Transcript Details

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Test Your Skills and Learn From Experts on IL-13 Inhibitors in Moderate to Severe Atopic Dermatitis

Announcer:
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Dr. Alexis:
IL-13, what's its role in atopic dermatitis? Well, turns out, it is a key driver of inflammation and barrier dysfunction in atopic dermatitis. It plays a central role in the pathogenesis of this disease.

We all recognize atopic dermatitis as being an extremely common—very, very common, highly prevalent, immune-mediated disease that we probably see on most days. It affects 3 to 20% of children globally. Symptom onset is most common pretty early in life—3 to 6 months of age. In fact, among children who are diagnosed with atopic dermatitis, the overwhelming majority develop it by the age of 5.

However, about 1/2 of cases persist into adulthood. And then there's this cohort of patients who are diagnosed as adults. And it's estimated that 25% of cases may report symptom onset during adulthood, and this has been an understudied patient population, that we're beginning to appreciate more and more.

We recognize atopic dermatitis as characterized by cycles of flares of redness, and scaling, and itching. And from real-world evidence, many of our patients with moderate to severe atopic dermatitis are not well controlled at all. They have an average of almost two flares per month, and 74%—so almost 3/4 of patients—reported not having any remission of their symptoms in the past year. So this speaks to the lack of control among many of these patients who are not yet treated as well as they can be.

So thinking about the immunopathogenesis and the role of IL-13. So IL-13, we know, is a key Th2 cytokine. And what's its role in atopic dermatitis? Well, its role involves barrier disruption as well as the downstream immunologic cascade that is Th2-driven, that we know characterizes atopic dermatitis.

So it contributes to epidermal barrier dysfunction by downregulating the expression of key structural proteins like filaggrin and loricrin, and other structural proteins. There's even reduced expression of antimicrobial peptides in the epidermis, and this contributes to increased development of Staph aureus colonization.

There is increased chemokine expression and eosinophil recruitment, pruritus which we'll talk about some of the interesting cross-talk between the immune system and the sensory nervous system, contributing to itch. There's also a great deal of evidence that elevated IL-13 levels correlate with disease severity. And targeting IL-13 with biologics has been shown to have efficacy in improving atopic dermatitis signs and symptoms, that we're going to be going through the data later on in the program.

So when we think about epidermal dysfunction and how much it plays a key role in the pathogenesis of disease and the signs and

symptoms that we see in our patients, this compromised epidermal barrier lead to increased permeability to pathogens, to irritants, to allergens, increased transepidermal water loss, contributing to greater xerosis, which is such a common feature of this disease.

Filaggrin mutations, which are one of the more prevalent genetic factors associated with atopic dermatitis, and reduced filaggrin expression, disrupts corneocyte integrity and impairs hydration, and IL-13 actually reduces filaggrin expression as well. So we've got genetic mutations in filaggrin that contribute to lack of expression, but we also have the effects of the Th2-driven immune cascade in reducing filaggrin expression.

We see reduced ceramide content in the stratum corneum as well, and IL-13 is associated with some of that reduction.

There's suppression of the antimicrobial peptides, as I mentioned, leading to microbial dysbiosis with Staph aureus colonization and, in some cases, secondary infection.

When we think of the clinical and histologic features of atopic dermatitis, we immediately recognize how heterogeneous the presentation is. And while histologically spongiosis is a key hallmark, clinically, depending on whether it's acute, subacute, or chronic lesions that we're looking at, we might see oozing and crusting in the case of acute cases, subacute more scaling and redness and chronic, more lichenification and thicker papules and plaques. And depending on the anatomic location, we see a great deal of variability in the morphology, so very heterogeneous disease and a spectrum of presentations all falling within atopic dermatitis.

We might even see differences depending on the age of the patient. Different racial, ethnic backgrounds and skin type can also play a role in altering what we see clinically.

So thinking about beyond IL-13, we have other factors that also play a role in the pathophysiology and also represent potential targets of our therapies. So therapeutic targets to help control this immune-mediated disease including oral hydrocarbon receptor and IL-4 and in addition to IL-13, TSLP, IL-31. The JAK-STAT pathway, of course, is a target, because many of these cytokines that are key to the pathogenesis of atopic dermatitis depend on JAK-STAT intracellular signaling through the JAK-STAT pathway to modulate their effect.

And then we have OX40 and OX40 ligand interactions, which play a role in amplifying the Th2 response and sustaining it as well. And we're seeing some medications in development there.

So very, very exciting time as we have a better understanding of the complex pathophysiology of disease and have all these additional targets for our therapies.

Now, when it comes to itch, which is, of course, the number one symptom of atopic dermatitis and contributes greatly to its adverse effects on quality of life, we really have a better understanding today of the non-histaminergic pathways and the cross-talk between the immune system and the sensory nervous system.

It turns out that on the sensory neurons, we have receptors for IL-4, IL-13, IL-31, TSLP, and others at creating this cross-talk between the immune system and the sensory nervous system, leading to the sensation of the itching. So when we inhibit these key cytokines in the Th2 immune response, we get this improvement in itch through this pathway, among other mechanisms too.

So let's revisit our patient case having that background of the pathogenesis and role of IL-13. So we've got the 34-year-old patient here with severe atopic dermatitis still waiting in the waiting room. She complains of persistent symptoms of redness, scaling, and itching. She's tried topical corticosteroids and emollients. It's been worsening over the past year, difficulty sleeping probably contributing to challenges at work with lack of sleep.

So post-test, having heard about the mechanisms of disease and thinking about the various signs and symptoms in this patient, what is the role of IL-13 in atopic dermatitis? Which of the following best describes its pathophysiologic contributions?

Is it: A. IL-13 enhances keratinocyte activity but leads to abnormal differentiation, weakening the skin barrier and increasing susceptibility to irritation; B. IL-13 modulates immune signaling but skews the response towards an overactive Th2 profile contributing to chronic inflammation; or C. IL-13 influences fibroblast function, but instead of promoting effective wound healing, it disrupts normal tissue repair and regeneration; or D. IL-13 disrupts the skin barrier, increases pruritus, and perpetuates inflammation by promoting Th2-mediated responses.

Alright, looking forward to seeing your responses as they come in, and to see if there's a difference between the pre and the post.

Alright, excellent. So we're seeing the shift in the proportion of folks with the correct answer, the best answer. Even though there might be elements of truth to some of the other answers, the best answer is indeed D, which is IL-13 disrupts the skin barrier, increases pruritus, and perpetuates inflammation by promoting Th2-mediated responses.

So in this way, it plays a central role in the pathogenesis of atopic dermatitis and really contribute to that perpetual cycle of itching and

scratching and inflammation, and would help to explain our patient's persistent symptoms despite treatment with just corticosteroids and emollients.

So with that, it turns out I didn't even involve my colleagues in the case; I decided to go it alone. But it's my pleasure to introduce Dan Butler from Tucson, Arizona, who's going to talk about mastering the evidence for IL-13 inhibition in moderate to severe atopic dermatitis. Dan?

