called barzolvolimab, which is an injectable. It's looking, actually, at a dosing strategy of every other month, which could actually be a very interesting, either as a starter or transition from some of the drugs that might be thought of as early. But barzolvolimab actually also has very good early onset data, so it's not a slow starter by any means. It actually works as early as week one, just like remibrutinib does. So it'll be interesting to see where this fits.

The other one that's being looked at very carefully is povorcitinib, which is probably going to make it to market for hidradenitis suppurativa before it does for urticaria. But the data for urticaria is still very strong. The early phase two results show some promise. It's a Janus kinase one and two inhibitor, similar to those that are on the market for atopic dermatitis, but it also has some really good activity with the way that it's the early process of urticaria. So it has some good mast cell activity and looks at eosinophils, B cells, and Janus kinase one and two in the type one and two side. So I'll be very interested to see where that fits.

And then there's some other molecules in trials that are early phase. I don't know if they'll actually come out, but they're very similar to remibrutinib in the way that they go after not only Bruton tyrosine kinase, but also several other similar enzymes in the approach. It's going to be very fascinating to see where these all work in the process.

Dr. Jackson:
Finally, if you can leave our listeners with one takeaway for the next CSU patient who walks through the door, what would it be?

Dr. Bhatia:
My biggest pearl to everyone is to just be aggressive. Don't be afraid of anything with these drugs when it comes to treating urticaria.

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You can only imagine how much these patients are suffering between lack of sleep, the fear of the next flare, and the quality-of-life issues. I think we really just have to put our foot on the gas especially as dermatologists. We have to take full account of these patients. These are our patients. We don't have to automatically punt them over to the allergist to get some mystical lab panel or some testing that doesn't exist.

I've spoken to several allergists, and they ask me, "Why are your colleagues so afraid to treat hives? There's nothing we're doing that's a magic wand." And I try to teach that as much as I can to my dermatology colleagues, and hopefully they stick with it.

The other part of the equation is just to make sure the diagnosis is clear, and make sure we're not missing urticarial vasculitis or mastocytosis, because those can be very serious down the road if they're progressing. And also just do the workup carefully. Don't just label someone as chronic spontaneous because we haven't done enough workup. A mediastinal mass that hosts the Hodgkin's lymphoma can easily present as urticaria. It's the same with several different blood disorders, thyroid diseases and anything else. So do the workup carefully, but there's no need to follow labs on any of these drugs. I would get them started as fast as we can and get them out of their own way.

Dr. Jackson:
And with those valuable insights in mind, I want to thank our guest, Dr. Neil Bhatia, for joining us to talk about remibrutinib and dupilumab for CSU. Dr. Bhatia, it was great having you on the program.

Dr. Bhatia:
Thanks, Steve.

Announcer:
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