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Overcoming the Challenges of Atopic Dermatitis Treatment

Dr. Walker:
Welcome to *DermConsult* on ReachMD. I'm Dr. Robert Walker, and joining me to discuss the difficulties of treating atopic dermatitis is Dr. Peter Lio. Dr. Lio is 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, welcome to the program.

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

Dr. Walker:
To start our discussion, Dr. Lio, what makes atopic dermatitis particularly challenging to treat compared to some other skin conditions?

Dr. Lio:
It remains one of the most challenging things. And it's funny; it actually has a reputation historically for being difficult to treat. There's this incredible transcription of an oration from 1850s where they're basically pointing out that it is one of the most challenging things in dermatology, and it pushes clinicians to their absolute limit. I think there's a number of aspects of it. First of all, it's probably not all one disease. We, at this point, lump everything together because we do the best that we can given the tools we have, but I think there really is going to be a breakthrough—hopefully, in our career in the next 5 or 10 years where we're going to be able to better subtype these differences that occur between individuals. For example, we think some people primarily have a barrier deficit. There's some problem with the skin barrier, probably a big genetic component; although, now we've identified a number of environmental components. Other people seem to begin with more of an inflammatory or immune dysregulation issue. So at the very least, there seems like there are a couple of subtypes, and we really do need to get this better in terms of personalized medicine.

The other piece is that it is a disease of vicious cycles. So I think as it runs its course, it continues to go faster and faster around that cycle. It strengthens itself with the itch-scratch cycle, with the dysbiosis of the microbiome, with the barrier damage. And then there's a whole behavioral piece that happens, and this is for both kids and adults. If your sleep is disrupted for months or even years, you become different state; everything starts to kind of change. So it takes some time and energy to push back against what I like to call the pathogenic pillars, to push back against the inflammation, the itch, the barrier problem itself, the dysbiosis and the behavioral piece. All of these pieces have to get righted before we can get there, so this makes for a really challenging condition for patients and families.

Dr. Walker:
You mentioned the genetics and environmental factors. Could you touch a little bit more on how they play a role in the development and the persistence of atopic dermatitis?

Dr. Lio:
I think we have lived through the phase where we really began to understand that there was a genetic basis for a lot of diseases, and that was exciting. Even when I was in medical school, there was the thought that, "Wow, we're going to find the genetics for everything, and we're going to understand all of disease," but it dried up after a certain point. The easier, more genetically predisposed conditions, they were sort of picked off early. It was like, "Aha, here's the one gene, the one protein. This is a deficit; we can figure this out to some degree." And then we were left with a whole host of conditions that really didn't quite fit into that rubric.

But there are some genetic issues that we see with atopic derm. The most famous, the one that I often talk about as being the breakthrough for understanding, was the gene called FLG. It encodes for a protein called filaggrin, and filaggrin plays a number of roles. It not only is playing a role in the structural strength of the skin—it actually helps build the barrier—but Mother Nature is so magical,

when it breaks down, it becomes a part of natural moisturizing factor, and that allows us to keep water deeper in the epidermis. And it also has a role in regulatory effects of certain enzymes, so it's an amazing thing. And it turns out that there definitely is a group of patients who have this deficiency, usually a mutation in FLG, and they are at much, much higher risk for atopic dermatitis. In fact, as far as I understand it, it is the single highest known genetic risk factor.

But with that being said, it only explains a pretty small minority of patients. And in fact, depending on where you go in the world—a lot of the original work for this was done in Northern Europe, there it's a little bit higher—as soon you leave that population, it turns out that it seems to be barely affecting most of the other populations around the globe. So that's part of the story and at least gives us some insight—maybe there are people that have a genetic barrier defect, and that makes sense, and then the environmental things have really been kicking off in the last couple of years.

And I have to say, Dr. Ian Myles—he's an allergist at the National Institutes for Health on the East Coast—he has done some really groundbreaking work looking at some of the pollutants. And in fact, it turns out that there is a chemical called isocyanates, or diisocyanates more specifically, that are found in wildfire smoke, are found in certain exhaust from some vehicles, are found in some volatile organic compounds, off-gas paints and different chemicals. And it turns out that these are incredibly toxic to our microbiome and to our skin barrier, and we've seen this connection. People that are exposed to more of these chemicals—again, if you're in the wake of the wildfire smoke, you have a much higher rate of developing atopic dermatitis. And this is now starting to unravel an environmental cause for many patients, which is both really exciting and also kind of chilling that that's part of why we're seeing such a huge uptick in atopic dermatitis in the past few decades.