Dr. Butler:
Thanks so much, Dr. Alexis. First of all, you're never alone. Shawn and I were right behind you the whole time ready to step in. But that was a great tour of the mechanisms underlying this really common disease.

And, you know, obviously this is something that we're, you know, challenged with every day, you know, whatever practice model you're in. But now we're really getting to understand those disease mechanisms, which I think then educates us on how to take those next steps forward with our patients, to be able to say, alright, here's a treatment, here are the mechanisms by which it's working. What do you think? What would you like to do? And so that's what we're going to do in this section, is mastering the evidence for IL-13 inhibition in moderate to severe atopic dermatitis. So what we're going to go over some of the treatment recommendations and hopefully help you all navigate, not necessarily giving you the answer or even feigning that there is a correct answer, but rather helping us all navigate what now is a busier, more option-full discussion with our patients when we're treating them with atopic dermatitis and eczema.

So as you know, we always start with a case. So let's talk about the case. Here's a 42-year-old male with refractory, moderate to severe atopic dermatitis. So current presentation—of course this patient is struggling, there's intense itching, widespread lesions, and poor quality of life. The medications, as most patients have already been on—this patient's been on topical steroids, and then every once in a while they get systemic corticosteroids when they're flaring. And this dermatologist is talking with the patient about a biologic that specifically targets IL-13. When they do a laboratory evaluation—which, step aside here, we don't typically do for atopic dermatitis, but can certainly be helpful in the complexity and holistic nature of the disease—they find that there is an IgE elevation as well as an eosinophil elevation, with CRP and ESR being elevated as well at 4.1 and 30, respectively.

So pre-test, which of the following biologic therapies would be the most appropriate choice in targeting IL-13 specifically to improve the patient's barrier function and reduce inflammation?

So we already found out that IL-13 helps with barrier function and reduces inflammation. But which of these biologics specifically does it through the IL-13 mechanism? We'll wait a second for everybody to get to work through this, and then once we have the answer there, we'll move on to that navigation that I was talking about.

Alright, perfect. So we have a pretty decent split between the biologics, and let's dive into that so that we can tackle the post-test when it comes up.

So as we know, IL-13 is a key driver of inflammation and barrier dysfunction, and now we have ways to directly attack it. So here is the broad schematic of every systemic AD medication that's come out in the last 10 years. So before this, we had the more historic immune suppressants, which were really developed for the more immune-focused conditions like transplant immune suppression, we were using things like methotrexate, cyclosporine, azathioprine. These were sort of historic ones that we all got really comfortable using.

But we had a revolution about 10 years ago when we first got to see dupilumab. And you'll see dupilumab there, which is an IL-4/13 inhibitor. So it inhibits both IL-4 and IL-13, but it does this specifically by blocking the IL-4 receptor alpha subunit of that receptor.

Then, as you look at those top options, you'll also notice lebrikizumab and tralokinumab. These are the IL-13 specific inhibitors—ding, ding, ding. So these are the ones that specifically target IL-13. Dupilumab targets IL-4 receptor alpha, which allows it to secondarily block IL-4 and 13. But as far as direct IL-13 inhibition, lebrikizumab and tralokinumab are the ones you're looking at.

And then the newest kid on the block is the IL-31 agent, nemolizumab, which works similar to dupilumab in that its effect happens at the receptor level, not by blocking the cytokine specifically.

So those four are our usual suspects when it comes to the biologics. When someone refers to the biologics for AD, those are the four that we have now, and I think there's probably some more coming.

Now, if we flip to the inside of the cell or the bottom part of this slide, you'll see the JAK inhibitors that are available for treatment. So these are oral agents, not biologics. We consider them systemic options—systemic immune-suppressing options—and there we have baricitinib, and abrocitinib, and upadacitinib. So these, again, are a little bit different in their classifications, not specific biologics, but we'll talk a little bit about them anyway because they are wonderful options to use in certain circumstances.

So let's start to tease these all apart. So the interesting thing about this slide is that AAD is getting faster and faster at updating things. This is the AAD 2024 guidelines for systemic therapies for moderate and severe AD. And interestingly enough, last week, well after these slides were established, we actually got an update on these guidelines.

So here, the guidelines show that for moderate to severe AD, dupilumab and tralokinumab were considered first-line therapy, and then we had added lebrikizumab and nemolizumab there with question marks, because they came out in 2024 so we couldn't know if they were actually added recently. They were both added to the 2025 guidelines.

So long story short, those four biologics are considered first-line because of their safe and effective profiles, and we're going to get a little bit more into those.

After that, you see at the bottom of that slide the JAK inhibitors that we talked about—upadacitinib, abrocitinib, and baricitinib. Those would be considered second-line for failures, or those who didn't tolerate. One asterisk to baricitinib is it's actually not available for atopic dermatitis or not FDA approved for atopic dermatitis in the United States. It is for alopecia areata. So you may see a couple of things, that's why it doesn't have that FDA stamp there.

And then over on the stage right here, you'll also notice the methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, systemic steroids. These are the old historic relics of the past, which we still dive into when we need to, but now we have much safer and more effective options, so they have gone out of favor as certainly first-line agents.

So as we dive into the biologics, I think it's really important to start to see them in comparison. And this is a busy slide. But each one of them sort of offers a little bit of a unique nuance. And again, I'm not going to try to go over this entire slide in detail, but a couple little things to point out.

So dupilumab, the first biologic that was commercially available about 9 years ago, it is the only one that's available for over 6 months of age. Tralokinumab and lebrikizumab, the IL-13 inhibitors, they're the ones that actually allow us to extend dosing profile. So when we're treating somebody and they get really good control, we can actually, by FDA approval, extend their dosing out from q2 weeks to q4 weeks, which is a huge boon for the patient to have less injections. And then nemolizumab, with its unique mechanism of action, actually starts at that q4-week dosing.

And then, of course, I would be not doing my job to just highlight that the warnings for each are quite mild—things like conjunctivitis, which is reversible after treatment or discontinuation of the medications, and then hypothetical risks of parasitic infections for the IL-4 and 13 targeting agents, as well as avoidance of live vaccines for the IL-31. Long story short—and we're going to dive into this a little bit more—these are very, very effective. So the warnings are pretty mild at best.

But it's a crowded market. So how do we figure out which one to use in the right patient? So we already talked about some of the differences in the biologics, so you know, you potential benefits of q2- to q4-week dosing. We want to look at failure rates of one versus another. We also love sort of the group profile, which is that none of them require any lab monitoring. And then we should also know the common side effects for each group, things like conjunctivitis we see in dupilumab, tralokinumab and lebrikizumab. We don't see it as much in nemolizumab.

And long story short is we are now trying—we're in this era where we're trying to sort of differentiate between all the different available products. And this is a little bit of why we're here today, is to help us all work through that.

