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Targeting IL-13 in Moderate to Severe Atopic Dermatitis: Forging a New Path to Improved Disease and Patient Outcomes

Announcer Open:
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Ms. Faleye:
Welcome to today's presentation on Targeting IL-13 in Moderate to Severe Atopic Dermatitis: Forging a New Path to Improved Disease and Patient Outcomes. This program is provided by Partners for Advancing Clinical Education in partnership with Practicing Clinicians Exchange, and is supported by an education grant from Lilly.

I'm Terry Faleye. I'm a Dermatology PA at DermSurgery Associates in Houston, Texas. And I'm pleased to present alongside Dr. Jonathan Silverberg, Professor of Dermatology and Director of Clinical Research at George Washington University School of Medicine and Health Sciences in Washington DC.

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Learning objectives: Recognize the burden of atopic dermatitis and its impact on patients, detail the targeted mechanism of action of IL-13 therapy in moderate to severe AD and its potential impact on disease and patient outcomes, incorporate patient-specific preferences and goals into treatment clinical decision-making discussions.

And so, before we get started, today, we're going to kind of assess our understanding and our knowledge in regards to AD. So, which of the following statements is true regarding the impact of environmental factors on overall AD burden? A: Symptoms are most improved in seasons with colder temperatures; B: Those from a low socioeconomic status have more severe symptoms; C: Maternal dietary exposures during pregnancy increase AD risk for the child; or D: Prolonged breastfeeding offers long-lasting protection against AD development?

What is the rationale for considering an agent targeting IL-13 as treatment for severe atopic dermatitis? A: Agents targeting IL-13 are more likely to have a favorable safety profile; B: Agents targeting IL-13 had demonstrated superiority over other biologic agents for AD; C: IL-13 is thought to be a major T2 cytokine contributing to skin symptoms; or D: IL-13 is the only interleukin that contributes to AD pathology.

Nick is frustrated with his AD regimen. He has missed his pills about two to three days per week and forgets to apply moisturizers frequently. How should you address therapy barriers? A: Explore reasons for nonadherence and consider options with other dosing frequencies; B: Express sympathy about the burden and re-educate about the importance of adherence; C: Refer him for neuropsychiatric testing, as it seems likely he has comorbid mental health concerns; and D: Share literature about improved disease outcomes if he can take his therapy as prescribed.

When choosing therapy, how often do you currently ask patients which atopic dermatitis symptom is having the most impact on their

quality of life? A: Never; B: Rarely; C: Sometimes; D: Frequently; E: Always; or F: Not applicable.

How often do you currently consider an agent's mechanism of action when designing a plan to treat moderate to severe AD? A: Never; B: Rarely; C: Sometimes; D: Frequently; E: Always; and F: Not applicable.

How often do you currently incorporate shared decision-making with a patient when choosing a therapy to treat AD? A: Never; B: Rarely; C: Sometimes; D: Frequently; E: Always; and F: Not applicable.

First, we'll start off and we're going to be talking about the burden of atopic dermatitis and its impact on patients. We know that with atopic dermatitis, it affects 11% to 25% of children. And the onset most common is usually between the ages of 3 and 6 months of age. Of those patients who are diagnosed with AD, 60% of them develop the condition by the age of 1, and 90% develop it by the age of 5 years of age. It affects up to 10% of adults, and 10 to 30% of pediatric cases persist into adulthood. And 1 in 4 adults with atopic dermatitis report adult onset of symptoms.

So, when we're talking about the epidemiology of AD, especially when we're talking about race and ethnic minorities, it's also good to know that those people who are living in urban areas are more likely to have atopic dermatitis than those from rural and suburban areas. We know that 9.6 million children with atopic dermatitis in the U.S., and from that percentage, 19.3% tend to be about black Americans and 16.1% European American. And then out of the 16.5 million adults with atopic dermatitis, you can see the breakdown here as well, that 10% of those patients being African Americans, 30% Native Americans, 13 with Asian Pacific Islander, and the 11% white American. So, you can definitely see that the higher prevalence of AD is in black children in urban areas, and so, it's one of those things that definitely kind of take a look at.

So now I'm going to go ahead and hand it off to Dr. Silverberg, and he's going to be talking about the clinical presentation, variability, and ___ 05:27.

Dr. Silverberg:
Thanks very much. So, atopic dermatitis is a very heterogeneous disease. You know, it can look different in terms of just different morphologies and different subsets of patients. It can look different in terms of the distribution of lesions and the different types of morphologic patterns by age. In infants, we tend to see more lesions involving the cheeks, the forehead, scalp, the head and neck area in general, often can look a lot more like cradle cap, or sometimes just more acute oozy, weeping type of eczema. In toddlers, we tend to see more extensor involvement. So, the extensor of the forearms and shins often thought to be because they're crawling more. And we certainly can see a flexural involvement as well, even in the young infants. As we get into older childhood, we'll tend to see a lot more of that flexural involvement. Involvements of the back of the hands, but certainly can involve the face and other areas too. And then we get into the adolescence, we start to see a lot more of hand eczema, palmar involvement, head and neck involvement, and then that progresses even more so into the adult realm.

And I think it's important just to note, while flexural eczema is sort of the more classical distribution of lesions that we look for, in many studies, particularly in studies outside the United States, when looking at non-white patients, we often see less flexural involvement. So, keep in mind that flexural involvement is by no means diagnostic in of itself, and, you know, not necessary nor sufficient in order to make that diagnosis.

Now, when we think about, you know, some of the variations, and I touched upon this a little bit already, but studies have shown, you know, patients, whether there's studies done in Africa Proper, Afro Caribbean patients in the UK, African American patients in the United States, that identify with more post-inflammatory hyperpigmentation, have been reported to have more either follicular eczema or follicular accentuation, which is a fairly distinct phenotype, that doesn't really happen as much in white or Caucasian patients. And there's also a challenge that comes up with darker phototypes in general, which is challenges assessing erythema because of pigment masking.

In studies done in Asia that have shown more well-demarcated or psoriasiform lesions compared to patients of Northern European descent, more prominent scaling, more lichenification, more psoriasis-like lesions in general.

And what we've seen across the board throughout the United States is that amongst the non-white patient population, more delays in diagnosis, misdiagnosis, more perhaps unnecessary biopsies being done, delays to initiation of therapy, and even delays in terms of just specialist referral that come up.

