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## Advances in the Management of Moderate-to-Severe Atopic Dermatitis

Dr. Leo:

The past few years have brought changes to how we understand and treat atopic dermatitis, changes which have ushered in questions such as: What is the atopic march, and can it be prevented? How and when should a biologic be used for eczema? And what about in infancy? And what treatments are currently in the pipeline?

Hello, I'm Dr. Peter Leo, and I'm joined today by my colleagues, Dr. Eric Simpson and Dr. Mark Boguniewicz, in today's program to discuss these challenging questions. We also have Pam with us. Pam is a nurse, but also a patient of mine, who's joining us today to share her journey with atopic dermatitis.

Dr. Boguniewicz, maybe you could start us out by explaining to us: What is the atopic march, and how do you think about it in your practice?

Dr. Boguniewicz:

Sure, Dr. Leo. The atopic march is the progression of several diseases, typically starting with atopic dermatitis followed by food allergies, asthma and allergic rhinitis, and some would even consider eosinophilic esophagitis as a late manifestation of the atopic march.

Dr. Leo:

Pam, maybe you can make it real for us. Do you feel that you had any experiences with the atopic march? Do you feel you have other conditions that were related or connected with your eczema?

Pam:

Well, my eczema obviously has been since I was 6 months old. I had no food allergies that I know of. We did do the whole thing, the whole testing of different foods, trying different foods. Nothing really came up to be allergies for me in that sense, but I did have the seasonal allergies. I was allergic to dust and I was allergic to... I had hay fever when I was young, the green grass, as plants were dying in the fall, so my allergies were year-round, so that really made my skin much worse throughout time, and I'm 64, so it was a process.

Dr. Leo:

Interesting, so no food allergies or asthma but definitely some other things like rhinitis and maybe even the seasonal allergies with eye involvement as well.

Pam:

Right.

Dr. Leo:

Dr. Simpson, when you think about the pathophysiology of atopic dermatitis, we've come a huge, huge way from where we started, even 10 years ago. What do you think about how our understanding is shaping the ability to develop new treatments?

Dr. Simpson:

Yes, so we're realizing that all inflammation in the skin is not the same, so patients with psoriasis have a certain type of inflammation in their skin, which is completely different than patients with atopic dermatitis. Patients, and dermatologists who treat psoriasis, have been fortunate. They have understood these molecular pathways; they have been able to block those pathways and actually bring patients with severe psoriasis a lot of help. There's maybe 7 or 8 targeted treatments for psoriasis right now, and patients have really done well with those. In atopic dermatitis, we haven't had those. We haven't had those targeted approaches. So, we're starting to understand that the inflammation is different. It's more of what we call a type 2 cytokine disease, and so we're understanding it's a different molecular pathway, a different communication pathway, and we'll be talking about how we target these type 2 cytokines to help this condition.

Dr. Leo:

It's amazing, because we really see that the development of therapies goes hand in hand with an understanding of the molecular mechanisms of a disease, and we've had such a dearth of knowledge about what's truly driving it, we haven't had good targets, but finally we're getting there.

Dr. Boguniewicz, when you think about moderate to severe atopic dermatitis, which is a group that really suffers... If you're on the milder side, some of the basic things like good moisturization or topical corticosteroids, they can give a lot of relief, but as you get more functionally severe, maybe it doesn't even necessarily look bad, but as you're more refractory and not responding, we really have needed some help there. Has your approach changed in recent years, or what have you begun to use more recently to help with those more difficult patients?

Dr. Boguniewicz:

Right, so for sure our approach has changed or has evolved based on some of the exciting work that has come out in the understanding of the disease, and there is so much in that. It's so easy to say topical steroids have been the key topical that we've been prescribing for over 50 years, but with that message comes the important thing about discussing the risk/benefits, because if we don't do it, patients go out and find that information on the Internet or from other sources, and then that leads to all sorts of misunderstanding. Then we find out that patients are hesitant to use those medications, for example, even during a flare, and so we're always chasing after that inflammatory process has already started.