And as I go through some of the studies in the coming slides, I want to highlight something that I think is really important, which is that despite the fact that we're going to be scientists and clinicians and work through data that helps us figure out who's the right patient for each biologic, I do like to sort of put an umbrella over all of it and say, you know what, these are really great medications. Certainly, the four we have out, they've helped a ton of my patients, and we're still trying to figure out which one is perfect for the right patient. But boy oh boy is it nice to have something, or some things to be able to give a patient when before it was always having to read them a long list of side effects, to be able to go on mycophenolate or cyclosporine.

So long story short, I like to put that umbrella out there. But with that being said, let's get into some of the comparative data.

So the first piece of comparative data that I think is important looks at all of them. So it's looking at all the ones that were available at the time. And it was 13 trials, 32 total treatment arms, over 7,000 patients. This was a network meta-analysis where they basically take all of the clinical studies that were done on these medications, and they try to compare some of these similar endpoints.

Now, the asterisk to any network meta-analysis is that you really can't compare the medications. Even though they're looking at the same endpoints, there are unique differences in each study, so we have to take this with some level of skepticism and caution and vigilance as to its results. But I think there's still some valuable takeaways as we are, you know, working through which is the right

biologic for which patient.

So in this study, they actually included JAK inhibitors, which were upadacitinib, abrocitinib, and baricitinib, but they had the three first FDA approved biologics. So they had dupilumab, lebrikizumab and tralokinumab as well.

And the results, not surprisingly, showed that the highest efficacy was seen in the JAK inhibitor. So upadacitinib was number one, that was at its highest dose of 30 mg. Number two was abrocitinib, which is the other JAK inhibitor, at its highest dose of 200 mg. And then upadacitinib at its lower dose, that's 15 mg.

And then overall, you started to see very similar efficacy when it looked at the biologics, including lebrikizumab, dupilumab, and then of course adding abrocitinib and baricitinib at their lower doses. Well, baricitinib, that's its higher dose.

But long story short, I don't want you to get lost in it. It looked like the JAK inhibitors were more efficacious, but that the biologics, including dupilumab and lebrikizumab, were absolutely effective at the levels by some of the lower JAK prescription rates.

So what did we take from this? We take that yes, JAK inhibitors outperform anything that's in the biologic realm, but everything is looking pretty good from an efficacy standpoint. And we have to start to look at the datapoints to be able to really tell the difference there.

So how do we find good datapoints here? I'm running forward too fast. We start to look at what available head-to-head data is there. And the head-to-head data—this is not a network meta-analysis, so we can take some conclusions from this—looked at the king of the JAK inhibitors, upadacitinib, with the first biologic out on the market. And as you would imagine, upadacitinib was better and faster at skin clearance in this 24-week study. But it did look like dupilumab, the biologic, had a better safety profile. So there was less infections that was in the biologic category.

So again, you're looking at risk-benefits, and a head-to-head study is probably the best way to be able to value that. So this head-to-head study really was transformative when we started to think of how we can guide people in biologics, because they really had the crown when it looks at safety profiles.

And I often—at least in my practice—that's really the first place I go: is this medication safe? And this study told us absolutely, dupilumab has the better safety profile than upadacitinib, the JAK inhibitor, despite upadacitinib's superior efficacy.

So let's dive into some of the more minute data from the biologic trials. So the LIBERTY AD CHRONOS trial was looking at dupilumab's efficacy in adults. So this is basically our ability to study the older, or the adult population, who are taking dupilumab.

And what you'll notice here, without having to dive into all the minute data, is that delta between the orange bar and the dark blue and lighter blue bars. So essentially, this is the pattern of efficacy rates as graded by IGA scores and EASI-75 scores, which are the clinical results scores that we look for in these clinical trials. We're looking for that delta. And in here, you see a significant delta at week 16, at week 52 for both IGA scores and EASI scores. And that delta is something you're going to see a lot of across these slides.

So dupilumab across its population looks pretty darn good. But how about when we take it a little further out? Does it maintain efficacy? And the answer is absolutely.

And then, of course, the question we always have to ask is about safety. So does it maintain its great safety profile over time? And this is a real gift, because if we have a 24-week study, sure we can extrapolate something from that, but certainly the open-label extension of 4 years in this trial was something that we could really take a lot from. And over those 4 years, we found that that safety profile sustained.

So that's really, really healthy when we're looking at sort of broadly the biologic realm. Despite the fact that it's new in this last decade, we now have the better part of a decade telling us that the safety profile is really good. So we didn't see any major signals of infections. The only major thing that we like to see with these patients—or we don't like to see it, but we see it with these patients—is conjunctivitis, and that was certainly something that we continue to see, but not in a dangerous realm.

So in addition to that safety profile, the efficacy profile, we started to look at, again, trying to find the right populations for each medication, we started to look at subgroups and demographically unique subgroups.

So this was a racial subgroup analysis from these LIBERTY trials, the SOLO 1, SOLO 2, and the CHRONOS. And it was found that, not surprisingly, in all these racial subgroups—White, Asian, Black, African American—you did see strong efficacy for dupilumab, just as you had seen in that initial trial data. And we're going to actually look at that type of data across many of these biologics. So just prepare yourselves.

And then, similarly, we didn't see any absolute jumps off the page with this racial sub analysis for dupilumab in these trials for the safety profile. So we were seeing very similar safety profiles across these populations, which again emphasizes the safety of the biologic class

in general.

So now we jump back into a network meta-analysis. We saw the CHRONOS trial, we saw the efficacy data for the general population, the subgroups. So now let's see how the biologics compare with one another.

So again, network meta-analysis, we can't take too much from this comparison because these are very different study designs. But long story short, in the comparison of these two, it was found that dupilumab plus topical corticosteroids demonstrated superior skin clearance, itch reduction, and quality of life scoring as compared to tralokinumab plus topical corticosteroids.

So this was a great addition to our discussion, because it allowed us to finally compare something that targeted the IL-4 receptor alpha unit, which secondarily allows that 4/13 inhibition, versus tralokinumab which was the first IL-13-specific inhibitor. So this was another one that we were able to add to our work. And this was really important for us to be able to see the differences in these and ultimately make comparisons. But you can see we're seeing really similar trends as we dive into this data, which is we're seeing in network analyses that the JAK inhibitors remain the king as far as efficacy, but safety continues to show strength for all the biologics.

Now, I want to dive into another specific look at an IL-13 inhibitor. This is tralokinumab. So if you scroll back to that network meta-analysis that we just looked at, that was the one that was compared specifically with dupilumab, and showed some lower efficacy rates.

Nevertheless, still a really great medication, as shown in the ECZEMA 1 and 2 trials, where you're looking, again just focusing on the delta between that orange bar and the blue bar, where you still see really great efficacy profiles, you still see a strong delta between those two bars. And that's really what we're looking for across these different endpoints. So in this circumstance, they're looking at Investigator Global Assessment of 0 or 1, which essentially means the patient is completely clear. And again, you're seeing very strong comparative data for tralokinumab as compared to placebo in this 16-week trial.