Here are some examples of some of my own patients with atopic dermatitis and just showing a little bit of that spectrum. While these all look different, these are all atopic dermatitis. In patients with darker phototypes, we'll often see, again, less of that light pink or dull reds as seen in that middle image in a lighter-skinned patient. But when you look on the left and on the right, what you'll appreciate is maybe more maroons, what looks more violaceous in its appearance. Also still that ill-demarcated eczematous lesions, but not, you know, the

nature of the quality of the erythema is different. We can also appreciate on the image on the far right, a lot more lichenification, a lot more xerosis and dryness. It's sometimes very challenging even to tell apart just profound xerosis from lichenification in some patient populations. But just recognizing these are all just different presentations of the same disease.

When you think about the impact of environmental on atopic dermatitis, there's a lot of different outside-world triggers. There's the emotional component, stress triggers, you know, emotional factors that can worsen the disease. We see this more prominently in the adult patients with atopic dermatitis. There may be a role of diet or nutrition, and I would just want to be cautious and how I present this because there are certain foods that can sort of have nonspecific proinflammatory effects, but much of the time it is not a food allergy, and we don't necessarily think about food allergens as triggers of atopic derm. That doesn't mean that diet isn't important though in the disease. And then there are other things in terms of air quality, small particle air pollution, climate factors, like, you know, cold, dry weather in certain areas, you know, whereas in other places, it could just be the intense heat and humidity that can be driving factors of the disease.

When thinking about the comorbidities, this is an area that I think has really grown tremendously in terms of our understanding and appreciation. We've known forever about the role of the atopic comorbidities: asthma, hay fever, food allergies, etcetera. And the presence of these disorders is part of the diagnostic criteria for atopic dermatitis. But more recently, we've recognized – and this is now part of the American Academy of Dermatology's guideline update on comorbidities, that other immune-mediated conditions such as alopecia areata, urticaria, potentially even vitiligo, etcetera, are increased in patients with atopic dermatitis. Much higher rates of depression and depressive symptoms, symptoms of anxiety etcetera, that happen. More cardiovascular risk, although the absolute risk of this is quite low, but still something that is increased in patients with atopic dermatitis. And even impacts on bone health in terms of osteoporosis and bone fractures. Skin infections of all type are increased in patients with atopic dermatitis. This is another one that is part of the diagnostic criteria for the disease.

So, what are some of the challenges and concerns we face with current therapies? Well, most of our therapies work reasonably well in the short term, but the challenge is that you kind of stop them, whatever it might be, whether it's topical, whether it's oral, whether it's injectable, and the disease often can start creeping up again. So, that requires long-term adherence. And that's not always easy for patients to pull off, especially if it's talking about a twice-daily topical medicine or a once-daily oral medication. Different therapeutic modalities are going to be preferred by some patients over others. Some patients like topical, some hate them. Some are okay with orals, some can't remember to take them and can't swallow them. Some patients, you know, are okay with injectables, others will tell you, 'Heck no, I don't ever want to use an injection.' So, you know, there's a lot to take into account in terms of treatment preference.

Of course, adverse event and safety profile is so important. And we have to take that into account for any of our systemic therapies, and even to an extent with a lot of our topical therapies in terms of tolerability concerns or thinning of the skin with topical steroids.

Other issues that come up with some of the novel agents and specific adverse event profiles with some of our newer therapies, cost and access always a big challenge. You know, we're so happy to have novel therapies that bring innovation to the field, but on the other hand, they often usually come with a price tag that's high, and that leads to barriers in terms of access.

And then, you know, a number of remaining clinical questions in terms of how do we select the right drug for the right patient and have a more precision medicine approach? And how do we identify who are the patients who are at highest risk for different, either treatment benefits or adverse events on the flip side of things?

So, I'm going to turn it over now for an interesting case presentation, so we can learn a little bit more about these principles.

Ms. Faleye:
Thank you, Dr. Silverberg. So, we're going to be talking about Luke. Luke is a 7-year-old boy diagnosed with atopic dermatitis at age 8 months. Currently with moderate severity, and has difficulty with focus and hyperactivity in school, wakes frequently through the night, also lives in an apartment in a large city with his mom and two siblings. Schedule impacts ability to travel for office visits, which is not fun. Wrestles competitively, which is awesome to see. What we see with Luke is that he's never been to a dermatologist. Primary care providers prescribe topical steroidals, patient's been on triamcinolone 0.1%, but little improvement is noticed. So, basic management, lotion applied twice daily, bathes one times a day for 20 to 30 minutes and uses Dial soap and washcloths.

So, the first thing I notice when we're talking about Luke is the importance of education. Well, we can definitely reinforce a shorter bath time, because what we see with a lot of times with atopic dermatitis patients is that these patients are burdened by this dry, itchy plaques. And so, I'll tell patients that hey, you know, shorten your bath time; that way, it's a case where you're not drying out, you're not having as much extensive flares. Dr. Silverberg?

Dr. Silverberg:
Just at a high level, just sort of, you know, my 30,000-foot view when I see a case like this, is there's a lot going on, and probably too

much going on. You know, at that point, I started to realize, okay, yeah, well, we could probably optimize topical therapy a little bit. And we could talk about trigger avoidance a little bit, but we're probably at that point where this has become so, you know, intrusive in not just Luke's life, but in the whole family's life, that we're probably going to need to think about how do we step things up a little bit, and how do we do that in the safest way and the most feasible way possible?

I think one of the challenges that comes up is because there's so many different ways in which atopic dermatitis can affect patients' lives, that we end up having these like, you know, 14 different interventions, whether that's three different topical therapies for different parts of the body, but then we're telling them, okay, you know, wear cotton and don't wear wool. And, you know, maybe don't play sports, because that's going to flare them up and like – and all of a sudden, it's like everything in life is getting messed up. And at some point, I realize, like, you've got to bite the bullet and just work on getting stronger and tighter control in order to just give back some of that quality of life, and not have to worry so much about all these different, you know, challenges and coming into the office all the time, and all these other burdens that are happening.

And, you know, it varies by age, it varies by what our options are, and access, and all these other things. But at that point, I usually say, okay, it's time to reset, let's think about what our other options are. And you know, sometimes parents and patients, they're not emotionally ready to go to something stronger, but at least I plant that seed early on, and they say, look, I'll try to optimize therapy and we'll give it a fair shake, but there's a very good chance 3 to 4 weeks from now, we're probably going to need to step it up anyway. So, just emotionally start thinking about like, what therapies you would be more comfortable with, what could we do, and then take it from there.

