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IL-31 in Atopic Dermatitis: Targeting the Itch Cytokine

Announcer:
You're listening to *DermConsult* on ReachMD, and this episode is brought to you by Galderma Laboratories. And now, here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *DermConsult* on ReachMD. I'm Dr. Charles Turck, and joining me to explore the role of the interleukin-31, or IL-31, cytokine in atopic dermatitis is Dr. Peter Lio. He's a Clinical Assistant Professor of Dermatology and Pediatrics at Northwestern University Feinberg School of Medicine and a dermatologist at Medical Dermatology Associates of Chicago. Dr. Lio, thanks for being here today.

Dr. Lio:
Thank you so much for having me.

Dr. Turck:
Well, to start us off, Dr. Lio, what is IL-31, and what role does it play in driving chronic itch in patients with atopic dermatitis?

Dr. Lio:
IL-31 is fascinating. Sometimes it's referred to as the master itch cytokine, and it really does seem to play an important role for itch. What's remarkable is that it is actually secreted by a number of different cell types, and it also has receptors on a number of different cell types, including immune cells, but also, most importantly, on neurons. So it can be a very direct signal for itch in the nerve endings in the skin. But of course, that's not all it's doing. It also plays a role in inflammation and fueling the immune response, and remarkably, there's also receptors on fibroblasts, so it seems to be playing at least some role in the skin barrier and collagen remodeling. And we see this, particularly, in some of the chronic changes like we might see in prurigo nodularis or some of the thick, lichenified skin of atopic dermatitis. So it's interesting that it is a separate concept from the IL-4 and IL-13 that we know a lot about, but it also seems to be playing a really important role in this itch, inflammation, skin barrier, and remodeling pathway.

Dr. Turck:
And as a follow up to that, how does IL-31 contribute to the inflammatory cascade in atopic dermatitis?

Dr. Lio:
It's funny because it's easy to dismiss the inflammatory aspect of it. You can focus just on the fact that it's driving itch. But yes, it really does seem to very much play a role in inflammation, and it seems to be part of this TH2 pathway of inflammation driving some of the same kinds of inflammatory mediators that we might see with IL-4 and IL-13. And in fact, it seems like in some ways, IL-31 is a downstream effect from IL-4 and IL-13 that is also feeding back into driving inflammatory cells.

We're all trying to figure out, to some degree, is there one or the other that's predominant? But it really doesn't seem to be the case. It seems like these guys are all playing a role in inflammation and you can modulate it a number of different ways. I often talk about this idea of a diagnosis ex juvantibus. You know what something is by what actually helps it. And what's remarkable is that we've seen that blocking IL-4 or IL-13 alone with a cytokine blockade can help a lot of patients with atopic dermatitis. But now, we really have evidence that has passed some of the most difficult, most rigorous testing through the FDA, and we can see blockade of the IL-31 receptor also results in improvement—not only in itch, but also in inflammation.

Dr. Turck:
Now, what does the evidence tell us about IL-31 signaling as a potential therapeutic target?

Dr. Lio:
The evidence shows us that it can resolve this inflammation pretty quickly and durably for a number of patients. One of the fascinating things about the IL-31 receptor alpha inhibitor that we now have in the United States—this nemolizumab, which is really exciting. We've known about it for quite some time, and remarkably, it's been out in Japan and maybe some other markets under a different name, but the same compound. Nemolizumab is the same monoclonal antibody that's blocking. So we actually have maybe a little bit more evidence than for another new medication that just came onto the market. We have some real-world evidence.

And what we see is that it really is effective for not only the itch component of atopic dermatitis, but really for the inflammatory aspect as well. And that alone is proof that we often talk about atopic dermatitis as the itch that rashes, and it's been this age-old concept that if we could just block the itch, would that completely heal the skin as well? And the science tells us that it's probably not that simple, that for some patients at least—and again, it might be that there are different subtypes within this condition, and that's one of the most exciting things, thinking about how we can better personalize or go towards precision medicine for individuals. But globally speaking, the itch often is one of the triggering events for inflammation and can result in this cycle, but inflammation by itself really does seem to be in an imbalanced state; there's an increased number of these inflammatory cells in the skin, and a number of inflammatory cytokines are elevated. Thus, when we block them, we really can see both itch improvement, and that's part of it, but also, very direct decrease in the inflammation even with this IL-31 pathway alone. And that's pretty exciting.

Dr. Turck:
For those just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Charles Turck and I'm speaking with Dr. Peter Lio about the role of IL-31 in driving chronic itch and inflammation in patients with atopic dermatitis.