As you would imagine, there are other things that were included in these trials, other endpoints with really great maintenance of response up to 52 weeks and beyond. And then, of course, they added the ECZEMA 3 trial to this.

Again, you don't have to know all the names of these confusing trials, but just know that the early trials were done without corticosteroid additions, topical corticosteroids. And in ECZEMA 3, they did the topical corticosteroids as an option in both the placebo and in the treatment groups with the IL-13 inhibitor, and it showed the exact response, as you would imagine, which was more patients got clear, as shown by IGA scores of 0 or 1, and more patients were able to get to that EASI-75 score when they added the topical corticosteroid.

So again, if we're thinking thematically, not getting lost in the data here, this is showing that tralokinumab still has an impressive efficacy profile, despite the fact of its prior comparisons.

As you know, we did want to make sure that the subgroup analysis is still shown, which shows unique signals in each population. So Asian, Black, and White population still had great data for EASI-75, EASI-90, which again are clinical endpoint scores, IGA 0 or 1, which is another clinical endpoint score. So long story short, we're seeing themes across these. While it's not perfect for one single population, it's pretty good for all of them, and that's what we take away from this longer-term data.

In addition to looking at the safety profile of these racial subgroup analyses, which basically shows exactly what you would expect, which again, this biologic, like the others, has a fantastic safety profile—nothing that jumps out, nothing that would be different from the other biologics.

And last but not least in the IL-13 inhibitor category, I want to take a closer look at lebrikizumab and its trials of ADvocate 1, 2 and ADjoin. So is the most recent of the IL-13s to be approved. And what this did is it looked at short-term, 52-week data, which allowed us to evaluate clinical efficacy at that point, and it showed really remarkable differences. So that IGA score—you're going to see the delta here in a minute—but 43.1% of patients responded a clear or almost clear level as compared to the 12.7 at the placebo rate. That's, you know, about a 3.5 times improvement when compared. So that's that delta that I'm talking about, and that's a really important piece here.

And then ADjoin was the more longer-term data that we had for this. And what I love to see about this—and there's a couple other slides about this—but of the patients who were good responders, you saw 80% of them on long-term data continue that response. So that's another piece that we like to share with our patients, which is this isn't just some short-term solution, perhaps like the steroids they've been on before. This is a medication that, for months and months and even years, can provide clearance, and that's what this study showed.

So again, we're just adding to the menu that shows how clean these medications are with an impressive safety profile.

So this is exactly what I was talking about. This is when we looked at the extension from week 16 to week 52, and you'll see there those blue lines, they stay up pretty high—85% when you're looking at the different dosing protocols for lebrikizumab. But the one that really sticks out to me is for the patients who were responders to lebrikizumab at week 16, even when they came off the medication—look at

that—almost, you know, 1/4 of a year later, 3/4 of a year later—60% of them were still under control, 66% of them. So that durability of response is pretty impressive, and this is measured by the Itch-NRS Pruritus score, and improvement of greater than

4 is pretty much a standard for the community as showing really great itch control. So long story short, there's a durable response here, whether you stay on the medication or after you can discontinue the medication.

As you would imagine, we have to look at some of the safety data. And again, as you would imagine, the safety comes back really impressive with lebrikizumab, as with the other biologics. Conjunctivitis was the biggest signal that we saw, but again, nothing that required serious AEs or discontinuation at a level that was unprecedented. In fact, you can see there that the discontinuation rates, or the serious AE rates, and the AE rates were actually higher in the placebo group than they were in the usage groups.

The next thing that we're going to show you here, because we did it for dupilumab and for tralokinumab, is the racial subanalyses groupings. And as you see, their strength maintains across racial subgroups. As you can see, the delta of the placebo there at the bottom, as compared to the lebrikizumab groups. There's really strength across all populations, which is so important as we maintain inclusivity in our clinical programs. And similarly, there's no signal from a side effects standpoint that affects one subgroup over another.

So that's a great add to our menu of options, our skill, our toolbox that we could provide the patient.

So again, this is highlighting those outdated AAD 2024 guidelines, which are now the 2025 guidelines, and include not only dupilumab and tralokinumab, but have lebrikizumab, the IL-13 inhibitor, and nemolizumab, the IL-31 inhibitor. And I'll just point out there that there's a conditional recommendation that systemic steroids are not used. I think now we have these other options. We have other things that we can absolutely use that are more effective.

So this algorithm, again, has been added to, but the themes are stable, which is, if you have a moderate or severe patient, your first-line options should be the biologics—dupilumab being a 4/13 inhibitor, just a 13 inhibitor, tralokinumab and lebrikizumab, which are the 13 inhibitor specifically, and nemolizumab, the IL-31 inhibitor.

So I want to show you this one last time to look at that network meta-analyses that we talked about a little bit earlier. So if you look at the very top there, this is showing that the JAK inhibitors are the kings when it comes to efficacy. But if you look at the biologics, which are your safest options, you'll see great efficacy data for lebrikizumab, the IL-13 inhibitor, and then, of course, dupilumab and tralokinumab follow lebrikizumab, dupilumab being 4/13, and tralokinumab being 13.

So I believe we're going to go into the post-test really quickly. But the key take-homes is everybody needs their own tailored regimen. So you want to make sure to use your new optionality, use the efficacy and safety data that's unique for each one to be able to come up with a personalized approach. Each one has a little bit of a nuanced difference to it, but long story short, they're all safe, they're all effective.

So let's return back to the patient case. So this is our patient. He's struggling. His dermatologist is considering an IL-13 inhibitor, of which there are two on the market. So I ask you once again, which of these options would be most appropriate for targeting IL-13 when considering safety profiles as well as efficacy profiles?

And again, I will just give you the spoiler alert here that IL-13 is the key. Alright, yep, we always have this split here. Hence why I keep pushing for IL-13. Dupilumab secondarily blocks IL-13, so lebrikizumab would be the correct answer there. But I totally understand the split answer, and it's totally fair that there's confusion with those two, because this is a hypothetical situation.

So IL-13 plays a central role, as we heard from Dr. Alexis earlier, and lebrikizumab, of those options, is the only one that specifically binds IL-13.

So I don't think I've ever said IL-13 more times in my life, but I'm going to say it one more time as I introduce our next expert here. This is Dr. Shawn Kwatra, and he's going to talk about IL-13 inhibitors in practice. Dr. Kwatra, please take it away.

Dr. Kwatra:
Yeah. Thank you so much, Dr. Butler, Dr. Alexis, really, for the great presentation. So it's my honor to also discuss the next level—so patient candidacy and also treatment advancement strategies. And a really good way to start discussing this topic is with a patient case.