I do love the idea more and more of telemedicine to help for a lot of patients, there's a limit to what you can do. And since COVID, I've been using a lot of telehealth to supplement, and I can tell you first and foremost, it – nothing replaces a good old-fashioned in-person visit. So, maybe you start with a more complex patient like this in person. But once you've got a good treatment going and you just need to monitor, the whole point of why I want them on a good therapy is to make their lives easier. I don't want to bring them in unnecessarily. So, if I can use telehealth there, I love it. Because oftentimes it's more of, well how are you doing? And if the answer is great, I didn't need to make you drive 3 hours in order to tell me that, you know, we could really establish that and do refills through telehealth. So, I think there's a lot that we can build into our practice, you know, dynamics that can really make life easier and more feasible for patients and for caregivers.

We've got to be cautious about how we are educating patients and families around the fundamentals. My experience is patients will often come in with a perception that, 'Oh, this is a pediatric disease that will burn out by adulthood.' And yeah, it happens in many. But for so many of our patients, they've had it lifelong and it doesn't go anywhere. But when they have this false expectation or false hope, 'Oh, it's just going to disappear anyway in the next 2 to 3 years,' they don't appropriately use the therapies because they're just waiting for something magical to happen and change the course, when that's never coming. So, I don't want to be too negative, I'll say, listen, I hope that one day it goes away on its own and burns out, but I have no way to predict that. And we need to think about what kind of treatment options we can develop here or treatment programs we can develop that will be safe and effective for long-term use, because as far as I can tell, you're going to need to be using something for the foreseeable future. And that, at least I don't want to take all the hope away, but it sets that realistic expectation, this is about that marathon and don't think that you're just going to sprint this and somehow in 3 weeks, this is going to be over.

Ms. Faleye:
Okay, so we're going to be opening up into our part of the discussion that's going to be targeting IL-13 and novel mechanisms of action in atopic dermatitis. So, here are some of the new and emerging therapies for adults. We obviously have ___18:19 here, and it's indication for mild to moderate atopic dermatitis, used as a topical cream BID. We drop down, and we also see so far as the oral agents available, so far as in regards to the systemic JAK inhibitors for moderate to severe. And so also, when we drop down, we can look at dupilumab. Dupilumab in itself has been approved since 2017, and is moderate to severe, and it's an IL-4 receptor inhibitor that's given every 2 weeks; sometimes it could be dosed every 4 weeks as well, too. But today, obviously, we're going to be highlighting and really talking about IL-13, and just in this box here and just kind of talking in regards to ways that these drugs in themselves add to the atopic dermatitis paradigm.

So, I'm going to turn it over to Dr. Silverberg, and he's going to be talking about the pathogenesis of atopic derm and lead us through.

Dr. Silverberg:
Great. Thanks very much. So that's a whirlwind we're going go through, and in part because the field is rapidly evolving here. So, there's a lot to know. But there are some high-level principles that I think are going to serve you well to know across the entire toolbox, the different options out there.

So first, there's been a long-debated discussion of, should we think of atopic dermatitis as inside out? Or outside in? Outside in is, I

think, intuitively the way most dermatologists will think about it, which is, you know, it all starts at the barrier; something – some damage happens to the barrier, whether it's genetically predisposed with flagger mutations, or whether it's just a brutal dry winter that makes the skin super dry. But whatever it is, once there's that damage to the barrier, that will now lead to the increased expression of so-called alarmins which will now cause inflammation in the dermis. And then once that inflammation kicks off, it sets off this cycle and further worsens the barrier. And for a subset of patients, this is probably the direction in which things go.

But there's also evidence to suggest that for some patients, the inside-out hypothesis might be true, which is that really the root cause is some kind of central issue related to inflammation. And there could be a lot of different things that have been implicated, whether it's genetics, others, but that – at either in the blood or in the tissue, there's this increase in inflammation, and then those inflammatory cells will lead to barrier disruption. And then once there's barrier disruption, that leads to more inflammation. It almost doesn't make a difference what is the root cause, because in truth in all patients, both aspects are relevant, right? The barrier issues are relevant, and certainly the different immune dysregulation aspects are also going to be relevant.

Regardless of which hypothesis we think about though, central to that would be the, you know, T helper 2 cell is the primary effector cell that we know of in atopic dermatitis, and their prototypical cytokines, which would be interleukin-13, interleukin-4, and some other cytokines that they produce as well like IL-31, etcetera.

In the discussion of which of these cytokines matters more, is it the IL-4? Or is it the IL-13? This has also been an area that's been highly debated, but more and more, we're starting to recognize that it's probably the IL-13 that matters, if not almost all of it coming from the IL-13, but certainly playing the dominant effect, much more so than IL-4.

Here, we can see sort of some of the different effects of the different cytokines. So, interleukin-4 and interleukin-13, conceptually have very similar or overlapping functions, except when we look in the skin and atopic dermatitis, what we find is, it's all about the IL-13; the expression is at the IL-13 level where we find minimal if any detection of IL-4. But they technically can do similar things in terms of leading to barrier disruption, in terms of leading to more inflammation in the skin. In the case of IL-4, in particular leads to more Th2 differentiation, but IL-4 and 13 both playing a role potentially an IgE class switching and an upregulation of other inflammatory cell types.

Interleukin-31 is another one of the cytokines produced by T helper 2 cells. But this is a little bit different. This has direct effects in terms of triggering itch on peripheral nerves, and oh, probably other things that it does that we don't yet know, we don't really understand all the biology of IL-31 yet.

IL-13 and IL-4, though, have receptors on peripheral nerves too. And they can amplify, they don't directly trigger it, but they can amplify the signals for itch in atopic dermatitis as well.

So, when we – now we've got these cytokines, and we'll focus now in our conversation about IL-13, but this is true for other cytokines as well, they're going to bind to receptors, they're extracellular signals, but they're going to bind to receptors on cell membrane. And then they're going to – in order to transduce, a signal intracellularly, it's going to set off these enzymatic cascades. And in the case of IL-13, in particular, and also true for IL-4, IL-31, and other cytokines important in atopic dermatitis, the signaling intracellularly happens through the JAK-STAT pathway, in particularly with – through the JAK1, you know, pathway through STAT6, and that will ultimately lead to impacts on gene transcription.