Going beyond topical steroids, for close to 20 years now, we've had topical calcineurin inhibitors that are approved in this country down to 2 years of age. The problem is that they carry this boxed warning that is concerning to our patients and their families, so again, we need to educate them about the risks/benefits. And most recently we've had crisaborole, a topical PDE4 inhibitor for patients with mild to moderate disease. So, if that still isn't sufficient at that moderate to severe end, or the patient just needs to be putting on these ridiculous amounts of topical medicine—that's just not practical, especially if you get to school age or older patients

Dr. Simpson:

Or overuse.

Dr. Boguniewicz:

Of course—then we think about systemic drugs. Now, the irony here is that the only ones that are approved in the US are systemic steroids, and yet, that is a class of drug that we are strongly advising patients not to use or to really minimize their use. All of the others, including cyclosporin, methotrexate, mycophenolate, azathioprine, are not indicated for atopic dermatitis for any age, and yet, we've been forced to, over the years, to use those; but again, there you have to have a serious discussion about risks versus benefits.

Dr. Leo:

Now, Pam, when you think about these, you've actually experienced them as a patient.

Pam:

Yes, absolutely.

Dr. Leo:

Can you tell us, how did they work for you? What was your experience?

Pam:

Well, I mean, when I was younger, we only had the ointments. That was it. You only had the topical things. You could soak in Domeboro, you'd wrap up in plastic, and, you know, they helped a little bit, helped the itch a little bit, but if I was in major problems and just itching, I would be—go to the ER, get some Benadryl, start on prednisone. That was the end-all be-all to clear up. And you know as well as I do, then you flare afterwards if it truly is going to continue.

Now, I finally realized that prednisone wasn't going to help anymore. I needed something more, so I finally... And I think the dermatologists that I saw were not comfortable with—they didn't understand the process, and it was frustrating for them I'm sure too, but there was never a plan of care. Do the ointments, whatever. Nothing really helped, so I did research and I found an atopic dermatitis doctor. Dr. Leo took me on as a patient. Thank you. And we went through the whole gamut of things. You know, I did the bleach baths, the wrapping up with the ointments and everything, and I just said to him, "There's got to be something more." So we did the cyclosporin. I broke out into infections. That didn't work for me. Methotrexate, you know, my cholesterol went up, but my skin didn't get any better. Then I was on the apremilast. I think you pronounce... I don't know if I pronounced that correctly, but that I had weight loss, which I loved, but the skin didn't get any better. So I went through all these, and I'm like, "I need something. Nothing... You know, this itch is driving me crazy." It's all about the itch, the non-sleeping, not being able to do the things you love to do, so those are the frustrations.

Dr. Leo:

Thank you, Pam. Dr. Simpson, what about the shift from systemic immunosuppression—we heard from Pam sort of how when you just shut down everything, you can have the risk of infections; of course, none of these drugs are labeled—to now what we're seeing as more targeted therapy?

Dr. Simpson:

Sure. Yes, I think the nice thing about what we were talking about, the pathophysiology and kind of better understanding these immune circuits, is that we can now identify what are the most important cytokines and inflammatory pathways to target. And so, there is a new drug that's FDA-approved for atopic dermatitis in adolescents and adults for moderate to severe disease not responding to topical therapy and who are candidates for systemic therapy, and that's dupilumab. And we talked about Th2 cytokines and type 2 cytokines, and it turns out that dupilumab targets IL-4 and IL-13, and those are 2 very important cytokines that are overabundant in the skin of patients with atopic dermatitis, also overabundant in the blood, in the system in patients with atopic dermatitis. And so, fortunately, that has now been targeted, and patients are really getting significant relief. We did some of those studies, phase III studies of dupilumab in adult patients, and when I talk to my patients about the data, I say, "You can expect about a 70–80% reduction in your atopic dermatitis," which is on par or much better than any of these traditional systemics that we've been using. And you can also... I tell my patients, "Even without the use of topical steroids, that you can expect over a 50% reduction in

your itch level as well.” So, in my practice, the addition of dupilumab has really changed my practice, changed my patients’ lives, and has been just a great addition as an option for these patients who are failing topical therapy.

Dr. Leo:

So, by being targeted and just really picking on IL-4 and IL-13, it has a very different side effect profile than the traditional immunosuppressants, but it’s not free of all side effects. What are you concerned about, or what are you counseling your patients about?