So this is a 13-year-old female that you can all think about presenting with persistent, moderate to severe atopic dermatitis. Thirteen-year-old female with widespread erythema, pruritus, lichenification, quality-of-life disruption, and poor school performance. Also, history of asthma. Has had topical steroids and also oral steroids for severe flares and phototherapy. The IgE is 2300, eosinophils 9% as well.

So let's move along. We'll, of course, come back to this case, but we want to do our pre-test questions here. Considering the patient's clinical presentation, history, and lab findings, which of the following factors most strongly supports initiating an IL-13 targeted biologic

therapy for atopic dermatitis? Let's pick one of these. I'll give you all a moment to do that.

Great. So let's keep going. Okay. So today we're going to talk more in this section about evaluating the candidacy, disease severity, and also patient-centered outcomes using IL-13 targeted therapy for atopic dermatitis.

So let's first talk a little bit about when to advance therapy. So I think this is an area where a lot of patients suffer because therapies are not offered to advance at appropriate times. So the most important things to consider are persistent symptoms despite optimized topical therapy, flare-ups impacting quality of life, and itch and sleep disturbances.

So for example, in the pre-test question, in the case as well, we had a patient who had severe symptoms despite topical therapy. That's it. That's enough. That's the most important thing needed to trigger the systemic IL-13 targeted therapies, is the persistence of symptoms even though you're on topical therapies and they've been optimized. So very important. We see many patients who have been passed around for years just on topical steroids, sometimes with striae. And I would personally even argue that using a very targeted biologic-type agent is safer, more efficacious and safer than using long-term topical steroids. So very important to consider that point.

Monitoring treatment response. There are some important scales for clinical practice—the EASI score—Eczema Area and Severity Index, the Investigator Global Assessment, or the SCORAD. There are also some itch severity scores, which are from 0 to 10, or sleep quality, or Dermatology Life Quality Index.

So advancing therapy—someone's been on topical steroids; that's enough to advance therapy. We prefer our biologic or small-molecule JAK inhibitor therapies. We have greater efficacy and safety than non-specific immune suppressive or modulating agents like methotrexate, cyclosporine, corticosteroids.

And then patient-centered conversations we want to have are talking about expectations of biologic therapy, long-term benefits, but balancing that with any safety concerns or profiles, and shared decision-making as well.

So that's the forefront. Let's actually hear about everything from a patient's perspective. We'll ask the team to play this slide—the video—so that we're able to actually hear a patient's experience, and then we'll go from there.

Let's have the team play the video.

Patient:
My AD flare-ups really vary, and that really depends on if the medication treatment plan that I'm on is effectively managing my AD. And when it is, it could be once a week, once every 2 weeks. However, when the treatment plan is not effective and not working very well, flare-ups could be as often as 3 times a week, and sometimes go on for weeks or even months on end.

And no doubt, when my skin is not doing well and it's in a flaring state, it really does impact everything from the choice of my clothes to the activities that I'm able to do, to how productive I am throughout the day. All of these are impacted by my AD. Having AD has direct relation on my mood and my overall emotional well-being, and that is because when my AD is not being managed and the itch is out of control, it impacts my sleep, which then impacts my ability to just function properly as a human being, as a mother, as a wife.

Having a doctor who understands what it's like to live with AD, as well as a bit about my lifestyle, has really helped in terms of just the entire journey—you know, keeping an open mind to try different treatments, and you know, perhaps stopping certain treatments, has really played a role in my journey. Having family that's very supportive, very understanding, who are there for me whenever I need makes a huge impact, as well as finding community, finding others who are going through similar experience, really just helps lighten the burden of this experience.

Dr. Kwatra:
Alright, so that's always helpful to hear the patient's perspective. And now what we'll do is also look, as we're transitioning, so look at some of the clinical assessment tools. So patient comes in, what are some of the tools that you're going to be thinking about?

So you can see the Eczema Area and Severity Index, where you actually grade different body areas by erythema. Many of these other factors, pruritus. The Investigator Global Assessment, in contrast, is based more on the appearance of lesions. So are these lesions—you know, how erythematous are they? How lichenified are they? Those are very important features. And usually need an Investigator Global Assessment of a 3 or 4 to qualify for a biologic or systemic therapy. There's also the SCORAD and the POEM as well. So there's quite a litany of different measures, but I'd say IGA and the EASI score are the two most important to document, especially in your notes.

And where I practice, patients have to fail topical steroid therapy—a medium and high potency—and a topical calcineurin inhibitor, depending on the insurance usually. So usually we do that at the first visit, quick follow-up as well if we're thinking it's greater body surface area or greater itch disruption. I ask everybody on a 0-10 scale how severe their itch is. That would trigger systemic therapy.

So let's also talk about a case. The case is of April. So I just skipped over that so I'll bring it back up for you because I want to focus on many of these different metrics, bringing in the life of the patient.

Meet April, 15-year-old Black female, presenting to dermatology with an increase in bothersome itching, especially the last few weeks, affecting her sleep and school. And her atopic dermatitis was diagnosed in early childhood at age 5, full-body itching, redness, and scaling is from the age of 9, also with obesity, asthma as well. She is a high school freshman, lives in New York City, eats fast food regularly, and unable to exercise. Usually the increased flares from sweating. So Mom and her two sisters have AD or allergic disease. So here we see a patient who's having effects on her sleep and school, as well. Also has a comorbidity of asthma. And also patient has family members that have a history of atopic disease.

So let's do her review of systems: psychiatric, got depressed mood, anxious; occasional wheezing; itching and rash. And you can see that patient has around a 17% body surface area with eczema around joints and the face, and a SCORAD around 48. So let's go through this treatment timeline. The patient was diagnosed with AD at age 5, had lukewarm baths, gentle cleansers, and moisturizers. Age 8, you can see they used topical corticosteroids. Age 11, phototherapy. Age 15, crisaborole as well. But all of these therapies hasn't helped the patient.

So there's a few different aspects of this case. First, assessing April's current management of her AD. Well, tried topical steroids, tried even a non-steroidal therapy for atopic dermatitis. Tried therapy. Those are all a number of therapies and they haven't controlled her sleep. She's having psychological and psychosocial disturbance. It's affecting her quality of life very significantly. So remember, the most important thing for escalating to biologics and IL-13 targeted therapies in particular are, you know, failure on traditional therapeutics, topicals, which she has done.

Which assessment tool for you guys? I think there's many, but what you need in your notes is probably the IGA score first—Investigator Global Assessment. And then Investigator Global Assessment is able to look at, as I mentioned, the appearance of the lesion. So that's like a direct takeaway for clinic, is being able to mark it from 0 to 4. So 4 is very severe redness or erythema, so dark or deep, bright red marked in duration or elevation, like lichenification, oozing, and crusting; 3 is noticeable erythema; 2 is mild, so that's like you know, a little bit more mild, but noticeable, whereas 3 is distinctly noticeable redness; and then 1 is barely noticeable redness or induration, like lichenification; 0 is not affected at all. So 0 is nothing, 4 is the worst. So that's a good way to guide it.