Now, when thinking about IL-13 effects, in particular, there's a lot there. And I mentioned this already, it impacts on keratinocyte function, aware when we've got increased IL-13 expression and activity in the skin of atopic dermatitis, we get decreased skin barrier, proteins expression, decreased epidermal lipids, increased transepidermal water loss, and xerosis, decreased antimicrobial peptides which might increase the susceptibility of skin infections, and potentially even systemic infections. There's actually even some suggestions of profibrotic effects in general for IL-13. That's probably less important in atopic dermatitis, but may certainly be relevant in other fibrotic disorders in dermatology, and then I mentioned already as well, the amplification of itch that happens. So, the IL-13 is not just playing a role in inflammation, but really in the sort of the totality of the immunopathogenesis of this disease.

Now, we've got two targeted IL-13 blockers that are either approved or in development. So, tralokinumab was the first of the monoclonal antibodies to bind to the free interleukin-13 cytokine. And this one is currently approved in the United States and many other countries around the world for the treatment of moderate to severe atopic dermatitis. And then we've got lebrikizumab, which is also monoclonal antibody targeting interleukin-13. Now, there are some nuance differences in terms of how they bind. They're both binding the cytokine, not the receptors, but they do have some nuance differences were there – one may impact the so-called decoy receptor, whereas one may not. But the decoy receptors – we don't know what the decoy receptor even does with respect to the – its function in atopic dermatitis, so we're not sure how important that really is. But there certainly are, you know, differences in terms of pharmacokinetics and binding affinity and how long these medications will last. And we still have a lot of data to glean from that, but recent disclosures have suggested there are differences between these medications.

Some considerations around tralokinumab, again, FDA approved already for adults, moderate severe atopic dermatitis. We have some delays in terms of the approval for adolescents, but we're looking forward to getting approval for adolescents hopefully in the next few months. And it's got a lot of shots. So, the loading dose is 600 mg, the maintenance dose is 300 mg, but each shot is 150, so it's 4 shots up front, 2 shots every other week with an option for an every-4-week maintenance dosing in patients who do really well in that initial induction period with every-2-week dosing. And since it's a subcutaneous injection, we recommend you know, self-administered, generally speaking, or can be caregiver administrated as well. But it would be rotating injection sites, anyplace where there's subcutaneous fat. Generally clean safety profile, similar to what we've seen with dupilumab. But we do see ocular ophthalmic adverse events come up like conjunctivitis, keratitis, dry eyes, etcetera, which can appear.

Now when we think about the efficacy or examine the efficacy, the main studies that were performed were the ECZTRA-1, ECZTRA-2, which were monotherapy studies, no background topical therapy used. So, there's two different phases of the study. So, these data are looking at, amongst those patients who did well in the initial induction period, in the first 16 weeks, could get re-randomized to getting either continued every-2-week dosing, or a maintenance dose of every 4 weeks or a placebo. So, a treatment withdrawal. And what was observed was that there are high rates of maintenance of response with the continued every-2-week dosing, but even amongst those patients got every 4 weeks, that spread-out dose, and even a large subset of patients on placebo, were able to maintain good responses, you know, essentially 36 weeks after getting that initial induction response at week 16. So good maintenance and durability of response amongst those who respond well early on.

There are a ton of other secondary endpoints that improved in terms of itch scores, and, you know, improvements at week 16 and at week 52. There was also the ECZTRA-3 study done with topical corticosteroids, which was able to reproduce a lot of these results and showed additional efficacy to be gained when combined with topical therapy. And so, in the real world, I think we all recommend using this therapy in combination with topicals.

The adverse event profile overall, looking quite clean; the eye issues being the only ones that came up other than injection site reactions with any sort of commonality to them. But most of these not leading to treatment discontinuation. And interestingly enough, lower rates of skin infection observed with the tralokinumab treated patients. And this is likely a testament to the efficacy of the medication. Because when you've got a good, you know, effective medication in atopic dermatitis, we expect it to reduce skin infections that are the result of poorly controlled disease.

Now let's turn to lebrikizumab. So lebrikizumab at the time of us recording this is still investigational, it's not yet approved in the United States, but we're looking forward to approval within the next few months. We've got phase 3 readouts already for multiple trials. So, the main flagship studies would be ADvocate1 and ADvocate2. Monotherapy, again, no background topical corticosteroids. Here, we're seeing the primary efficacy time points and the kinetics to get there, which would be the IGA clear or almost clear at week 16 and the EASI-75's at week 16. And what we're seeing is, you know, highly statistically significant improvements achieved for these endpoints with lebrikizumab versus placebo. And interestingly enough, especially for the IGA clear or almost clear, no indication of an ___29:28, of a plateau of efficacy, suggesting that if you went beyond week 16, there would be even more efficacy to be gained. This is dosed at – as a loading dose at, you know, essentially day 0, another loading dose given at week 1, and then it's going to be – or week 2 I should say, then there's going to be a maintenance dosing given every other week, which essentially only one shot, so it would be half as many shots compared to tralokinumab in that respect.

And looking at other endpoints – I know this is a busy slide and summarizes a lot of data, but we've seen highly statistically significant improvements in terms of itch improvements, in terms of more robust reductions in lesional severity, not only at week 16, but even as early as week 2 and week 4. So, showing good efficacy and good rapid onset of effect, likely because of that double loading dose but something that I think will be a nice advantage when we're using it in the real world.

Adverse event profile, overall quite clean, similar to what was previously observed with dupilumab and with tralokinumab.

In terms of the efficacy seen in the ADhere study. So, this is in combination with TCS, we do see good efficacy achieved overall at week 16. And for IGA clear or almost clear, similar efficacy as was observed with the ADvocate1/ADvocate2 study, but when we look at the other endpoints, like EASI-75, for/4 point reductions in itch, we see here clearly a boost in efficacy when used in combination with TCS. And again, you know, there's a large subset of patients who can do very well on monotherapy, but I think it's reasonable to say in the real world to patients, a good idea to use in combination with TCS early on. And if you get clarity and you don't need to use TCS, great, but hold on to those topicals, because you may benefit from them in addition to using lebrikizumab.

From the ADhere study, safety profile overall quite consistent to what we saw with ADvocate1/ADvocate2. And similar to overall what we had seen with the class in terms of type 2 blockade.