Dr. Walker:
So moving into the clinical realm, can you tell us about the challenges of managing long-term atopic dermatitis in both pediatric and adult populations?

Dr. Lio:
We often talk about the goals. First, we have to get somebody clear in the first place. That's the first hurdle. The second hurdle is keeping them clear safely. And then the third hurdle is making sure they can keep up whatever regimen or treatment protocol that we have them doing. And it turns out all of these are challenging. The first hurdle is usually something we can take care of. For almost every patient that I see, I can get them better briefly. I can do intensive topical therapies. I can do wet wraps. Of course, we have powerful systemic agents that are very effective. The problem really is that second hurdle. Can I keep you better safely over time? And that really is a challenge because it turns out a lot of our most powerful treatments, they work great in the short term, but they're not ideal for long term.

So I'll give you an example that I see literally every single day that I'm in clinic: a patient who says, "You know, Doc, they gave me this topical steroid, and it works great when I put it on. It clears me up pretty quickly. Within just a few days, I'm better. But then they said, 'Don't use it all the time.' And the thing is, as soon as I stop, basically the next day I'm flaring up again. So what can I do?" And that's a good example of a situation where the correct answer is definitely not to keep using the steroid without a break because we know that not only can damage your skin, it thins the barrier, can lead to permanent changes like stria, the stretch marks on the skin; but also, some people, especially kids, can absorb a lot of that and start getting systemic issues, so it's absolutely not right to just abuse and overuse topical steroids.

But what I find is a lot of patients are told that over and over and over. Sometimes they'll see three or four people before they get to me, and we're working really hard to dispel that myth that that's not the only thing we have. We have other things. And for a patient like that, then we need to start thinking outside of the box and talk about our nonsteroidal agents. We start talking about our systemic therapies. That could be everything from phototherapy—we use narrowband ultraviolet B—all the way up to our biologics. We now have three biologic agents in atopic derm, which is fantastic, our oral JAK inhibitors, and then we even have our legacy treatments, which are sort of the immunosuppressants, like cyclosporine and methotrexate. So we have all of these things. And then if you see someone like me, I'm also integrative-minded, so I'm interested in things like acupuncture and hypnosis and mind/body therapies and natural treatments, so I'll try to bring some of those in for the patients who are up for it. Some patients are; some patients aren't. But I'll offer that as some things we can do as well, and it really is something we can do for most patients. We can get most patients better.

But that being said, it does take a lot of work. It takes some shared decision-making of figuring out what's the best way forward, and it also really needs some anticipatory guidance, because these more powerful systemic treatments, they do have side effects like any medicine, right? It's crazy to say, "Oh, it's totally safe," right? There's no such thing. Even water, the gift of life, is not totally safe. You can drown in it. You can overdose on water, so we have to always remember those risks and benefits for everything that we do.

Dr. Walker:

For those just tuning in, you're listening to *DermConsult* on ReachMD. I'm Dr. Robert Walker, and I'm speaking with Dr. Peter Lio about treating atopic dermatitis.

So, Dr. Lio, we spoke a bit earlier about the challenges associated with atopic dermatitis, but now let's discuss how we can better care for these patients. What roles do diet, allergens, or lifestyle modifications play in managing atopic dermatitis, and how do you incorporate them into your treatment plans?

Dr. Lio:
The truth with the diet and lifestyle modifications is one of those difficult truths to hear, I think, that the answer is probably somewhere in between, that they're the secret of everything, and all you have to do is cut gluten and dairy and you'll be cured, and the other extreme, which is "Ah, it's a bunch of baloney. It doesn't do anything." Right? So the truth, like a lot of things, is a subtle balance in between, and it depends on the patient. I will say that if you look in aggregate as a group, the patients that I see with moderate and severe atopic dermatitis, many of them, if not—honestly, in my clinic, most of them have done some really intensive dietary changes. They have tried extreme diets. They have done it in good faith. They've often had a number of different people that they've seen from dieticians, nutritionists and naturopaths sometimes who will counsel them to do things. And I can just tell you, the school of experience is that for these patients, it really has not been enough to move the needle, and that's important to know. So that does not mean it doesn't work for somebody. It just means that I can say with 100 percent certainty that it doesn't work for everybody because I meet those patients every day, and that's hard.