So we talked about this before, but April would absolutely be a candidate for biologic therapy because she failed these topical—traditional topical therapies, that's the key piece.

And would your treatment decision be altered if April didn't have asthma? For me the answer is no. If your disease is not controlled, I would still escalate to biologic therapy, especially if sleep is affected, quality of life is affected. Even a simple thing like asking patients about their itch score. What's the worst itch they've had in the last 24 hours? 0 to 10, if you have over 5 or 7, we know that you actually have a lot of inflammation in your blood. We know that's deeply affecting your quality of life in many different domains. So in this situation, I think we'd want to go to biologic therapy either way. But sadly, we're still seeing, every clinic I'm seeing patients with years of topical steroid use and inadequate disease control. So I think forums like this are so fundamentally important to be able to change the narrative about how we treat these patients. And what I'd like to see is, you know, earlier utilization of some of these new breakthrough therapeutics.

So it's important to recognize is that there is some variability in the clinical presentation of atopic dermatitis. You can see here from these pictures that it can look a little different, so you can have more affected areas on the cheeks in infants, forehead and scalp, also the extensor extremities and flexural creases. You can see in adolescents the face, the neck is the common areas, palms and soles. And adults also flexural creases or some of the hands and feet. Those are all important areas.

Some variabilities in especially in darker or different skin types. You can see that you can have oftentimes in African American patients, more popular, follicularly-based eruptions, especially many African American children with follicularly-based papular lesions distributed throughout the trunk, is a common misdiagnosis, but a common presentation we see all the time. I practice in the inner city Baltimore, so I see a lot of these presentations. Also post-inflammatory hyperpigmentation, so a little bit darker hue to the skin. It's less noticeable to erythema, so that's an important factor to keep into account. And then also we see, you know, more pink and red erythema in light skin. And we know that also many Asian individuals are more likely to get a psoriasiform appearance of scaling, which is important because if you do a biopsy, you could show psoriasis or psoriasiform dermatitis, but it could actually still be eczema. So that's important to keep track of.

So why don't we look at some photos now, more especially with this variability based on skin type. You can see the erythema also in these Caucasian individuals, and the excoriations in the hand. And then you can also see the significant lichenification in some of these other pictures. And you can also see different areas of erythema, scaling as well in these different skin types.

So I'd also like to address a very friendly, easy-to-use, straightforward tool called Atopic Dermatitis Control Test, or ADCT. This is validated, brief, and easily scored, self-assessment tools, those 6 questions to evaluate the different dimensions of AD: control, relevant, identified as being relevant to both patients and clinicians. So overall, severity of AD symptoms, frequency of itch episodes, so intense episodes of itching, extent of AD-related troubles, frequency of sleep impact, and impact of AD on daily activities, and impact of AD on mood or emotions. Can be self-administered by patients or using routine consultations. And it's designed to help facilitate discussions.

So I'll actually show you guys a little bit more of all these different questions. If you give these patients this tool and the patients get a 7 or greater, then it actually triggers, you know, utilization of the need for systemic therapy utilization. So over the last week, how would you rate your eczema-related symptoms? So none, mild, severe. Days of intense itching episodes because of your eczema. Over the last week, you've been bothered by it. How many nights do you have trouble sleeping?

How does your eczema affect your daily activities? How does your eczema affect your mind? Your emotions? So these are really relevant questions that can help to measure things.

Okay, so let's revisit our case, shall we? We'll go back to that. So again, to remind you, this is our 13-year-old female, severe atopic dermatitis, redness and erythema throughout, itching, lichenification or skin thickening, sleep disruption. Has used topical steroids—remember, that's the most important thing to trigger being eligible for these biologic therapies—have failure with topical steroids, but then this person also got systemic steroids and flares, and phototherapy. The IgE is 2300, eosinophils 9%. These blood biomarkers can be helpful because they're actually surrogate biomarkers of increased IL-13 or type 2 inflammation, if you know that the IgE or eosinophils are up. So it can be helpful to see these different markers.

So let's do the question now. Okay, so considering the patient's clinical presentation, history, and lab findings, which and lab findings, which are the following factors most strongly supports initiating IL-13-targeted biologic therapy for this patient's atopic dermatitis. So let's see what we get here.

Okay, can we see the results? Yep, okay, great, wow. The audience did a great, great job here. Okay, so 79% again highlighted that, you know, topical steroids. Despite appropriate use in topical steroids, you're still having severe disease, that's the most important marker.

So that is excellent, and you can see that failure of standard treatments, despite multiple interventions, are what's needed for biologic-based therapy.

So some key takeaways, IL-13 drives atopic dermatitis pathology. So we know that it impairs the skin barrier, and we know that that's really important in AD that you have an impaired skin barrier. So filaggrin is like the brick and mortar of your skin barrier. And what I would say is you can think about IL-13 as like a demolition crew that weakens that mortar. When IL-13 levels rise, filaggrin, the brick and mortar of your skin, that production drops and the barrier falls apart, leading to increased water loss, allergens sneaking in, and infections flaring up.

So you really can think about this in many different ways, but if you have IL-13, it's causing more of those holes to appear. Put a biologic therapy, starting IL-13, lebrikizumab, newer generation IL-13, greater efficacy, also have the first-gen tralokinumab, and then dupilumab, which has been FDA approved since 2017 as well. So these agents are improving barrier function, reducing inflammation and pruritus, so having effects on all of those different tailored domains. So very important that we target all of those different aspects in the disease.

So let's keep going in identifying biologic candidates. We know that these are all important features: moderate to severe AD, failed topicals, frequent flares, severe itch. You want to be a little bit careful in patients who are pregnant, immunosuppression, ocular side effects. Monitoring therapy and also being able to advance therapy, doing an EASI score and IGA, also other scores, Itch Severity score, DLQI, if you need, poor quality of life, sleep disruptions are all features for advancing therapeutics. Patient-centered biologic discussions, conjunctivitis, injection reactions. Luckily, most of these biologics don't actually have much laboratory monitoring at all either, which is great. So that's, I think, a great way, you know, to tie it all together.

So I think those are really our high-level overview. I think what I would say is that the unifying analogy is IL-13 is truly like, in many ways, master conductor of a dysfunctional orchestra. So it gives the wrong cues to every section it tells the skin barrier to weaken, it tells that immune system—immune cells—to overreact. It fires up the nerves, lowers the barrier for the nerves to fire off itch signals, and the fibroblasts lay down scar tissue. So when you have IL-13 leading this dysfunctional orchestra, the result is a symphony of chronic inflammation, relentless itch, tissue inflammation, remodeling. So it's very important to silence that conductor. And so IL-13 is one of the sparks that keeps relighting the fire. We know that from non-lesional skin, normal-appearing skin in an eczema person, you still actually, in many cases, have higher IL-13, even in the blood. So it feeds the flames, the itch, weakens the skin's protective shell, and also helps develop some of that inflammation in the skin.