Now, there are a number of ongoing studies for both tralokinumab and lebrikizumab. In the case of lebrikizumab, we've got adolescent

studies that have been completed that we're waiting to see publication of, we've got longer term extension studies that are ongoing that we're going to have continued monitoring going on, and then pediatric studies as well, and some other novel phase 4 study designs looking at interesting subsets of patients as well that are very clinically relevant. For tralokinumab, we've got the adolescent studies. I believe the adolescent study is pretty much done, although we haven't seen all publications yet for the results. And hopefully we'll get adolescent approval within the next year or so. And then there's ongoing open-label extension studies happening for not just adults, but for adolescents as well.

Other emerging therapies in atopic dermatitis, further behind though, we have nemolizumab, which is an inhibitor of the interleukin-31 receptor alpha subunit. So that blocks the interleukin-31 pathway, also subcutaneous. We also have two novel topical therapies, topical tapinarof, which is an aryl hydrocarbon receptor modulator. And then topical roflumilast, which is a PDE4 inhibitor. Both are creams, both already FDA approved for psoriasis, and both hopefully will be approved within the next 12 to 24 months for atopic dermatitis.

So, I'm going to turn it back to Terry now and we're going to have another case discussion which I think you will find very informative.

Ms. Faleye:
Thanks, Dr. Silverberg. So, we're now going to be talking about Brody. So, now I got a 16-year-old. Not only that, so Brody has worsening moderate to severe atopic dermatitis, and his symptoms have been kind of – had started when he was running track a few years ago. So obviously, warmer weather started causing more flares and they are increasingly difficult to treat. He runs several miles per day. And not only that, has large BSA involvement, cracking and bleeding, and impeding his ability to practice and compete in a way that Brody would like. But Brody is interested in running college and would like to qualify for a scholarship. Go Brody. So, we've got dupilumab every 2 weeks. Not only that, having lukewarm baths with gentle cleansers only, bleach baths two to three times per week, and generous application of ointment immediately after bathing and before bedtime. Lotion in the morning.

We're talking about Brody here, and it's like, wow, how is life for – I mean, as a track and field athlete, and just in general, just suffering so far with atopic dermatitis. How does this experience really impact him? You're talking about the different triggers, as far as heat, sweat, exercise, all those things. It can be very debilitating, especially when we're talking about these patients. It can be very impactful. But the one thing that we obviously know is the social stigma that is associated with atopic dermatitis. Dr. Silverberg, I know that you probably see a lot of atopic dermatitis patients, do you come across patients like Brody all the time so far as in your practice? What's your word of advice for them? Not only that, but just how do you deal with patients like him?

Dr. Silverberg:
You know, I don't know if there's a one-size-fits-all answer on this, but, you know, trigger avoidance for some patients, you know, they'd rather stay off all medicines if they could, right? And they say, 'Well, you know what, if it means not wearing wool, I can wear cotton fiber, I'll be okay.' Right? Or something like that. And then other patients are like, 'Well, how am I supposed to go to work if I can't wear a uniform or if I can't wear dress clothing that they expect me to?' Or like, I can't function,' or 'You're telling me I can never play sports ever again, because heat and sweat will flare me up. Like, that's not a solution, that's just destroying my quality of life.' So, I think, you know, it's a personalized decision about how we deal with trigger avoidance. And I feel like sometimes we may cause more harm than good by telling them to avoid all of their triggers, taking all the fun out of life, when you could just as easily just give them a therapy that works well, and they can enjoy life.

The stigma issue is, I mean, I hear things that patients tell me, and I just wonder, like, people just need to learn to keep their opinions to themselves sometimes. Right? But it is what it is. But it emphasizes why it's so important for patients to shut the itch down so that they're not caught scratching, because when they're scratching, they're embarrassed, or to shut down the visible lesions because then people ask them these annoying questions. And it impacts them at work and school for sure. And it impacts them in social settings. So, these are all the reasons why we want to get them better. There's no question, you get them better, their self-confidence improves, their mental health improves, you really are improving all of that.

So, you know, for me, at the risk of sounding a little bit like a cowboy, because I don't think I'm too much, but, you know, I do believe that you want to try to get the tightest control possible, and then it becomes a personalized decision of, okay, well, how do we get there? Does it mean switching gears altogether, and switching therapies? Should we be layering stuff on top? And again, that's all part of that shared decision-making and personalizing it to the individual patient.

Ms. Faleye:
Yeah, I agree. And because patients like Brody, it's a case where, you know, he may be totally fine, you know, injecting himself. Or he may not be, and in those situations, just like you said, is it an oral that best fits this patient? Is it an injectable? Or when is the right time so far as to pivot if he's having good efficacy in the beginning and then all of a sudden, it's starting to wax and wane? And those are – it definitely becomes that dialogue, and that constant dialogue, that we have at each follow-up visit to make sure that, okay, are you doing good? You know, is it we're still working? Still working the way it was? Do you feel like anything's changed. Because sometimes, it's so

important with the education with these patients, because it's amazing how many patients know certain things are available in the market and a lot don't. And so some are kind of hesitant, 'Don't touch it. You know, leave it be, it seems like it's doing okay.' And so, but what is okay? Especially when we know that we can – it's, you know, is it good? Can it be better? If it can be better, then let's get there. But sometimes it's definitely a – this is definitely a conversation that's constantly being talked about.

Dr. Silverberg:
Absolutely.

Ms. Faleye:
Alright. So we're going to dive into, better together and obviously practical strategies for shared decision-making. So, when we're talking about access to derm, patients will come and say, 'It's so hard to get into see a derm somewhere in some part of the world,' and it really is. It's a real thing of knowing that okay, when we're looking at the breakdown so far as in dermatologists in certain counties, and obviously, looking at the populations in so far as density. And not only that, looking even just in relation when we're talking about people who live in poverty and looking at the breakdown, just socioeconomic when talking about blacks or Latinos, or whites, and just looking at the breakdown across the country, we see that a lot of times, especially in areas when we're talking about areas that are more urban, a lot of times sometimes it's very hard, especially in some areas, whether it be in the south or even north, sometimes it's hard for some patients to even have access to a dermatologist in those areas. And there can be a plethora in some regions of the world where there's like, wow, there's a lot of derms concentrated. And there's some areas where not so much. So, we know that definitely, I think it gives us an appreciation. Because I know here in Houston, we have a lot of derms at our disposal, and just a plethora in our region. But to know that, you know what, in certain states, that's not the case. And just the access, because sometimes when you have a less amount of derms within a concentrated area, then you know what, it takes longer time to finally get into one. And what's that patient doing within that period of time? So, this is what it kind of just breaks down by specialist and by population on what we're looking at.