Dr. Simpson:

Sure. I’d say the 2 most common and what I counsel my patients on is the development of conjunctivitis, so that’s irritation of the conjunctiva, so patients... This occurs maybe in 10–20% of patients. In some of the clinical trials that are in clinical practice... Some of the studies from clinical practice show that number may be a little bit higher, maybe even 20–30% of patients. And the symptoms of conjunctivitis from dupilumab range, but they can often be dry eye, a little bit of redness and irritation, sometimes tearing, but in the trials so far, most of those—most of that conjunctivitis is mild to moderate, and most actually resolved while the patient was still on therapy. I would be interested to hear from Pam if she had experienced anything like this on your treatment.

Pam:

Well, I did have the dry... I’ve been on dupilumab now for 2 ½ years—no, 2 years, just over 2 years probably—but I do have the dry eye, but I think that keeping up with it and realizing that you’re going to need more drops, you just stay on it, especially after the injection. You know that that’s going to be time when it’s going to be higher, so I do the drops every couple hours. I just take them with me and do the drops because I’m not going to get off dupilumab, no.

Dr. Boguniewicz:

Can I just interject? That’s an interesting observation because dupilumab has now been studied and approved in both asthma and chronic rhinitis with sinusitis and nasal polyps, and in those diseases you don’t see that frequency of conjunctivitis. We know that a number of our patients start out with conjunctivitis, but I think what Dr. Simpson and what you, Pam, have described is really a real phenomenon that we see in atopic dermatitis.

Dr. Leo:

Thank you. Pam, so you had, as you’ve described, experience with dupilumab for the past couple of years, but before that, you even got to try tofacitinib, or tofa.

Pam:

Yes. Thanks to you, yes, I was able to do that, which...

Dr. Simpson:

What was that like?

Pam:

The tofa at least took the itch away. I mean, I think if you know your patients, it’s all about the itch. You cannot live with that itch. Just think of one little mosquito bite. Think of that all over your body. I mean, it’s just amazing that it just takes everything away. It’s just all about the itch. But the tofa did take away the itch, so I was relieved. I just realized that it took that away, but it didn’t clear up my skin, so for me, I mean, that’s been a godsend. The dupilumab has made my life so different. It really has. I mean, my skin is... While it’s not perfectly clear—and I still want it to be perfectly clear, so I still am looking for the perfect drug—at least it’s something that was for our disease. It’s been terrible that we’ve had nothing except ointments. Now we at least can see the future of other things to try that are going to work with you. So, I don’t have the sleepless nights. I’m not scratching all the time. And I don’t care if I have to do a shot every day. To get the relief that I got is great.

Dr. Leo:

What about some of the other JAK inhibitors that are being developed and some of the other antibodies in biologic therapies that are

in development?

Dr. Simpson:

Yeah, I mean, Peter, you've been—it seems like you all have been on the forefront of trying new things and trying targeted therapies. Tofacitinib is a JAK inhibitor, which is a really exciting area of development. So, I'll start with the targeted therapy. With the advent of dupilumab and by blocking IL-4 and IL-13, now we understand that those are really important cytokines to the disease, and so other companies and researchers are trying to say, "Hey, what about if we just block IL-13 alone?" And so there are 2 drugs, trailakinumab and lebrikizumab, who target only IL-13, not the IL-4 and IL-13 like dupilumab, and they have positive responses in their early studies, and they are in the last phase of studies, so it will be really interesting to see if they can get the same efficacy that dupilumab has with maybe fewer side effects or a different dosing strategy. Other possible cytokines that have been targeted, IL-31, which is the itch cytokine, that's also a type 2 cytokine. It's an interesting molecule. The receptor for IL-31 is on the nerves, actually, and we call it the itch cytokine, and the early studies have shown it has really significant and rapid reduction in itch. I think the outstanding question is: How much is it going to help the rash part of the disease? And then other targeted therapies... Your skin, actually, is also a source for cytokines, and so there are some phase II studies to show that these more proximal or more upstream cytokines that can begin inflammation—that we are starting to target those and seeing some interesting effects, such as TSLP, interleukin 33 and interferon alpha. So, those are the targeted... That's what I think is really interesting coming down the pipeline.

