Transcript Details

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Hitting the Target in Atopic Dermatitis: Interdisciplinary Team Training for Leveraging IL-13 Inhibitors to Address the Burden of Disease

Announcer:
Welcome to CME on ReachMD. This activity, titled “Hitting the Target in Atopic Dermatitis: Interdisciplinary Team Training for Leveraging IL-13 Inhibitors to Address the Burden of Disease” is provided by Clinical Care Options, LLC dba Decera Clinical Education in partnership with Smart Patients.

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Dr. Singh:
So, why are we talking about this? So, why is this subject important, and what do patients feel and want when they’re thinking about their moderate to severe atopic dermatitis? So the first set of slides we’re going to talk about the answer to some of these questions. And when we ask patients, “What has impacted your ability to receive the care that you want for your AD?” the barriers, the main barriers were related to access, and that could be access to healthcare professionals who they felt understood their disease, which was the number one answer, access to culturally understanding professionals, but then access in general, such as are they able to get the care that they need, or are they inhibited with some barriers, including missing work, insurance coverage, transportation, and then, of course, cost. If it’s not something that you can afford, then it’s hard to access the medication. So in general, patients have a lot of concerns you can see across the board affecting about a quarter to a third of patients receiving the care that they wish they were getting for their AD. And when we ask patients, “How important are each of the following treatment factors when making your decisions?” you can see most patients are looking for something that is effective. So 72% of the time they are willing to try something and to buy in if it’s going to be effective. And then, of course, they want to hear about risk-benefit ratio. So they want it to be effective, but they also want to minimize side effects and control their disease, so reduce relapse.

So, now, when we start thinking about more advanced therapies beyond our topicals, how well do patients understand the side effects of advanced treatments like injectable medications? And most patients actually do not have a really good understanding, so they report limited understanding of the side effects, with over half saying not at all or not very well, so it means patients don’t really know what their options are and what the side effects may be, so to make an informed decision. And one of the questions is Why is that? So, why don’t patients feel like they know everything? And I think part of it is they feel that perhaps their healthcare professional didn’t educate them as well as they would’ve liked. So most patients, 33% felt that they did not receive a very thorough education about recognizing treatment-related side effects, and 26% of patients reported they received any information, so that means only 26% reported they received any education, which means that 74% of the time patients are reporting they did not receive any education, so it’s hard to think about taking that next step to a biologic. The patients want something that’s effective, they want something that’s going to work for them, but it’s hard for them to do that when they don’t feel their provider understands it very well—or explained it to them, actually, is probably a better interpretation.

So, if we look at how the patients replied kind of in these open-ended questions, if we start in the upper left, something that was uniform is that patients with moderate to severe AD have complex treatment journeys, ups and downs—we all know this—roller coasters,

valleys, and they have cycled through a lot of treatments, including topical steroids, sometimes systemic immunosuppressants and biologics. And here you can see some quotes there that someone was put on methotrexate and they were very happy, but they were so afraid of it because they didn't understand it or what it was, and then with someone else on dupi thought within a few days their eczema started to recede significantly and were very happy.

Addressing access, insurance and cost barriers, insurance restrictions and cost barriers were very common, patients reporting that it took forever to get something approved, or they got an approval, but it was short, and then they lost it, and then also having trouble finding the information that they needed to advocate for what they wanted and turning to the internet or other sources. And then we all know about this, the hoops that as providers we have to jump through of step therapy, where you have to try something and it may get denied, or you have to fail something before you could try maybe a better or more appropriate medication.

Obviously, safety concerns were reported, and patients reported both expected and unexpected adverse events. And here you can see some of those quotes listed on this slide, someone saying they didn't—they got the drug, but then they didn't know how to use it, or they didn't know how to inject themselves, or they didn't understand some side effects, such as stinging or burning with some of the topicals.

Okay. And then finally, when we talk about patient healthcare provider communication, patients with moderate to severe AD, their experiences really varied depending on their relationship they had with their provider, and some felt things were amazing, that "Honesty and openness increased my confidence in my healthcare provider," where others felt like "Maybe my provider didn't listen or didn't understand what I was saying." "I got blank stares," or "I felt dismissed," or "The docs haven't really talked to me about my treatments and why they work." And if patients don't feel that confidence or they don't understand why they're doing something, it can be hard for them to get buy-in and to try something new or to make that step to a biologic.

So to kind of address some of these concernings (sic) that patients may have, let's talk about the pleiotropic role of IL-13 in atopic dermatitis or understand what the IL-13 is doing so that when we target IL-13, we know kind of why it might be working. And so, when we think about what causes atopic dermatitis, or I should say what's happening pathophysiologically, we all know, especially in a dermatology clinic like this, that AD is a chronic inflammatory skin disorder, and it's driven by immune dysregulation as well as barrier dysfunction. And often those two things go together, that barrier dysfunction can drive immune dysregulation and vice versa. Immune dysregulation can then drive barrier defects. And we know IL-13 is a key Th2 cytokine that's central in the role of AD pathogenesis, particularly in acute AD, and we know IL-13 contributes to that epidermal barrier dysfunction. And how it does that is it downregulates (unintelligible 00:06:42) and other structural proteins so that we lose that tight great epithelial barrier at the skin. And that epidermal barrier dysfunction, I always tell my patients, it's almost like having an umbrella with holes in it. Like, when you have a barrier that's supposed to protect you but it's not working properly, then that allows our irritants and allergens and things to kind of cross through that barrier, get into the lower layers of the skin to promote inflammation. And so once that inflammation is started, then we get the expression of our Th2 cytokines and chemokines that then lead to kind of inflammatory cell recruitment. And then obviously, also, IL-13 can act directly onto the sensory neurons to promote itch, and so that's some of our neurogenic itch. And so that we know when we think about IL—So that's what's happening kind of in the skin on an immunologic level, as illustrated kind of in this figure, but we know that in patients who have severe disease, they'll have elevated levels of IL-13 in their blood. And then targeting IL-13 with biologics has been shown to be efficacious in improving their symptoms of AD.