So, we're talking about barriers to self-management, and we know that barriers, it's a hard thing, especially when we're trying to definitely educate our patients in regards to their disease. And so, lack of information and confusion about disease and treatments is a real thing. Because so often we find that, just like we said before, there's so much lack of information. And unfortunately, patients have a hard time getting it to see an actual derm, then you wonder where they're getting their information at? You know, they come in with a ton of creams and they're just like, 'I use this, I use this,' and you just say, where did you get all of this stuff? And so unfortunately, that leads to confusion. And so, the ability that – so the barrier it being that, you know what, the education piece that is so necessary to educate these patients about not only the course of the disease and the type of dermatitis, but the treatments that are available.

And then not only that, hearing conflicting and concerning information about treatments. You have some patients that come in and they're just like, 'I don't want any steroids,' you know, or, 'I'm never going to use one,' and sometimes it's more so to educate and say, okay, what is the use of topical steroids, how it impacts them, how it helps their disease, the limitations that are in regards to it. And you have some that only want to use topical steroids and you tell them all the options that are available today. And you mention injection and they're running for the hills. The time commitment for non-pharmacologic and pharmacological aspects of therapy, there's time in regards to educating our patients and the therapies that are available. But not only that, it's the time requirements sometimes do it. I can't imagine for some patients who are constantly applying cream after cream after cream, and sometimes just the burden of, you know, wow, how much time does that take? So, when you're talking about BSA of, you know, if you have significant body surface area, how much time is required to actually put all that on? And you say to do it twice a day? And you're looking at you like, are you serious? So sometimes it's knowing that, the undesired in so far as therapy aspects, the adverse events so far as whether it's cream or ointment, or whether it be the smell of it, or just the feel that, you know, in some skin tones, it may be hard to rub in cream and feel like it doesn't go in all the way, doesn't vanish, or is it going to have this weird residue so far as to it. And then obviously, the doubts of efficacy can be there as well, too, when patients have tried numerous agents over the years and been promised and sold that it's going to work. It's a journey, definitely not a sprint.

And so, I'm going to go ahead and turn it over to Dr. Silverberg and just talking about the discordance between patients and HCPs about atopic derm.

Dr. Silverberg:
Thanks very much. Now, this is a really important issue, because I think we assume that we're able to just see everything on the skin and know the whole story. And that's not always the case. In fact, much of the time, it's not. What we see from the data – and there are several different studies that have looked at this, this is one particular study that showed really a lack of concordance between how we perceive the skin versus how patients themselves are seeing the skin. So, there's differences in terms of the assessments of severity. There's certainly differences in terms of the goals. For patients, you know, it's all about quality of life and itch. And yet for us, you know, we'll think – we'll look at some downstream sequelae, sleep disturbance, a lot of times we're just looking at the skin and not even taking

into account the symptoms and the quality-of-life impact that patients are experiencing. So, we definitely need to align better in that and have more communication there.

If it's the worst of the worst patient, then we're probably all aligned, right? You won't miss the most severe patient out there. Then the patient knows they're very severe, you know they're very severe, a lot of alignment. But it's – where you could really mess up, so to speak, is to miss those moderate patients and not appreciate just how much it's impacting them. Yet, even amongst those patients who the physician didn't rate higher as being more severe, but the patient felt they were higher, their quality-of-life impact was just as high and maybe even worse in certain respects. So yeah, when it's both, then the impacts can be even greater. No one would miss some scenario because they're so bad. Yeah, we're all aligned, but keep in mind, we're missing, in clinical practice routinely, large subsets of patients who are really being debilitated by their disease, and need more in the way of therapy.

So, you know, I think this brings up the issue of shared decision-making and how to identify these patients. And, you know, Terry, how do you go about this in terms of clinical practice?

Ms. Faleye:
I mean, a lot of times, especially with my patients, some are not very bothered it, you know, they don't have very much itch. And then obviously, you have a patient, they can have even smaller amount of body surface area and all of a sudden, the world is caving in. And so, I do find that definitely meeting each patient where they are is so, so, so very important. I find that a lot of times I just try as best as possible to definitely educate these patients in regards to truly the course of this disease. Because there are some patients, if they've had atopic dermatitis for a long period of time, then a lot of times it is definitely more so trying to not tell them, okay, everything that you've kind of experienced up to this point has been what it is, okay, let's kind of forge a path forward. But then also you have some patients that it's completely new to them and all of a sudden they're in their adolescence and having atopic derm and they're just like, 'What is this? What's going on here?' So I find that, number one, educating and giving them as much of the potential options that are available on the market, at least from a treatment algorithm standpoint and finding what meets them, because I can think in my head hey, you know, I think this is what's best for you this is what's best but at the end of the day, I want buy-in. I want my patients to feel like, you know what they're being heard, number one, coming in through the door, because so often patients feel like, you know, 'Do they really hear me?' I want them to know that, you know what, I hear you. Do you agree with – this is the place that, you know, let's start here and then let's see if this works. And then, you know what, if next time you come, if we're doing better, awesome. If we're not doing great, then let's try to get better. And we've got other options available. But I try to have patient buy in as best as possible because I find that it makes things so much easier in the long run.

I find that, you know, number one, actively listening and engaging our patients is so very important. Patients want to be listened to. They don't want to be talked to, they don't want a lecture, but they want to be heard. Because a lot of times, sometimes they have gone their whole lives and feeling like nobody hears them. And you finally come into the room, and the minute you listen to him, it's amazing. It's like there's this burden that's lifted off their shoulder, they immediately feel better. And so, the importance of just engaging our patients, I think the minute we're able to do that, you kind of have a patient for life, and they're willing to kind of listen to whatever you're telling them to do. And because they're just like, 'you know what they heard me, they heard me, right on.'