You mentioned tofacitinib. You've been on tofacitinib. This is JAK inhibition.

Pam:

Mm-hmm.

Dr. Simpson:

And those are the nice thing about JAK inhibitors is that they're oral, so you can take a pill instead of a shot. And they actually don't block the cytokine, but they block the cytokine signal within a cell, so they go into the cell and can block how the cytokines talk inside the cell. And there are actually 3 companies in phase III looking at oral JAK inhibitors for atopic dermatitis, moderate to severe, and they're actually very interesting. The data really support your experience in that they have rapid itch reduction and really significant reduction in atopic dermatitis.

Pam:

I'm so glad that we're doing things for adults, but what are we doing for infants and children?

Dr. Boguniewicz:

It's interesting that and certainly gratifying that the companies that are developing the new treatments are looking at younger populations because so many of the drugs previously were studied in adults with recalcitrant, severe disease. Maybe the right population is a younger population that's not necessarily gotten to that really severe phase of the disease, so we need more studies. And since we've discussed dupilumab here, we recognize that we need to be going into a younger patient population. So, while it's currently approved down to 12 years of age, we have done studies in children with severe atopic dermatitis down to 6 years of age, and hopefully, that data will lead to an FDA indication, but there are studies going down to infants as young as 6 months of age, which is pretty remarkable.

So, I'd like to ask Dr. Leo, I know that you've recently published a case series on the off-label use of dupilumab in a pediatric population, so, can you share those results with us?

Dr. Leo:

Absolutely. You know, they were all situations where we felt we had exhausted everything, and unfortunately, you can get to that point pretty quickly because there are very few things approved for these moderate to severe kids, so we did sort of the next natural step, which in pediatric dermatology, frankly, we're pretty used to doing. We take things that are indicated for adults and try them in kids after having a long discussion with the family. These are, again, kids who had failed a lot of the traditional things, and the family felt the quality of life was at such peril that doing something like this was worth the risk, and I'm happy to report that it was, as you

might hope, very similar to what we've seen in the adolescent study and the adult study. They all kind of nicely mirror each other, really nice improvement, relatively nice safety profile, obviously in a very limited cohort. So, to me, it's more of the promise that this makes sense for this group of patients who is certainly underserved, who certainly suffers a lot. Of course, the whole family suffers. When the patient is not sleeping, nobody sleeps, so we really feel we can help a lot, and I'm excited that there finally are some studies and that there is some push from the FDA to get these medicines to people who need them, because we know at the end of the day, this is still largely a pediatric disease, so if we're only looking at our adults, that takes care of them very nicely, but there's still a huge group that needs help.

Dr. Boguniewicz:  
Mm-hmm.

Dr. Leo:  
Dr. Simpson, what about the psychosocial aspect? We talked about the sleep ramifications on everybody, but we know that ripples out even further. There's a tremendous amount of interplay between this. How do you think about that?

Dr. Simpson:  
Yeah, I think you have to think as a dermatologist beyond the skin. When you're not sleeping your whole life and you have lots of inflammation in your body, you're at risk for developing anxiety symptoms, depression symptoms. Even things like ADHD and autism can be seen more commonly in patients with atopic dermatitis than those without, so I think it's important to understand all of the different dimensions of the condition and all the different ways it can affect a patient. I think there are simple ways to gauge this and understand this in your patients. Just ask. Ask about how the disease affects you, not just from a symptom-wise but in your whole life, and so I like to ask about school, work, activities, what kind of things does this interrupt in your life, and then ask about the other conditions that may go along with atopic dermatitis like the allergic symptoms as well, so asthma, hay fever, food allergy. And if it's a big component of the condition or is also there and has not been properly addressed, we use kind of a multidisciplinary approach and use our allergy colleagues, use our mental health colleagues, to help us take care of the patient.

Dr. Leo:  
And if that's not the perfect example of a vicious cycle, I don't know what is. You have a stressful event flaring the disease, the disease flare causes more stress, and you get stuck in a loop with this. Pam, you lived it.