And so if we dive in a little bit more into this epidermal barrier dysfunction and environmental triggers, it's kind of just as I mentioned, is once you have that defective barrier, that allows irritants and allergens to kind of cross through that barrier more easily, making the skin more sensitive, more itchy, and more likely to have disease. And again, this could be things like increased temperature, humidity, irritants, scents—we all know these—detergents, soaps, incorrect soaps and things like that, stress and allergens. And when we think about what are the key factors that contribute to this dysfunction that allows these things to trigger, it would be filaggrin mutations. We know when we have reduced filaggrin expression, that disrupts our integrity and impairs hydration of the skin. Lipid abnormalities, including decreased ceramide, will also weaken the skin barrier. And then once we have upregulation of our Th2 cytokines, including IL-4 and IL-13, that suppresses repair of the skin barrier, as well as barrier protein synthesis, and it promotes more inflammation—again, kind of cycling through, making everything worse. And then, as we all know, microbial dysbiosis are alterations to the microbiome at the skin, including Staph aureus colonization, an increase in Staph aureus at lesions to worsen inflammation and barrier dysfunction.

And so, when we think about what's happening at the skin—and again, this is probably a review for everybody in this audience—but when we look at normal skin, you can see—Let's see. Can you see my mouse? I hope. We have a really beautiful epidermal-dermal junction here, nice and clean, with a homogeneous thickness of the stratum corneum, and you can see nice and pink in the lower layers, no inflammatory infiltrate. However, when we get to an acute lesion, atopic dermatitis, we see the spongiosis, and then all this purple kind of infiltrating in where we get infiltration of T cells and macrophages as well as spongiosis. And then if we think about dyshidrotic eczema or dyshidrosis, when we think about it on our hands and maybe our feet, we get the thickened stratum corneum here at the top

with the spongiosis, and then the vesicles in our blue circles. And then again more acute AD on the upper right here, showing the spongiosis here kind of in these circles, as well as the infiltration of inflammatory cells getting recruited to the inflammation, and then finally progressing to chronic lesions with our hyperkeratosis, thickening of our stratum corneum, and then again still that inflammatory infiltrate and fibrosis.

So when we think about the—when we think about the components of the pathophysiology, here we can see a lot of molecules have been implicated when we think about the pathophysiology, including our acyl (sic) hydrocarbon receptor, which has been shown to strengthen skin barrier genes. We've talked about IL-13 as well as IL-4, which are key Th2 pro-inflammatory cytokines that are promoting that inflammation and recruitment of those inflammatory cells. And then once the epithelial barrier gets activated at the epithelium, we get release of our epithelial cytokines, IL-25, IL-33 and TSLP, which are sometimes called alarmins, that are activated when we get destruction at the epithelial barrier. IL-31 is involved in itch, as we all know, and suppression of filaggrin expression. And a lot of these cytokines will then signal through the JAK-STAT pathway, and so that's where we have our JAK inhibitors to kind of tolerate —to inhibit, I'm sorry—the signaling through the JAK-STAT pathway, and then newer molecules in clinical trials that target OX40, OX40 ligand, which kind of triggers that T lymphocyte response and our memory response of allergens and antigens, and then finally, S1P, which is a signaling molecule that inhibits proliferation and induces differentiation. So these are all different components when we think about the pathophysiology of AD, all that have some molecules in development or FDA approved to target for AD.

And so now, as we know, we now talk a lot about the neuroinflammation in AD, or kind of the neurogenic itch. And so, what we know when we think about neurogenic itch is that there are several cytokines, including IL-31, IL-13 and IL-4 that will bind directly to the sensory neurons and then signal through the JAK pathway, including JAK1, to cause some itch. And so we know IL-31 is important in acute itch, IL-13 in chronic itch, and then histamine also is more common in acute itch, and then IL-31 also in chronic, so just kind of showing that not only is this inflammatory infiltrate causing inflammation and destruction of the—not destruction but inhibition of filaggrin expression in the skin barrier, but we can also get itch directly through the direct signaling through the neurogenic pathways.

And so, when we think about the role of adaptive immunity, again we get—here's our epithelial barrier on the—or kind of our cartoon of the skin, and we get either scratching, microfissures or other things, and we get our allergens and irritants that can cross through here and then activate our immune response here in this kind of drawing here. And then once we get activation of our immune response, including activation of our Th2 arm of our immune system, which then leads to our increase IL-4, IL-4/5 and 13 in acute lesions. And then in some patients, particularly, you know, of non-White patients, maybe some of our Asian or Hispanic participants, we may see some increase in IL-17 and maybe IL-22 and IL-23. And then chronic lesions we see some TH1, and then that kind of leads to our inflammation.

In addition, some of these cytokines can then react directly with the sensory neuron to promote itch. And so here you can see kind of that inflammatory cascade, and here are all the molecules that are either FDA approved or under development to try to target all along these signaling pathways, including ours that target IL-13 alone, which would be tralo and lebri, and then those that target our IL-4 receptor, which will inhibit IL-4 and IL-13, which would be dupi, and then some of the others, as you can see, targeting IL-17, IL-23, and our OX40, OX40 ligand molecules that inhibit that. So here we are with kind of a nice overview slide of where we are in 2025 when we think about targeting the adaptive immune response.