So, it's not only that, it's accommodating various economic and appointment needs, just like you said, Dr. Silverberg, I mean, telemedicine is an amazing option that has definitely opened up doors amazingly, obviously, facilitating closer follow-up when needed and desired. Because a lot of times there are some patients that are going to need closer, tighter follow-up, especially when we have them on different systemic therapies that are available on the market today, then a lot of times sometimes for our subsequent bloodwork monitoring or whatnot is available. But I think that just keeps me on tight with these patients, because amazingly need some will come in and they say, 'You know what, it's not working anymore.' You ask them, well, you know, are you still taking the medication? 'Well…' And that's always the funny part. You know, all of a sudden, you're like, did you miss the last dose? 'I haven't taken it for about 2 weeks,' so then it's like, okay. So definitely that close follow-up is definitely needed and just a reminder.

And they consider patient goals, their preferences, and cultural skin practices as well, too. Because at the end of the day, we want, I mean, the patient's goals to align with our goals, and symbiotically, it definitely works together when we're all kind of working towards a common goal. But at the same time, it's also knowing their cultural practices and, you know, take into consideration that skincare practices, that's very different. I know that definitely how perception, even African Americans a lot of times, some may not have as much of the plaques, and they're concerned with just the pigmentation change. And they're worried about that. And you're just like, you know what, let's kind of – let's go back to making sure we're tackling that inflammation, versus we may not see that as much in Caucasians or other ethnicities.

But also, you know, assisting with medication access and support resources, it's a big deal. Just like you said, Dr. Silverberg, a lot of times, we have a great amount of options available to the market today, but with that comes a cost burden, sometimes that may be

associated with it. And sometimes access may be hard, or sometimes it's just the lack thereof of knowledge of how to gain access. And I think that's where our offices hopefully provide a resource for these patients and education of how that, you know what, the burden sometimes of the cost is there, but there are ways to get access to these medications. And that's where it kind of comes into play.

So, I'll go ahead and turn it back over to you, Dr. Silberberg, in regards to just looking at just the shared decision-making in regards to factors when we're talking about other healthcare professionals as well.

Dr. Silverberg:
Yeah, I mean, I think we covered most of this already, but the data have shown a lot of these points already, you know, that trust is so important. That, you know, patients do like the idea of shared decision-making, they want to be engaged in their care. High proportions of patients, saying that, you know, what matters to them is that their healthcare provider values their input, that it's not just this old school paternalistic way of practicing medicine, empathy matters. And then there are other considerations, which, you know, vary. They're not as important. And it's an interesting, almost like a control, in a sense, to see, you know, same gender didn't matter as much. But where the real unmet needs were, are in those areas of trust and those things that we discussed already. So, patients are far more open-minded than we may give them credit for, but they want you to be open minded to their concerns. And, you know, other things that come up that can impact or play a role in terms of a shared decision-making, it's just, you know, patients have different concerns, but they don't always feel comfortable. You know, you have to give them permission to express themselves, because when you're just rushing through the visit, that's a subtle clue that you don't care.

You have to be willing to ask the open-ended question to hear what bothers them. And then listen. They need, you know, for some better health literacy than others, have a better ability to articulate those concerns. And some of these are different medical concepts that are not even sure to put into words but are important to them. And, you know, that's where the visit matters and how we do things in practice, giving enough time, not giving off the sense that we're just trying to get out of the room as quickly as possible, engaging the patient, having the right body language and engagement that comes up, and having the appropriate follow-up so we don't run into all the issues that Terry so eloquently, you know, outlined before.

So, you know, Terry, what are some of the things that you're aware of or that you use in your practice setting to assist in the shared decision-making process?

Ms. Faleye:
A lot of times I have a lot of literature that's around the office and obviously handouts and different things like that, and resources. A lot of times, you know, when you prescribe something and by the time they've gotten down the freeway, they've forgotten everything that you said. So, it's amazing, a lot of times just pamphlets or just brochures or handouts, just delineating, okay, what you're needing to do, what you're going to do, you know, in the next couple of days, at least before you come back, so far as to follow up. So, I mean, the key thing for me is I find that aids, worksheets, all those things are definitely available, really, as a team approach. It really is just trying to get patient buy-in. And I just find if I'm able to do that from the very beginning, it definitely helps along the way.

It's also the impact of social determinants. When we're talking about race and looking at different areas, or just different cultures in itself, we know that definitely, for those patients that are ethnic minorities, they are more likely to have treatment-resistant disease. Also experience poor social determinants of health, because of socioeconomic support status, a lot of times that can be a definitely a big burden. When you're making less than $30,000 a year, and you're being told, you know, your medication or your tube or your cream, you know, maybe $100 to $200, or whatever, that's a real, you know, eye opener when you get to the pharmacy. So, those in itself, what ends up happening is that patient may not pick it up at the pharmacy, and then all of a sudden, they come back for follow-up, and there's nothing there. Even those patients who are African Americans and black race, the risk factors tend to be more moderate to severe in disease.

And sometimes, obviously, a lot of times these patients, you know, they suffer for years. I mean, it's amazing, sometimes you come across patients who have never seen anyone, and all they've done is just applied lotion. And just like you said, Dr. Silverberg, just hoping, they've been told that you know what, you're going to outgrow it, it's going to go away, just got to wait till you're like, you know, 18 or whatever year, and they're waiting and waiting and waiting. And then all of a sudden, it never comes. That really is what happens in these minority groups. Because a lot of times, it's the misinformation and miseducation, and it's just so sad to see, but it's our role to definitely try to educate these patients here.

So, when we're talking about strategies for decreasing racial and ethnic health disparities, keynote systematically just looking at increasing education and awareness amongst all healthcare providers. Strengthening the patient-provider relationships is so important in regards to patients just to have that buy-in. Obviously, increasing diversity and minority representation, I mean, a lot of times you come across people who want someone that looks like them that treats them and there's a relation of them saying, 'You know what, somebody looks like me, and they may understand my skin better than somebody else.' But I think it's just more so the aspect of just

having options.

And obviously increasing diversity in clinical trials. And what we're starting to see more textbooks are starting to reflect skin of color. And that way, a lot of times just so people know what it looks like, because sometimes it very much looked very different in African American skin than it does in Caucasian skin, especially when we're talking about these inflammatory disease states.

But expanding office hours for patient care makes a big deal when we're available after hours or after school or weekend visits, even telehealth, just like we talked about before. And I think the biggest thing, too, is overall, is definitely tailoring – just tailoring to each and every patient. If we can definitely meet each patient that comes through the door, I think that we're winning at the end of the day.