Pam:  
Just like I did, yes. My parents were elderly. They died within a 2-year period of time, and then I had to manage an estate for my mother with 9 siblings, so talk about chaos, I mean, and I would find when I would talk with them about different aspects... And the estate went on for 3 years, so it just made it even worse. Every time someone would call me, I'd flare up because, "What have you done now?" and "What's going on with it?" And that really was the nail in the coffin for me. That really turned the corner.

Dr. Leo:  
Dupilumab on quality of life, it's been studied; it's been measured. What have you found? And what does this suggest for therapies like this in general?

Dr. Simpson:  
Sure, that's the nice thing. I talked earlier about the reduction in itch, the reduction in the skin disease itself by 70, 80%, but some of the most gratifying stories you hear—and also, the data supports that—are these downstream effects of the condition. The dupilumab studies, even at 16 weeks, found that patients are sleeping better compared to patients getting placebo, that their quality of life is much improved, so better activity, better sleep, reduced pain, and that even their anxiety and depressive symptoms reduce just in 16 weeks of being on the drug. So, the data is really clear that it's not just—that dupilumab doesn't just improve the skin but improves itch symptoms as well as improves people's quality of life, and I find that most gratifying as a clinician.

Dr. Leo:  
Fantastic. Maybe, Dr. Boguniewicz, you can tell us a little bit about how you incorporate shared decision-making, especially when

you think about the pediatric patient and their family in your practice.

Dr. Boguniewicz:

Yes, so I think that it's going to depend on the age of the child, right? I think that, again, we need to start out by educating our parents, caregivers, about the fact that this may be a long journey and they have to deal with a chronic disease, that this isn't like an acute intervention for strep throat or an ear infection, because often times parents will describe failure of a treatment in their eyes, and then when you really question that, it turns out that, no, the medication is working; they just thought that it was going to lead to a cure, so when they discontinue it, the disease comes back, so we need to get a sense of the family's belief systems and what they are willing to accept. And we don't want to overwhelm them right away because there is so much complexity to this potentially. Again, we use different strategies. Sometimes a busy clinician may not have the time. Some families like written information, so you want to make that available. You want to give them credible sources to go to if they really like to find their information out there on the Internet. We give them written plans. We have nurse educators sometimes who may be much better at communicating things at a level that the family is comfortable with, and we want to make sure that they are accepting of the treatment, not that we're just dictating a certain treatment for that child. And as I mentioned, as we get closer to adolescence, we really want those patients participating in and knowing what this is really about. I don't know, Dr. Simpson, if you want to add to that.

Dr. Simpson:

No, I don't think so. I mean, I think the perfect time... When I use kind of a traditional shared decision-making approach is when we have choices to make and decisions to make, and I think moving to a systemic is the perfect time for that discussion, because it's not an easy choice, and there are options out there. So, there are off-label options, the traditional cyclosporin methotrexate; there's dupilumab now FDA approved. And so I have a conversation about what the goal is. Do I understand what the patient's goal is in treatment? What are their preferences? And then I go over the options, and I usually will talk about—still talk about their traditional options as well as dupilumab, go over the differences, go over the risks and benefits of each one and use language appropriate for that patient and try to empower them to then choose what sounds best for them and that it's in line with their preferences.

Pam:

You know, I think that the thing that helped or helps the patients the most is having an understanding of what the treatment is. Find the right person to partnership. You know, you want to find a physician you can speak with and that will give you guidelines. I want to see it in writing. A lot of them will throw drugs at you and say, "Go ahead and take these ointments" and don't go over really what you do and how much. Or you may have said that, but the patient doesn't hear that. They are like they hear that they're going to be clear, but they don't hear how much, where to put it, how long to do it, so you have to have guidelines.

Dr. Leo:

Thank you all for a wonderful discussion.

Now that we've shared Pam's experience with you, we would like to hear from you. Do you have a challenging atopic dermatitis case that you'd like us to discuss? Let us know by filling out the case submission form, and we'll contact you if your case is selected for discussion in our upcoming case series. That's it for today. Thank you for participating in this care team forum. Please don't forget to take the posttest and complete the evaluation to receive your CME credit.