And so, when we think about this Th2-mediated inflammation, the thing about once this inflammatory cascade starts, like once you start this inflammatory cascade, it's not as if the IL-14 or that response or the IL—sorry, the IL-4 or the IL-13 or IL-5 just stays in the skin and we only get skin. Once we get activation of these Th2 responses, either through barrier dysfunction or more likely allergens that are able to now cross through this defective barrier and cause differentiation of our dendritic cells to an inflammatory phenotype to then promote our naive T cells to differentiate to Th2 T cells—once we have that 4, 5, and 13 that are released, then they can go and do their effective functions. And this could be, again, increasing our IgE, increasing our total IgE, our specific IgE, to increase our eosinophils. And then also, these Th2 cytokines have been shown to inhibit—we all know this already—our antimicrobial peptides, and so that increases the risk of skin infection in these patients. And then once you have these cytokines, now they're in the bloodstream, and they can leave the skin and then migrate to other mucosal surfaces, and this kind of leads to when we start thinking about the atopic march or the development of food allergy, asthma, and allergic rhinitis in these patients.

And in addition, once you have this inflammation that's going on, that will go ahead and promote that itch-scratch cycle. And so once you start to get some inflammation, the skin becomes more sensitive to these irritants and allergens, and then that makes the patient more itchy, so then they start scratching, and then that causes more inflammation, and we kind of get this continuation of the itch-scratch cycle. And then these cytokines will react as, as I mentioned, directly on the sensory neurons at the C fibers to start signaling through the neuron, through the dorsal root ganglion and trigger, trigger that itch sensation, that neurogenic itch.

And so this happens acute as well as chronic, and so I kind of just talked about this already, where we get skewing of the immune

response, especially in our acute lesions to the Th2 phenotype with a release of IL-4 and 13, which can then react directly on the neuron to cause itch. In addition, that epithelial dysfunction will cause the keratinocytes to release TSLP, which can then also activate kind of other receptors, including our TSLP receptor to promote itch as well as TRP channels and direct calcium influx.

Okay, so now that we've gone over kind of what's happening at the immune system when we start thinking about this itch, we're going to go through these simulations. And I know there are some questions that were put in the chat. I'm not ignoring those. I think we're going to cover those at the end of the talk so—

Dan:
Hi, I am Dan. I've had eczema since I was a kid. Back then it would come and go. Some lotion, a mild steroid cream, and I'd move on. As I got older, it stopped fading between flares. Now it's every day, thick moisturizer morning and night, and strong steroid creams just to get through the week. The past two years have been the worst, constant itch, scaling, and recurrent flares that don't fully calm down. Nights are the hardest. I'm awake scratching when I should be sleeping. It's hitting my work. I'm tired, distracted, slower than I used to be. Simple things take more energy when your skin won't give you a break, and it messes with social life. I think about what people can see if I'll start itching in public. Sometimes I just say no to plans. Me and my primary care clinician were hesitant to use high-potency topical therapies, and I was referred to a dermatologist. I even tried phototherapy, weeks of appointments, and nothing really changed. I'm doing everything—daily emollients, high-potency topicals—and I'm still stuck in this cycle. I want itch relief that lasts, real sleep, and skin that doesn't control my day. My doctors never explained to me why and what triggers my itch. I am ready to talk about what's next, something that actually quiets this for the long run.

Dr. Singh:
Okay. So I know this is like—Hi, I am Dan. Let's see. Okay. So I know this is an AI-generated patient, so a little bit artificial, but I think we have all seen patients that are like this, especially in a subspecialty practice. But I guess the points of discussion here are, Are there any thoughts about this patient? Do we think Dan's experience is common? And how should we counsel and educate patients regarding the underlying drivers of the itch? And what are some targeted therapies that can directly address these factors?

So if anyone wants to put any comments in the chat, go ahead and do so, but otherwise, I will just say that this is certainly common. These patients get on the tilt-a-whirl or the roller coaster of using medications, getting things under control, and then they seem okay for a while, and then it comes right back, and kind of this kind of up and down cycle, and then the frustration. Like, once they have this bad disease, it starts to affect so many different aspects of their life, including activities I think was mentioned in that patient. Sleep was mentioned in that patient. Again, all very common. I see one comment in the chat about that this is common, and so with that, I think we can kind of move on.

And I will mention I'm—like, I'm on the guidelines committee, the Atopic Dermatitis Guidelines Committee for the AAD, and we did just recently publish a manuscript about these kind of nonallergic and allergic comorbidities with AD, and that's kind of sleep, anxiety, depression. All of that is on there and more common in patients with AD.

Okay, so what is the evidence that IL-13 inhibition for moderate to severe atopic dermatitis actually works? So this kind of leads to our next polling question, which is What do you perceive as a primary challenge in managing moderate to severe AD? Is it A) Diagnosing the disease and how severe it is? Is it B) Getting patients to adhere to the treatment that you've recommended? Is it C) Access to advanced therapies? Or is it D) Understanding the current treatment guidelines?

Announcer:
And polling is open. Please vote. We'll allow a few more seconds for incoming replies. And we'll go ahead and close that poll.

Dr. Singh:
Okay. So pretty evenly distributed across the line, just kind of illustrating that there are a lot of challenges and barriers, and to really kind of get at this, we really need to address all of these things. So thank you for sharing your experience.