So, now that we understand the pathophysiology behind IL-31, let's discuss the implications for clinical practice. Dr. Lio, how can we implement IL-31-targeted therapies into our management approach?

Dr. Lio:
Well, I'm so happy to say that we finally actually have a specific drug that will allow us to specifically target IL-31, and it does so by being a fully humanized monoclonal IgG antibody that binds to the IL-31 receptor. And as we discussed, that receptor is present in a number of different places, some of which we know. For example, the nerve endings, those sensory nerve endings—some which I think are a little bit surprising, like keratinocytes, macrophages, basophils, eosinophils, fibroblast—it's fascinating to see how many cells actually do have a receptor. So by blocking that, we really think we're affecting these neuroimmune mechanisms that are part of this.

And the beautiful thing about this practical aspect is that it's a biologic agent that's injectable. It's once monthly for everybody from the start. But what's remarkable is that after about four months or 16 weeks, patients who are doing well—if they've achieved the appropriate clinical response, if they're happy, and we're happy—we can then space it out to every eight week dosing. So every other month for atopic dermatitis. And that's also really freeing and really exciting for patients who maybe don't like needles or don't want to be beholden to an injection every two weeks, or even every month.

Being able to space it out makes it very, very easy. And what's nice is that it's in a well-tolerated formulation. Part of the magic about this particular formulation is that it's stable as a powder. In fact, it's stable at room temperature for up to 90 days, which is unique among the biologics, to my knowledge, at least with an atopic dermatitis. And presumably, you should refrigerate it, of course, but it can stay at room temperature for 90 days, presumably because it's a solid. And when you activate the little mechanical pen, it actually mixes it right there with some water. And then you give it a good shake, let it settle, and inject it right away. So, practically speaking, once-monthly dosing and then the ability to spread out every two months is really wonderful.

And then the subtleties of it, which are kind of neat, are that it can stay at room temperature for 90 days, it is very well-tolerated by patients, and one of the little things you might not hear about until you've done it—and I've been lucky enough to actually administer the loading doses to a number of patients now—it's a very small volume. It's only about 0.4 milliliters, and the other biologics that we're used to for atopic dermatitis are about 2 milliliters, so this is a fraction of that. And for whatever reason, it does not seem to hurt very much at all. Many of the patients have told me that they didn't even feel it going in, which is really exciting.

Dr. Turck:
And would you tell us how addressing IL-31 signaling could impact patient's qualities of life?

Dr. Lio:
With nemolizumab, we can see a really impressive impact on sleep and on quality of life—all of these important secondary impacts. In a clinical trial, of course, they tend to be looking at very objective things like the Investigator Global Assessment and the Absolute Peak Itch Score, and of course, the EASI score, the eczema area and severity index. But I really love the fact that there are a lot of these patient-reported outcomes, and increasingly, they're being discussed to look at quality of life. I'm very happy to say that not only do we

see it in a relatively short term, but even over the medium and longer term. When we look at one year and even two years of data, we're beginning to see these signals that it has a lasting impact on quality of life for these patients who respond and does so with a really favorable long-term safety profile.

Dr. Turck:
As we approach the end of our program, Dr. Lio, do you have any final takeaways you'd like to share with our audience?

Dr. Lio:
Only that just a couple of years ago I felt so alone and so completely flummoxed with these severe atopic dermatitis cases that I was seeing, and I had essentially nothing that was FDA approved. We were using all these medications off-label. We were hoping for the best for everybody. And I remember just feeling defeated and then, all of a sudden, we got our first biologic in 2017, and that changed everything and opened the door. And here we are, just a few years later, and we're in the midst of a revolution. All these incredible, different, unique options. And so, for the first time, I feel I can sit down with the patient and say, "Okay, you have been miserable, you have tried a bunch of topical agents. Maybe you've even been on prednisone multiple times. It is time for something different, and I'm so happy to tell you that I don't have just one thing to offer you, I have a number of things. And they're all a little bit different and we can explore them. Also, beautifully, if one doesn't work or doesn't fit for you for whatever reason, we now finally have something to fall back on." And that, more than any other message I can give, is really the key one—there's hope and new options for patients who've been long-suffering. And I really hope people can come out and ask about these new options and see if they're a good fit for them.

Dr. Turck:
Well, with those final and truly inspiring insights in mind, I want to thank my guest, Dr. Peter Lio, for joining me to discuss the pathophysiology behind IL-31 in atopic dermatitis. Dr. Lio, it was great having you on the program.

Dr. Lio:
The pleasure was mine.

Announcer:
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