So I think key features, we had really great talks by Andrew and Dan. It's great to be able to bring it back together.

So got another poll for you all: Do you plan to make any changes in your clinical practice based on what you learned in today's program? Alright, let's see the results. Alright, and then please take a moment to text in one key change that you plan to make in your clinical practice based on this education. And we'll leave this question up, but we're more than welcome to move along to our question-and-answer session.

So we'll start. Dan, I'll start with you. What's your spiel like when you, and then we'll see Andrew's take on it too. You got it—We are all in the situation. We have patients, they see us, they've been stuck on topicals for a long time, and we're talking about escalating therapy. And sometimes people are resistant. They still have a lot of symptoms. Any pearls that come to mind? And how do you counsel, how do you bridge that divide? We know that we only have a few minutes. And in many of these encounters, dermatologists, we have to see a lot of patients now. So what's your mindset, Dan, and then we'll see what Andrew thinks too. Any key pearls, how you approach that?

Dr. Butler:
Yeah, I mean, I think—well, first, I feel like I learned from you and Dr. Alexis, but it is an individualized approach, knowing that moderate to severe patients often require more systemic medications, you know, obviously, with the recommendation being biologics, and helping somebody understand that they don't have to live in this sort of, like topical cycle of, you know, 'I'm doing okay, I flare. I'm miserable. I apply topicals until the flare goes away. So I have a 2-week period where this is a real frustration, and this is happening over and over again.'

And so my suggestion is helping the patient understand that that cycle is something that the studies have shown that breaks when you go to escalated therapies with biologics, but also being patient with the patient, that if they're hesitant, you say, look, here are some things that I like to use as leverage or as scaffolding to make this decision. Are you sleeping? What is your activity level like during these flares? And those can be ways to sort of take a mirror back and say, hey, you know what? You know, like, these are pretty significant, and the topicals just aren't doing it.

So those are usually the ones that I like to use, the quality-of-life pieces. Dr. Alexis, I'd love to hear your pearls too.

Dr. Alexis:
Let me unmute myself first. Yes, thank you. You know, I take a similar approach, Dan. And I'll just highlight one other dimension to, you know, my interaction with patients when sort of bridging from topical over to systemic therapy. In very similar ways, I'll identify how much of an impact that atopic dermatitis is having on that patient and then inform them that they don't have to continue doing the cycle of flares and putting out the fire of the flares and not knowing when that next flare is going to be around the corner.

We can, today, with the agents that we have, we are able to bring the condition to more stability, have a smoother trajectory; no more roller-coaster ride, but a smooth ride of being clear or almost clear for an extended period of time. And we can do this by using safe and effective medications that are based on targeting mechanisms that we now very much understand in atopic dermatitis.

So I kind of bring them up to speed on the latest options and get them excited about how we understand the condition. It's not a mystery. We know where to target, and we have agents that target these key pathways, and we can bring them into an existence where they can sleep the full night and not have to be disturbed by itching. And they can be free of visible scaly, lichenified plaques that sometimes they normalize. They've had it for so long, and they think that there is no life without them. But it's amazing, once you put them on a biologic or other systemic agent, and they get to clear or almost clear, after years of not experiencing that, it's really transformative.

Dr. Kwatra:
Incredible. And Andrew, do you have any specific pearl? Because in my mind, you are the world leader in understanding and appreciating eczema in different skin types. I know I learn a lot from you. Do you have any pearls? Or like some of your—I know you've seen so many patients in your career, and so much great experience for people who may not have trained in very diverse environments

about appreciating atopic dermatitis severity in skin of color patients and when it may trigger, you know, a biologic or other type therapy? And some clues or suggestions about what's different, maybe from your expertise that we could help the audience with?

Dr. Alexis:
Oh, well, sure. Thank you, Shawn. So I think that first and foremost, there's a tendency for atopic dermatitis to be not just under-recognized, but even if you have the right diagnosis—atopic dermatitis—the severity, the assessment of the severity can be underestimated, particularly in patients with darker skin types, and this is often with an over-reliance on looking for erythema in its purest sense.

And you know, I understand that the word erythema comes from the Greek word erythros, which means red, and so classically we were looking for red. But we realized that in the context of more diverse skin types, that this red, this marker of clinical inflammation, may not just be purely red. Instead, I like to say that we broaden our color palette and include shades of, you know, hues that are violaceous, reddish-brown, gray. And when we broaden that definition, we can then really begin to appreciate more of the severity.

Using symptomatology, the patient's symptomatology, to really direct where to examine and also assess the overall extent and severity is also helpful. Palpation, side-lining, so you can really appreciate papulation and scale. And then I like to, as far as appreciating color differences, I like to look at first any islands of non-lesional skin to get a sense of the patient's baseline skin complexion and appearance. And then move to the lesional skin and do a delta in your head. And then you really see, when you look at the color change between the lesion and the non-lesional, then you start to really see the reds, and the violet, and the gray, and all the color palette that goes along with the inflammation that we call erythema.

So these are some of the things that I do.

Dr. Kwatra:
Great. I'm going to briefly touch on a couple questions coming in. Have you seen dupilumab shift the immune balance, sort of Th1/17 phenotype, which may exacerbate IBD? If yes, what is the risk? Any thoughts from you all on dupilumab shifting immune balance at all?

Dr. Butler:
I was actually just noticing all Nicole's questions. Great, great questions.

Dr. Kwatra:
Great questions. Yeah.

Dr. Butler:
Well, you seem to have a GI flavor to your question, so I wonder what your practice is.

So I personally haven't seen exacerbation of IBD, but it's theoretically a very reasonable question. I don't know if Dr. Kwatra, Dr. Alexis, have seen it, but we certainly see this—and you know, the word 'shift' is debated, whether it was just sort of an unmasking of a, you know, sort of Th1/Th2 hybrid with some Th17, that you block Th2, and then the Th1 side becomes more prominent. Or if we're truly shifting the immune system over, we've certainly seen that. And now dupilumab has, you know, a warning in its FDA label about the risk of psoriasis and arthritis, which are, as you probably know, Th1/Th2 diseases.

And then similarly, you know, along that same thread, you're asking about eosinophilic colitis. You know, there are certainly themes in the blockade of the, you know, atopic conditions, and dupilumab has indications in GI as you probably know, and probably the other learners here know as well, but it's indicated for eosinophilic esophagitis.

And the question is, does IL-13 blockade also protect against those? And it's a nuanced answer, because some of the IL-13 agents have been tried, you know, certainly in the pulmonary world, and they haven't worked as well, but there's probably still some efficacy.

So I send it over to Dr. Kwatra and Dr. Alexis if you guys have any anecdotal evidence of either IBD exacerbation or the IL-13s cross-talking with the GI system.