Okay, so what are our choices, or what do we have that's approved? And so here we have our FDA-approved therapies for atopic dermatitis, including our biologics kind of at the top, which are our injectables, and then our small molecules in the bottom, which are our JAK inhibitors here. And so, as we mentioned, dupilumab will target the IL-4 receptor. So this is the IL-4 receptor, this kind of purple part of the antibody or the signaling here. And so, when you inhibit the IL-4 receptor, we inhibit signaling for IL-4 and IL-13. We also have our IL-13 selective antagonists, including lebrikizumab and tralokinumab, both IL-13. There are some differences in the molecules for these drugs. So the lebrikizumab is, I think, a little bit better of a molecule, so in terms of the pharmacokinetics and dynamics with regards to how well it binds and how strongly it binds, and then nemo, which is our IL-31 receptor, and then, again, our JAK inhibitors, our selective JAK1 inhibitors, including abrocitinib and upadacitinib. So these would be our oral JAK inhibitors. Again, the JAK inhibitors are much less selective, and so with that you may see inhibition across multiple cytokines, but then that also leads to kind of more immune suppression

than our targeted biologics.

So, let's see. Here are FDA-approved biologic therapies kind of all together in one table. Again, dupi, tralo, lebri and nemo across the top. And then we just went through their mechanisms on the last slide. As far as the three on the right are 12 and above, where dupi has been approved down to age six months. Here you can see the timing of injection, again ranging from every two weeks to every four or eight weeks depending on the drug, as well as the dosing in our pediatric and adult patients. Each one of these kind of has their own sort of warnings or side effects. And of course, if we're going to inhibit Th2 cytokines, we need to think about parasitic infections, the conjunctivitis side effects, which we're going to talk about a little bit in a little bit more. And then some of these, not just nemo, has an indication to avoid live viral vaccines.

Okay. So, what is the effic—or what is the data for the efficacy and then the safety of these drugs? So, if we start first by reviewing the LIBERTY AD CHRONOS trial, which looked at the efficacy of dupi in adults, these were adult participants with moderate to severe AD, and all of these patients could also use topical corticosteroids and/or calcineurin inhibitors with the dupi, and they were randomized to 300 mg sub-Q either every week or every other week versus placebo for a year. And here you can see that the dupi worked. It worked, and it worked nicely. So, if we look at the percent of patients who got an IgA of 0 or 1, which would be a skin that's clear or almost clear, you can see both every two weeks and every week for the dupi at week 16 and sustained efficacy down to out to week 52, with about 40% of patients achieving this IgA score. If we look at a 75% improvement in the EASI or the EASI-75, again we see efficacy at 16 weeks in the 60, 60, maybe up to 70% range and sustained efficacy out to week 52. So again, here's our data for our efficacy of dupi in adults. Again, 40—remember these numbers—40% with our IGA of clear or almost clear and between 60 to 70% achieving the EASI-75.

Okay, so that was the efficacy. What about the safety? So this is now the LIBERTY AD open-label extension—so OLE stands for open-label extension—which looks at the safety of dupi for up to four years. And again, overall, these molecules are very—they're quite safe, so low rates of serious or severe infection. And in fact, infection decreases while they're on the dupi, and I think this is just because they have better skin control, as well as lower rates of non-herpetic skin infections. And then here are some of the skin infections of interest, including eczema herpeticum, herpes and zoster. And again, similar across the groups comparing placebo and dupi and then across the open-label extension.

If we next look at the efficacy of dupi across different race and ethnicities, so here is some data that kind of separates out our White patients from Asian and Black patients. And here you can see, first of all, there's some efficacy across all race and ethnic groups across Liberty AD, SOLO 1, SOLO 2, and CHRONOS. Maybe, I mean, these are overlapping confidence intervals, maybe a little less efficacious in Black participants, but again, overlapping, overlapping confidence intervals. And again you can see there is some variability in response, and the tightest is favoring dupi as among our White participants. And there can certainly be some variability of responses in our patients of color.

If we look at adverse events now across our different subgroups, again it's pretty similar across. The top is our treatment-emergent adverse events, and then the second row is our severe treatment-emergent adverse events, and then the third row is adverse events causing—making somebody stop the drug. And again, most participants continued with the drug throughout the study, and again, these are not clinically significant across the groups. And you can see conjunctivitis is common, maybe a little bit more common in our Asian and White participants compared to our Black participants, but again, pretty similar across the groups.

Okay, so moving on from dupi. What about our JAK inhibitors? So this is upadacitinib versus—I'm sorry, this is comparing upadacitinib versus dupilumab for moderate to severe AD head to head. This is the HEADS UP trial, which is 24-week head-to-head comparator that enrolled 673 patients, again the primary endpoints being EASI-75 and itch relief in IgA. And basically, you can see patients on upadacitinib had a statistically significant better response when looking at EASI-75, as well as faster itch relief at one week with the upa, the upadacitinib, versus dupi, as well as clearer skin at week 16 in the upadacitinib versus dupi. Safety, however, as we talked about, the JAK inhibitors are a little bit less selective, and maybe you can have a little bit more immune suppression, so there were some increased infections with the upadacitinib group compared to dupi, including herpes zoster and eczema herpeticum. And then on the dupi side, there was increased conjunctivitis, as we all know, is a side effect of dupi. And then obviously, injection site reactions would only happen with dupi as upa is oral.

So in conclusion, upadacitinib offers superior and faster skin clearance but a higher infection risk, and so, when we start thinking about which one of these medications should we choose, we really—this becomes shared decision-making where we need to talk about patients' preferences as well as risk factors with regards to some of the side effects and the balance of efficacy versus safety. And I also want to mention what's not on the slide is we all know about the MACE, the major adverse cardiac events, have as a warning on our JAK inhibitors. Again, this is borrowed from the experience in the rheumatoid arthritis literature, but it's certainly there. It needs to be discussed and certainly a part of our—especially our adult patients when considering these drugs.