And then obviously crafting an individualized plan, especially when we're trying to look at each patient. And when you look at this slide, you're seeing obviously, look at the greens and the yellow zone and the red zone, and obviously, you know, green means go, red is like ahhh, you know. And so, a lot of times the reality from this, and it's really just the takeaway is that it's really looking at each patient really, really differently. Obviously, our patients who have very clear skin or they have very, very mild disease, it's very different from those patients who are flaring when they come into the room and they are miserable. And so definitely our take and approach to how we develop a plan for them can be varied, quite different. But I think it's letting them know that we do have a plan in place, and then and how we plan to go about it. Because the hope is that we get that patient from the red zone down to the green zone, and they kind of know that versus keeping them in the red when they've been there for quite some time.

So we're going to go into another case discussion. So, we've got a 23-year-old female, who has been diagnosed with atopic derm since infancy. So, trying to become pregnant and not comfortable taking any systemic therapy during this process. She's recently moved to eastern North Carolina, humid weather and allergens exacerbating her symptoms. Seasonal allergies also worse than ever before, and lives in a rental home with her partner. So, to no surprise, difficulty sleeping, has stopped all oral therapy that she was taking before, and uses basic management only. So, Claire is using shea butter, petrolatum ointment, she's showering one to two times a day for 15 minutes, and using various body washes to exfoliate and try to get relief. So, she's interested in coming in, interested in discussing options for treating atopic dermatitis while trying to conceive, while pregnant, and through her lactation period. So, Claire's got a lot of stuff going on.

Alright. So, Dr. Silverberg, so we got Claire in the room. What's your advice for Claire? And she's all ears.

Dr. Silverberg:
Yeah. Yeah, I think some of the considerations at a high level are pretty similar to what we discussed earlier. But you know, with an older patient, we have more options to think about and more treatment, you know, opportunities. Often a little bit less risk aversion, so more of an openness, I think, to stepping up to a systemic therapy. But, you know, every patient has to be addressed individually. You know, and there's different – you can try combination therapy, but it starts to become unwielding pretty quickly, you know, in terms of the polypharmacy issues and access and challenges and – but to me, I think this is – I try to dive in immediately, using some of the principles we've already discussed around shared decision-making, understand what the goals are here, how do we get there? You know, are there barriers to using therapies? Are there preferences as we start to try to make the selection around newer therapies or more advanced therapies? And so, we'll try to do everything. But with an older patient that has more experience, there's often already a very clear sort of gestalt about what they can and cannot handle. They have a better sense of that, and it's got to work for them. I always tell the residents, I can prescribe anything, but if a patient doesn't use it, what's the point? And so, this is where we really have to understand, can they be adherent? Does it meet with their preferences? And if it does, then we'll probably be in good shape long term.

Ms. Faleye:
Alright, I totally agree.

Which of the following statements is true regarding the impact of environmental factors on overall atopic dermatitis burden? A: Symptoms are most improved in seasons with colder temperatures; B, Those from a lower socioeconomic status, have more severe symptoms; C: Maternal dietary exposures during pregnancy increase AD risk for the child; or D: Prolonged breastfeeding offers long-lasting protection against AV development. The answer is B: Those from a lower socioeconomic status have more severe symptoms. So, when we're especially looking at cold and hot temperatures, we know that they can both exacerbate symptoms of atopic dermatitis, but not only that, maternal dietary exposure and probiotic intake can be protective against AD development as well too. And then prolonged breastfeeding has demonstrated benefits for children's 1 to 3 years of age.

What is the rationale for considering an agent targeting IL-13 as treatment for severe AD? A: Agents targeting IL-13 are more likely to have a favorable safety profile; B: Agents targeting IL-13 have demonstrated superiority over other biologic agents for AD; C: IL-13 is thought to be a major T2 cytokine contributing to skin symptoms; and D: IL-13 is the only interleukin that contributes to AD pathology. And so, the answer is C: IL-13 is thought to be a major T2 cytokine contributing to skin symptoms, just like Dr. Silverberg kind of talked

about in the lecture today. There's no head-to-head data to support superior efficacy or safety of IL-13 targeting agents, but we do know that IL-4 also contributes to AD pathology. But we do know as well just like we talked about in greater detail, that IL-13 is thought to be a major cytokine, especially when we're talking about skin symptomology.

Nick is frustrated with his AD regimen. He has missed his pills two to three days per week and forgets to apply moisturizers frequently. How should you address therapy barriers? A: Explore reasons for non-adherence and consider options with other dosing frequencies; B: Express sympathy about the burden and re-educate about the importance of adherence; C: Refer him for neuropsychiatric testing, as it seems likely he has comorbid mental health concerns; and D: Share literature about improved disease outcomes if he can take his therapy as prescribed. The answer is A: Explore reasons for non-adherence and consider options for other dosing frequencies. Explore barriers to learn more about Nick's preferences and his therapy needs, because we definitely know that it's one thing to prescribe a medication, but if there's a reason or if there are barriers why Nick cannot, you know, use his medications, then we definitely need to know that. That way, you know, it needs to be changed and we can kind of transition. Engage patient in shared decision-making rather than paternalism, and also avoid assuming Nick needs a referral or re-education as an initial step.

So, after completing this activity, when choosing therapy, how often do you plan to ask patients which AD symptom is having the most impact on their quality of life? A: Never; B: Rarely; C: Sometimes; D: Frequently; E: Always; and F: Not applicable.

Now, after completing this activity, how often do you plan to consider an agent's mechanism of action when designing a plan to treat moderate to severe AD? A: Never; B: Rarely; C: Sometimes; D: Frequently; E: Always; and F: Not applicable. Now

Now, after completing this activity, how often do you plan to incorporate shared decision-making with the patient when choosing a therapy to treat AD? A: Never; B: Rarely; C: Sometimes; D: Frequently; E: Always; and F: Not applicable.

Thank you so much for joining us today for this on-demand webcast on atopic dermatitis. Find more educational coverage on AD at practicingclinicians.com. To receive educational credit, please click the link below.

Also, I want to say thank you to Dr. Silverberg for joining us today on this discussion in regards to atopic dermatitis. I really enjoyed working alongside with you today, but at the same time, just thank you so much for being a part today.

Dr. Silverberg:
Yeah, it's my pleasure. It was a great conversation.

Ms. Faleye:
Thank you so much.

Annoucer Close:
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