It's also hard because our society sometimes will put some pressure on them and say, "Well, you know, they're pushing all these medicines on you, but if you just cleaned up your lifestyle and did a little bit better and maybe started doing some yoga, you'd be clear." And what I respond to my patients is, "I wish that were the case. And I'm more than happy for you to eat well. I want you eating healthy because there's no doubt if we eat crummy foods, if we eat processed stuff that has a high glycemic index, for certain people they have, of course, sensitivities within their diet, things that clearly make them worse, obviously, that's gonna make you worse, but it does not follow that if we get you the cleanest diet of all time. That may not be the whole story." And in fact, again, for most of my patients, it's not. So diet and lifestyle are really important, and we'd be foolish to totally disregard them, but it's also important to do good anticipatory guidance. If patients want to try it, by all means they should, and they should be eating well and taking good care of themselves. That's going to be part of it no matter what. But don't be discouraged if that's not the whole story.

And the other piece I'll put to that is that even if I'm using a powerful medicine, I want them eating well; I want them taking care of themselves; I want them getting good sleep; I want them working on their stress; because at the end of the day, all of these pieces are going to be helpful. And my goal is not to be on a powerful medicine forever, that we often say that these are not going to be for your whole life, that we are going to try to get you better, break those vicious cycles and get it to the point where we can start removing some of these more powerful treatments so that you can be on as little as possible and as healthy as possible, such that I'm in the rearview mirror. If I'm doing it right, you'll just say, "Boy, that dermatologist was great. He really helped me when I needed help. What was his name again?" I don't want to be necessarily having to be part of their everyday life. I want their skin to be in a good place so that they can go live their life.

Dr. Walker:
So you mentioned therapeutic options earlier. In your perspective, how have you seen that landscape develop over the past decade?

Dr. Lio:
It has been absolutely crazy over the past decade. If you talked to me in March of 2016, I would have said we have essentially nothing. Well, fast-forward one year. In March of 2017, we got our first biologic agent—that was dupilumab—and then it sort of opened the gates. We suddenly had a pipeline. We suddenly had some new understanding. We suddenly had all this interest in atopic dermatitis, and we were like, "Finally." So we got some people to bring us some new ideas, and of course, we have now three biologics. We have dupilumab, tralokinumab, and lebrikizumab. We have two oral JAK inhibitors indicated for atopic dermatitis and approved in the US. That's abrocitinib and upadacitinib. We have some new topicals, a topical JAK inhibitor, and that's topical ruxolitinib, and a new topical phosphodiesterase 4 inhibitor, topical roflumilast. So it is a bonanza. And we also have a huge pipeline.

Dr. Walker:
Before we close, Dr. Lio, is there anything else you'd like to share with our audience today?

Dr. Lio:
I would just share that for the patients who are struggling, they are not alone. I'll see patient after patient after patient, I'll go room to room to room, and each patient feels totally alone. They feel like they've been singled out. And I always wanted patients to be able to get to know each other and see that they're not alone, that lots of people are going through this journey with them. And I will put in a

plug for the National Eczema Association, a wonderful national nonprofit organization that is focused on patient support. Disclosure: I'm a board member, but I am not paid. I am a proud volunteer and a donor to the NEA, so I do not get any money from them, but I do give money every year, probably because I think they're really trying to bring patients and families together. They do a lot of educational outreach. And just at the very least, tell your patients about it so they can see, hey, there are some more resources, there are some more ideas, and there are people who are really trying to get them better from all angles, not just pushing medicines, even the quirky people like me who are interested in the natural therapies as well.

Dr. Walker:
With those key takeaways in mind, I want to thank my guest, Dr. Peter Lio, for joining me to discuss unmet needs in treating atopic dermatitis. Dr. Lio, it was great having you on the program.

Dr. Lio:
The pleasure was mine.

Dr. Walker:
For ReachMD, I'm Dr. Robert Walker. To access this and other episodes in our series, visit *DermConsult* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.