So now, what about head-to-head dupi versus tralo with topical steroids for severe AD? Again, this is 575 adults with severe AD and inadequate response to topical corticosteroids. And so here, dupi plus topical corticosteroids showed greater efficacy versus tralo with the topical steroids at 16 weeks, and that includes improvement. And the EASI-75 are itch score, so that's the NRS, the PP. This is Patient-Perceived Numerical Rating Scale for itch, so that's kind of the blue, and then our quality of life, our Dermatology Quality of Life in the green. And so, basically, dupi plus topical steroids demonstrated greater odds of achieving these key endpoints compared to tralo, so better skin clearance, more itch reduction, and quality of life.

Okay. So, what is the evidence for tralo? This is the ECZTRA 1 and 2 trials, and again showing the percent of participants who achieve that skin that's clear or almost clear or the IgA of 0 or 1 at week 16, and here you can see there's a significant improvement in those who received tralo, but again, lower than our dupi participants. So here you can see between 15 and 24%. So there certainly is an improvement in the—compared to placebo in the patients who are able to achieve clear or almost clear skin, but this is lower than for dupi. If you remember, that was around 40. Here we're closer to 20, 25, and patients who—There was less use of the rescue topical steroids though with the tralo. So there was some improvement, less need for rescue, but a lower percent of patients were able to achieve that clear or almost clear skin. Patients with tralo also had improvement in their itch at—with a 4-point improvement in the itch numerical writing scale. And the patients who did respond to tralo though, it was a sustained response, so they continued to work to 52 weeks. And adverse events were comparable, so again showing that there is efficacy with tralo.

What if we look at efficacy now across racial subgroups? And again, you can see it's pretty, pretty equal throughout. Around 70 to 80% are able to achieve skin that's clear or almost clear, but when—I'm sorry, 70 to 80% were able to achieve a 75% of improvement in the EASI-75. Fewer were able to get (skip in audio) 90 lowest in our Asian participants. And then again, our skin that's clear or almost clear is here in the middle of the slide between 37 and 69%, maybe more efficacious for our Black participants compared to Asian. Here are adverse events across our different patient populations, and again pretty similar across the groups, and very few patients needed to stop the drug due to withdrawal.

Okay, so now let's move on to lebrikizumab. So these are the ADvocate 1 and ADvocate 2 trials looking at the lebrikizumab efficacy at 52 weeks, and here we see fantastic or very good efficacy, not the 40% that we saw with dupi and certainly not the 15 to 20% we saw with tralo, but instead we're seeing a 70 to 80%. So, when we look at our IGA skin that's clear or almost clear, we're up into the 70s now, 71.2% or 76.9% depending here at the top whether it was ADvocate 1 or ADvocate 2. And then at the lower half of the slide, we're seeing close to 80 or into the 80s for our EASI-75 response. So, again, also we're seeing an improvement in itch here with that 4-point improvement, so again showing efficacy with lebri. Ad although both tralo and lebri are both IL-13 inhibitors, I think this is evidence that the molecule matters. So, which one that you're using does matter, and I think that has to do with how well it binds and the affinity for the molecule for the receptor.

What about safety considerations with lebrikizumab? So here you can see rates pretty, pretty similar to the previous studies we looked at, but also, if we look at our serious adverse events, they're kind of low maybe in the first trial. It looks like it's only six participants, but it may be a little higher on lebri, but then you can see the percentages are flip-flopped when you get to ADvocate 2, so again, pretty similar across the groups. The exacerbation is listed as an adverse event, conjunctivitis again a common one, nasopharyngitis and headache. If we look at infection, in a herpes infection, you can see the rates at the bottom of the slide as well, pretty similar comparing placebo versus lebri.

Okay. What about in patients with skin of color? So this is the ADmirable study that looked at the efficacy of lebri at 16 wicks in people with skin of color and again demonstrating efficacy in the percent of patients that achieve an EASI-75 or an improvement in their EASI-90. So here you can see 69% will achieve an EASI-75 or 45% achieve EASI-90, And 45% of our patients with skin of color get to our skin that's clear or almost clear. And as far as our other endpoints, these are listed here, including improvement in itch, and 70% will get an improvement in their quality of life, again a 3-point improvement in itch, then goes from 60s to mid 60s, and then certainly an improvement in their quality of life score.

When we think about our patients of color, I think changes in pigment becomes very important, particularly important in patients with more pigmented skin tones. And so, if you look at this specifically, 33% saw improvement in lesions that were hypopigmented, in which 17% of these lesions improved to normal skin tone, and 63% saw improvement with hyperpigmentation, and up to 20% achieving back to normal skin tone. And I think this is a very important particularly, or can be very important particularly in our patients of color. And so here you can see a picture of a patient that you can see this improvement to a normal skin tone.

And, oh, I changed the slide, but I also want to mention—and I think this may come up later—but just as a reminder that I think—hopefully, everybody in this room knows this, but, you know, atopic dermatitis can look different in patients of skin of color. We know there are health disparities where the severity is often underappreciated or the skin is more severe before they get offered treatments or more advanced therapies, and this can be because the erythema or the redness that we see in all of our textbooks and all of our slides

is much harder to appreciate in patients with skin of color, and it may be—it may have more of that gray violaceous appearance or that papular follicular pattern, which may differ from our White patients. Sorry, if we go back here and look at safety again in our patients of color in our ADmirable study, you can see again very safe, most of the side effects are mild, maybe moderate, few severe, and just a low rate. Just about 4% had treatment-emergent adverse events.