Dr. Alexis:
I have not had any cases of my own where I've started a patient on dupilumab, inhibiting IL-4 and IL-13, and then having them develop any gastrointestinal disease, including the ones mentioned. So no, I've not had that experience. Dr. Kwatra?

Dr. Kwatra:
Yeah, you know, very similar. I personally haven't had any experience with the IL-13 inhibitors. But like Dan said, there is the small risk of this shift towards the Th1/17 axis. And I would say that's not unique to any one inhibitor. I think it's now a recognized phenomenon. I call it an immune-switching phenomenon. It doesn't matter which biologic you give, if you cut off one dominant side of a cytokine cascade, naturally, you will have a little bit of an imbalance. So we've seen that throughout therapies. I mean, if you even think about TNF inhibitors, you can get paradoxical reactions, you know, a drug like, say, dupilumab or any of these IL-13 inhibitors potentially, yeah, could cause Th1/17.

We also see IL-31 inhibitors, like nemolizumab, shifting to Th2. So we're actually going to learn more through real-world data how each specific cytokine blockade can then shunt you towards another axis. So I don't view that as an individual molecule issue, but a, you know, common feature of biologics. That's still exceptionally rare.

And then for IL-13 and eosinophilic colitis or GI, I think it's important to know that IL-13 is a major player across mucosal surfaces, including the GI tract. And we know it's implicated in the pathogenesis of eosinophilic esophagitis. And there's also some data for

eosinophilic colitis, where it promotes barrier dysfunction in the GI and tract eosinophil infiltration, much like atopic dermatitis, you're just looking at a different interface and barrier. And so I think that's why, you know, dupilumab has approval for eosinophilic esophagitis.

And also one reason, you know, we saw the blood eosinophil levels, or IgE, and you see that some of these therapeutics are having positive data, approvals—or positive reports across many diseases, so atopic dermatitis, prurigo nodularis, bullous pemphigoid, itching of unknown origin, and it moves on and on, even across disease domains.

And one of the common feature is if you have systemic blood inflammation that is characterized by high eosinophils, or IgE, that's correlating tightly with IL-13, and IL-13 can disrupt many of these different systems. So I think that's important to keep track of.

I, in my mind, I'm actually viewing many of these diseases on a continuum, and our labs are actually trying to develop a blood biomarker test to help us, you know, better phenotype. And what I'd like to see later, many years in the future, is using a biomarker to go through trials and approvals, because there's many similarities even among these different multi-system, different system diseases in terms of pathogenesis. It's a very important question.

Dr. Butler:
I would just add one more thing, Nicole, to your final question there, and I'll piggyback off what Dr. Kwatra was just saying, which is, you know, the hope there for your IBD patient who also has eczema, which is a very common duality—not as common as IBD and psoriasis, but certainly something we still see connected—is ideally getting somebody on something that's going to, you know, be two birds with one stone—two conditions with one stone. And you know, oftentimes we use the more broad immune suppression for those patients.

But I think the Holy Grail, like Dr. Kwatra was mentioning, was, you know, being able to profile somebody's immune system and then subsequently attack it with the available medications, albeit you know, be it a biologic agent or something that may be a little bit more broad in its suppression.

But you're totally right, for those IBD patients, we're looking for something that's going to cross-cover. And before, it was basically only, you know, methotrexate for your atopic dermatitis patients, but now we certainly have a couple others with the JAK inhibitors available.

Dr. Kwatra:
Absolutely. So let's see. We got a few more questions that came in. We have a question about consideration of biologics with any lichen conditions. I don't know if you guys have any experience or thoughts on that, using any of these biologics for, say, lichen planus, lichen sclerosus.

Dr. Alexis:
You know, it's a great question. I'm not aware of any studies looking at our current biologics for lichen planus or lichen sclerosus. And I've not had any personal experience using that off-label. How about you? Have you seen any developments there?

Dr. Kwatra:
Yeah, I actually have had one. I treat a lot of patients with immune checkpoint inhibitors as well. And so I had a patient with dupilumab treatment that actually got a little better with lichen planus that got better. There have been some reports of lichen planus. I also had some lichen sclerosus that seemed to improve, actually, with incredible itching. So I think a lot of these other diseases that we haven't profiled or haven't gone through trials, there's endotypes, you know, we're learning a lot just by the case reports and a few of these isolated reports coming out.

But I agree with you, it's totally, you know, unknown with, like, larger controlled studies. But it is incredibly fascinating how we're seeing in the real world now how response to therapeutics can actually in a way never before, help us understand pathogenesis and pathology and disease biology. So that's like the really fascinating, cool part for us to all see in real-time.

Dr. Alexis:
Absolutely. I guess I would add, mechanistically, we consider lichen planus more of a Th1-driven disease. So, yeah, don't automatically think of biologics for AD as potentials. But, you know, time will tell. It's understudied, lichen planus. So.

Dr. Kwatra:
Absolutely. Okay, so we have another question. Dan, when do you think about discontinuing biologic therapy or weaning biologics? And then we'll see what Andrew thinks. Already keep them on indefinitely? This is the question we all get.

Dr. Butler:
We get this for every symposium. It's a great question. And the answer is, I don't think anybody has the perfect answer. My strategy is this is I tell the patient we don't use the F word right away, which they always say, 'Am I going to be on this forever?' And I say, we don't use the F word. We try to give people control for 3 to 6 months. We say, look, you're going to be on this for 3 to 6 months. Let's see how

things are going. Let's see how you're doing 3 to 6 months later. You have the control here. You can come off of it, you can extend the dose, you can stay on it. It's up to you. So the answer is it's unique for everybody. We do see data, and we saw that in some of the lebrikizumab studies that I showed, of this remittive effect of the medications, but it's still TBD. So I try to get people to stop thinking that they're going to be, right when they start, on this indefinitely or forever and make sure they know they have control along the whole process.

Dr. Kwatra:
Great. Any other thoughts on that, Andrew?

Dr. Alexis:
Yeah, that's well said. And I find that patients are most concerned about that question, 'Am I going to be on this forever?' They're most concerned about that right in that initial consultation, like before they start the treatment. But once they're on the treatment, and they've experienced life with their disease under great control, I'm not getting as many patients saying, 'Can I get off the drug?' They actually are satisfied staying on it for the long term because of the benefits they're deriving from it, and I'm comfortable keeping them on it unless there was an adverse event that would stop that.

Dr. Kwatra:
Great. And then I'll just briefly answer the last question about a network meta-analysis. That's a statistical method that allows us to compare multiple treatments. So even if they haven't been tested head-to-head, it connects the dots and tries to use shared comparators, placebo. It's really, really complex. But I mean, my analogy, if you like sports, is it's kind of like March Madness, if you get a big bracket, and if one team doesn't play the other team, we can kind of guess who wins, you know, based on how they both did against, like, a different team, like say they both played this other team. But then imaging all the statistics in it. So network meta-analysis comparing all the treatments, triangulating through common opponents.

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