Okay. So here is our clinical profile of our IL-13 inhibitors again comparing across. So, again, dupi blocks our IL-4 receptor and then our IL-13 molecules, which is tralo and lebri, and then—and I think kind of the difference here is the lebrikizumab will block also across the IL-4 receptor complex. It has a higher affinity and a slow disassociation rate, so I kind of alluded to that before, that it binds tightly and then stays bound longer. And so all of these have been shown to improve AD severity and quality of life. And I think what lebri has going for it is it can have a sustained AD symptom and severity reduction. Because of the high affinity, some of these you can inject less frequently, and I think there is some data to think about lengthening the intervals for some of these drugs, particularly with the lebrikizumab. There's efficacy across all body sites and regions, including face, hands, and the body. And then the adverse events are pretty similar across the board.

Okay, so just we have our next patient, Amy.

Amy:
I'm Amy, a 36-year-old female. I've lived with eczema most of my life, but this past year it's been different, worse. I also suffer from asthma, which is well controlled with ICS, LABA. My skin is raw and itchy, and I've done a lot already with steroid and calcineurin creams. My atopic dermatitis covers a big area and keeps flaring. I use strong prescription creams, steroids and calcineurin inhibitors, plus daily emollients, and still the redness, itching and scaling keep coming back. The itch is nonstop. Nights are the hardest. I don't sleep. Then the next day everything feels heavier. It is very difficult to apply cream everywhere on my body. It's hurting my work and my social life. I plan my clothes, my schedule, even my mood around my skin. It feels like an itch-scratch loop I can't break. I have two kids, and I'm not planning pregnancy in the near future. I would like to know my options and understand what we can do next.

Dr. Singh:
All right. So this video, I think there are certainly some similarities with our last patient. So, what are some next steps for this patient? So, when we think about when is it that we would escalate to a biologic therapy, any of the ones that we talked about or a small molecule therapy, certainly if somebody is failing our topical therapies, but also along with that would be if they can't keep up with the therapies. So there's certainly been studies to show that if patients do exactly what we them, they bathe in lukewarm water for up to 15 minutes and then pat dry and use emollients and use their topicals, that whole routine takes an hour. And so then if— and then if you're asking them to do that twice a day, we're looking at two hours a day. It's like a part-time job, 14 hours a week trying to take care of their skin. So, if either the treatments aren't working, they can't keep up with the therapies, or obviously, if it starts affecting other parts of their life, it's affecting daily activities, activities they want to do, sleep, learning, concentration, anxiety, depression, kind of all of those things, all these participants would be reasons to think about escalating therapy.

Okay. So that leads us into when should we evaluate a patient as a candidate for an IL-13 inhibitor. And so this is when we start thinking about going beyond topicals. I just kind of talked about this in the context of the last patient. So we talked about persistent symptoms despite best topical therapy, frequent flares or exacerbations despite their therapy, or flares that are impacting their quality of life. They're not going to things or canceling things. I see mostly kids. I have had teenagers who quit the soccer team or quit the tennis team because when they get sweaty, it flares their eczema. I've had other patients who kind of withdraw from their social circles and their friends because they're embarrassed about how their skin looks and things like that. I mean, we've all had these experiences. Significant itch in sleep, that's also a thing, and if someone can't sleep, that starts affecting all parts of their life, including how they present when they're awake, how they're doing, how alert they are. And then when you can't sleep, that can also lead to mood issues and things like that.

So, how do we monitor if somebody's responding or if they have some of these issues? This is where we have some really nice questionnaires, which I'll go over in the next slide. If you want to look for these things, including itch, sleep, quality of life, and then how severe their eczema is, you can look by doing an EASI or a SCORAD. And then when we talk about our therapies, if you look at the guidelines, like we mentioned, there's these beautiful tables that show which ones are—have strong recommendations using GRADE methodology, which medications have a strong recommendation for or a conditional recommendation for or, perhaps, a conditional or strong recommendation against. And our strongest recommendations or that kind of strong recommendation for are with our biologic and our JAK inhibitors. And then there is a recommendation against oral corticosteroids because of rebound and things like that.

And then, obviously, if we think back to the beginning of our talk when we talked about what are patients concerned about, what are they looking for for their healthcare provider, let's just make sure we're addressing their fears; set the expectations from what they can expect on biological therapy, including the long-term benefits and safety profiles; and then of course, shared decision-making.

So here are our clinical assessment tools, if I can get back there. Here's our numerical rating scale that you can use for itch, just a simple 10-point scale how itchy do you feel. And then also pain. So I haven't talked about this much, but, you know, if we remember, the itch and pain are along the same neurons, so when those get activated, these patients could have pain. If you want to assess their AD control, there's an AD control tool, or you can look at a POEM, and then our Dermatology Quality of Life. So again, these are short, sometimes very short questionnaires that we can use to assess how the patient is doing and then how they respond to therapies.

I talked about this already. We know there's variability in clinical presentation depending on age and skin of color. I don't think we need to harp around this too much, but we know that the location of lesions may change depending on the age across the top of the slide. And then we did talk about the variability and presentation, where our kind of textbook pictures are often shown in lighter skin tones, where we're looking at that pink and red erythematous lesions; where in our darker skin tones, we may see the papular or follicular distribution, and then as well as changes in pigmentation, and then that gray, ashen, or violaceous appearance that may be harder to appreciate on a darker skin tone.

So here are some photos. Again, this is certainly more moderate to severe disease, again showing a White patient on the left and then a patient with a darker skin tone, a Black patient on the right. And here you can kind of see that gray, thickened gray distribution with some scaling, and then again here we can even see a little bit of papular distribution a little bit more widely here and that hyperpigmented kind of ashen experience, ashen appearance. And then in an Asian participant, again, maybe less likely to see erythema and it may be—it may look more kind of darker or chronic, and here you can see—Whoops, this is really important, so I don't want to go too fast through it. So here we can see kind of that violaceous or gray appearance, maybe a little bit more well demarcated, and again kind of lacking some of that erythema that we may see, that we're used to seeing in a White participant.

Okay, so I did talk about pain. So pain is actually common in patients with AD and often not talked about, and some of this pain, associated pain with AD, and this kind of patients feeling a little shackled by the pain or losing hope with being able to get treatment for the pain can really lead to some anxiety, depression, and even suicide ideation among patients with AD, which are all higher. And this has been shown in children. So here's our pediatric burden for pain, and similar has been shown for adults.

We talked about the impact of sleep—sorry, I'm just noticing I need to move a little faster here—so our impact of sleep, and here you can see sleep disturbance is common even among mild AD. Over half of patients, almost two-thirds, will have impact on sleep one to two days a week, so that's a lot. That's a lot of sleep disturbance, and it's across ages and across severities. And obviously, especially when we're talking about a pediatric population, if the child's not sleeping, the adults in the household aren't sleeping too, and so that's just another thing to kind of consider the impact on the whole family. Here's patient burden of quality of life, and here you can see just a big impact on quality of life that is proportional to severity of disease across age groups.

So we've talked about this already. AD is associated with increased depression, anxiety, shame, disgust, sleep disturbances, stigmatization, and as I mentioned, the suicidal ideation. Patients with AD are 44% more likely to have suicidal ideation and 36% more likely to attempt suicide compared to patients who don't have AD. And patients are 20%—20% of patients with AD will have depression, which is twice as high as the general population. And so we all know what these mental health effects come from. There's the toll that the itch and the sleep take, but also, when you have something so, you know, in your face affecting the skin and how you appear to the world and how you present to the world, that can really affect our wellness.

In general, you can see when patients—lots of patients are happy with their therapies, but not all. So up to half to up to a quarter and a half are not happy with their current therapies, as you can see, and so they may want to make a change. And even patients who are put on a systemic, you can see most patients are happy. They can have improvement, but just not always, and so sometimes we need to switch the systemic therapy somebody is on. And so, when we do this and we're thinking about making these changes, this is where shared decision-making is really important. We should talk to our patients, listen and engage, understanding what are their goals and preferences; how does their cultural skin care practices affect their thing; and how can we support patients making this decision?

We have one more patient. It's basically similar to the other one, teenage.

Jeremy:
I am Jeremy, an 18-year-old male. I've been struggling with AD since I was a kid. It used to flare and fade. Now it's everywhere, and it doesn't let up. I use prescription creams every day, and when it gets bad, I've taken short courses of oral meds. The itch quiets, then comes roaring back. I have been using ointments since childhood. I'm exhausted. My parents nag me to use them regularly, but they are greasy and difficult to use on large areas, especially when I play sports. The itch is intense, especially at night. I'm waking up scratching without even knowing it. Sleep's a mess. Showers sting. Clothes rub. At school I'm distracted and tired. It's hard to keep up when your skin won't give you a break. I'm worried about my grades. I cancel plans more than I want to. I'm always thinking about what people see and when the next flare will hit. This makes me anxious and depressed about how I look and feel. Creams and the occasional steroid

aren't enough. I need a plan that relieves my symptoms and the itch so I can sleep, work, and show up for my life.

Dr. Singh:
All right, so this case is just highlighting kind of the teenage aspect of this, difficulty concentrating in school, sleep, and then affecting activities, sports, and how they show up with their friends.

Okay. So here are our key takeaways. We know IL-13 can drive our AD pathogenesis by impairing the skin barrier with decreased expression of filaggrin and n and loricrin, increased inflammation and itch. Our biological therapies targeting IL-13 include dupi, tralo, and lebri, which help improve barrier function and reduce inflammation. Identifying candidates we talked about, including those with moderate to severe AD, those that have failed topicals or can't keep up with the regimen and then—or it's affecting their quality of life. And then, obviously, we need to monitor these patients and make sure they're getting better, and if not, advance their therapy. And we talked about our tools that we can use to assess, and then shared decision-making.

And so with that we'll go to the post-test. First question: A 36-year-old patient with longstanding moderate to severe AD has widespread erythematous, scaly plaques, itching, and they've tried topicals, and they want to know what is the best mechanism or how do drugs that target IL-13 work? Do they A) Strengthen the skin barrier by upregulating our barrier proteins? Do they B) Strengthen the skin barrier by down-regulating our barrier proteins? Do they—Does IL-13 increase Th2? By blocking IL-13, would that increase our Th2 activity? Or D) Does it affect the neutrophils?

Announcer:
And polling is open. Please vote. You have a few more seconds for incoming replies. And we'll go ahead and close that poll.

Dr. Singh:
Okay, so excellent. So the correct answer is A, that IL-13 helped strengthen our skin barrier by upregulating our barrier proteins, including filaggrin and tight junction proteins. The reason why C is wrong is because IL-13 is a Th2 cytokine, so if we block IL-13, that will decrease our Th2 activity. So I'm sure whoever, they probably just read this question quickly. So it decreases our Th2 activity.

Our next question: Mark has been diagnosed with moderate AD and struggling with itching, lesions, poor quality of life. He's tried topicals and wants to consider something else. What would be the most appropriate choice for targeting IL-13 alone to improve his skin barrier function? A: Dupi, B) Nemo, C) Lebri, and D) Upa, upadacitinib.

Announcer:
And please vote. Give a few more seconds for incoming responses. We'll go ahead and close that poll and share.

Dr. Singh:
Okay, so these are both our IL-13 inhibitors, so this is absolutely right. Lebrikizumab would be our only targeted IL-13 alone, where dupi would target our IL-4 receptor, which is 4 and 13. So the correct answer, the best answer to the response is C, but dupi also targets IL-13 just with IL-4 as well.

Okay, I think we have one more after this. So Mae is our 36-year-old with severe AD and eyelid involvement, and she wants to start a therapy. So, how do we handle it when someone has an ocular history? Do we A) Avoid it, avoid an IL-13 inhibitor forever because of the ocular history; B) Do we go ahead and initiate it, but then refer to our ophthalmology colleagues for support if symptoms occur? Instead, do we not use it and instead do oral corticosteroids? Or do we D) Delay systemic therapy until the eyelid symptoms completely resolve? Do we have the poll going?

Announcer:
Sorry about that. Give everyone just about 20 seconds to read through and answer real fast. All right, we'll give a few more seconds here, and we'll go ahead and close and share. Thanks for your patience.

Dr. Singh:
Great. And everyone got that right. The answer is B. So go ahead and start it, and if the symptoms recur, we will refer to ophthalmology. And almost always patients can treat through ophthalmology symptoms with either lubrication or sometimes other drops.

All right, so our final two post-test questions: How confident are you in identifying patients who may be a candidate for step up to a biologic therapy targeting IL-13? Not confident, somewhat not confident, somewhat confident, confident, or very confident.

Announcer:
Polling is open. Please vote. A few more seconds for incoming replies. And we'll close that poll and share.

Dr. Singh:
All right, excellent. So more participants are—We did kind of skew our curve to the right, which was the goal of this presentation, going

from not confident now to either somewhat confident or very confident, so excellent.

And then our last question: Do you plan to make any changes to your clinical practice based on what you learned today? Yes, no, or uncertain.

Announcer:
And the poll is open. Please vote. A few more seconds for incoming replies. We'll go ahead and close and share.

Dr. Singh:
Great. So I'm so happy to hear that the presentation was useful today and that you learned something that may affect your clinical practice, so thank you for being here. If you have a moment, you can scan this QR code to text one change that you plan to make, or you could put it right here in the chat, so I'll leave that open. And then I know we're a little bit past the hour, and I want to be respectful of everybody's time, but do we have time for a question or two while people are filling out the poll, or how do we—

Announcer:
Yes, if you have time, Dr. Singh, that would be fine.

Dr. Singh:
Yeah. Yeah.

Announcer:
Yes. Are you able to see those that are in the Q&A?

Dr. Singh:
Yeah.

Announcer:
Okay.

Dr. Singh:
Okay.

Announcer:
I'll let you address the ones you think you can get to. Thank you.

Dr. Singh:
Yeah, yeah. So we can, we can kind of go through these. So the first one: Can IL-13 inhibition alter long-term disease course or remission likelihood? So this is data that was not shown in this presentation, but I have seen data that long-term disease course or remission is kind of hinted at in some of the lebrikizumab data where patients were able to lengthen the interval and have sustained response with a lengthened interval or even after the lebrikizumab was discontinued, so I think the answer to this first question is "more to come." And especially as a pediatric specialist in allergy, immunology, rheumatology, I'm really excited about is there potential for this playing a role in the atopic march or the expression of other atopic diseases. So I think more to come and a really intriguing and an exciting thing that could be coming down the line.

The next question: For a patient who had partial response to tralo but still had persistent itching in six months, what would I suggest? I mean, I think a change. And so I think that was shown in one of the slides with the bar graph of how happy are you with your current therapy. Like, a lot of patients, even when they get some response, if they're still having incomplete response, it may certainly be worth a change. You could certainly try another IL-13 inhibitor. I think the lebrikizumab, it does have a better efficacy over tralo, as shown by the percent of patients that get clear or almost clearer, or the percent that get improvement in their itch. We also know the molecule is different, and so a little higher affinity and stays bound longer so—or you could try a different, you know, just switching classes as well. That would be a choice.

The next question would be: Any strategies to address patients with depression stemming from their AD? So I see my role in this as kind of screening so—but I am not qualified to treat depression. So my qualification is to take the best care of their skin as I can, and that may help some of their depression symptoms, but if somebody reports to me that they're depressed or if I do one of these scales and it comes up, then I refer them. And so I can tell you I refer them to a mental health specialist. So I ask because I think that's a part of being an atopic dermatitis specialist, but I don't treat. And in my template—Again, my patient population skews younger, but in my template on my visit note in Epic, I have questions that say like does—and it's often "Does your child" is what it says, but do they suffer from attention difficulties, ADHD, difficulty in school, depression, anxiety. And it's quick. Like, it just takes me 10 seconds in my visit. But if anyone responds yes, then I just address it, and I refer them to a mental health professional.

And then the last question is someone's already on dupi and doing well, but they wanted to know how long they will respond, and I think this is hard to answer. I always tell my patients that I don't have a crystal ball, but as long as they're responding, you can stay on it. We know from the open-label extension, the LIBERTY OLE, that, you know, if you have response at one year and you continue to take the drug, at four years of open-label, extension patients we're still responding. So again, I think it's just important to continue to have that conversation with your provider. And if at any point it's not working, don't give up because we have other choices, and we should try different medication so—

Okay. And I think what I want to leave this session with—and I think that's all the questions—is just for so long we didn't have all these choices, right? Like, all we could do is give somebody steroids and more steroids and then maybe oral steroids or maybe some broad immune suppressants, methotrexate or something like that, and monitoring for side effects, but this is a really exciting time to be taking care of patients with moderate to severe AD. We have so many more choices for targeted therapies that are safe, and we just need to make sure our patients have access to them. And really, we have an opportunity to make just such a difference in our patients' lives.

Announcer:
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