RESEARCH DEVELOPMENTS IN ATOPIC DERMATITIS

OVERVIEW

Welcome to this activity focusing on new research related to atopic dermatitis presented as posters at the 2020 virtual annual meetings of the American Academy of Dermatology and the American Academy of Allergy, Asthma, and Immunology. The posters focus on new data related to the use of advanced therapies for atopic dermatitis. Beyond discussing the methods and results of each poster, the faculty, Drs. Steven Feldman and Alan Fleischer, Jr., share their views on the implication of the trial results on clinical practice. They also discuss new evidence related to the burden of disease experienced by patients and caregivers and intriguing evidence pointing to the heterogeneity of atopic dermatitis.

Target Audience

This activity was developed for Dermatologists, pediatric dermatologists, allergists, and other clinicians who manage patients with atopic dermatitis.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Summarize the latest research developments in the pharmacologic treatment of atopic dermatitis with new and emerging agents
- Describe how new data and recommendations can impact clinical practices to improve care
- Incorporate evidence-based research into clinical practice

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The estimated time to complete the activity is 1.75 hours.

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Introduction

Steve Feldman, MD: Welcome to this program on atopic dermatitis. I want to start off with an introduction and overview of the burden of the disease. Atopic dermatitis is a common, chronic skin disease that affects up to 25% of children and 7% of adults. The symptom burden of atopic dermatitis, much of it due to chronic pruritus, is substantial. Emotional distress and disrupted sleep are common, particularly in children. Healthcare utilization and costs are higher, and functioning is impaired in children with atopic dermatitis compared with healthy controls.

There were 2 posters presented at the 2020 American Academy of Dermatology virtual annual meeting that provide further insight into the burden of atopic dermatitis. One poster was by Dr. Shawn Kwatra and colleagues. He reported on the results of an analysis of 2017 US National Health and Wellness survey data. The poster was titled "Prevalence and Impact of Psychosocial Comorbidities on Health Status Among Patients with Moderate-to-Severe Atopic Dermatitis in the United States: Analysis of the 2017 US National Health and Wellness Survey."

The study results were based on survey responses from 1017 adults with moderate-to-severe atopic dermatitis. Their mean age was 37 years. 74% were male, one-third had atopic dermatitis for less than 5 years, while one-third had atopic dermatitis for greater than or equal to 16 years. Three-quarters of them had a Charlson Comorbidity Index of zero. The analysis showed that nearly two-thirds suffered from anxiety, nearly half from moderate-to-severe depression, while one-third reported moderate or severe sleep difficulties. The severity of these 3 comorbidities was significantly associated with reduced physical and mental health status and work-related impairment.

The other poster was by Barbarot and colleagues, investigating the burden on caregivers and family of children aged 6 to 11 years with atopic dermatitis. Their poster was titled "The Family Impact of Atopic Dermatitis in Children Aged Six to 11 Years: A Cross-sectional Study in the United States, Canada, Europe, and Japan." The multinational study utilized an online survey involving 12,213 children with atopic dermatitis, although it was the caregivers and families of the patients who responded to the survey. The analysis was stratified according to disease severity: mild, moderate, or severe, based on patient global assessment in the past week.

Caregivers and families reported the impact of living with children with atopic dermatitis in the past week on the Dermatitis Family Impact questionnaire, a validated dermatology-specific tool to assess the impact of dermatological conditions on the health-related quality of life of family members with affected children. In the US cohort of 2,839 patients, the mean patient age was 9 years and 52% were male.

The study showed that the impact of childhood atopic dermatitis on the family was substantial, increasing, not unexpectedly, with disease severity. For example, in the US cohort, sleep was impacted a lot or very much in 15% of families with a child with mild atopic dermatitis compared with 54% of families with a child with severe atopic dermatitis. Similarly, 23% of families with a child with mild atopic dermatitis reported that emotional distress impacted their family a lot or very much compared with 54% of families with a child with severe atopic dermatitis. Also, in the US cohort, nearly 5 hours had been spent on care in the past week by caregivers of a child with mild atopic dermatitis compared with 11 hours for a child with moderate-to-severe atopic dermatitis. The majority of caregivers reported missing work during the past 4 weeks.

The findings of these 2 studies are consistent with numerous other investigations showing that the burden of atopic dermatitis is substantial, increases with disease severity, and affects not only the patient, but the family and caregivers as well. Consequently, treatment directed at reducing the burden of disease, both the burden experienced by the patient as well as the caregiver and family, is essential.

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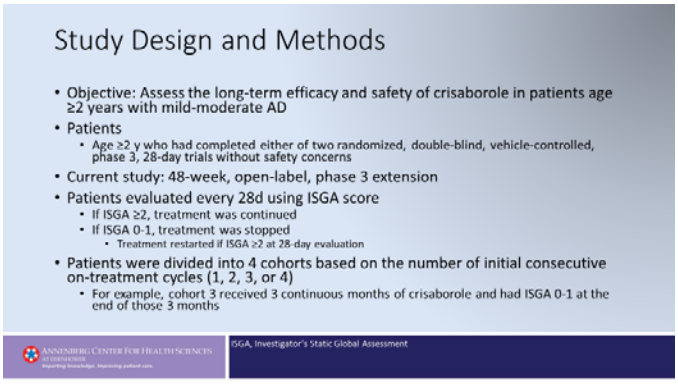
Efficacy and Safety Trends with Continuous Long-term Use of Crisaborole Ointment 2% in Patients with Mild-to-Moderate Atopic Dermatitis

Presented by Dr. Lebwohl and colleagues at the 2020 American Academy of Dermatology virtual annual meeting.

Steve Feldman, MD: To summarize, crisaborole was safe and effective over 1 year of treatment in patients greater than or equal to 2 years of age, with mild-to-moderate atopic dermatitis. Some patients, particularly those with greater disease severity, often required longer treatment to achieve clear or almost clear skin. Upon discontinuation, some patients maintain clear or almost clear skin for 1 or 2 months before they need to restart.

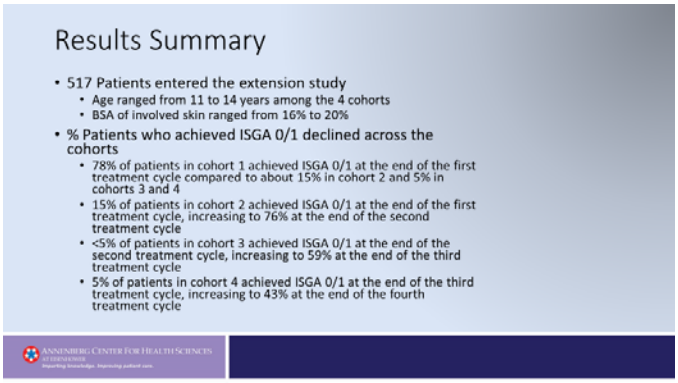
The chronic inflammatory nature of atopic dermatitis generally requires long-term treatment, often with breaks in treatment. Sometimes intended, sometimes due to poor adherence. Re-instituting crisaborole generally resulted in treatment response with some patients achieving clear or almost clear skin.



In this study, patients age greater than or equal to 2 years old, who had completed either of 2 randomized, double-blind, crisaborole control, phase 3 trials, without safety concerns, were eligible to enroll in this 48-week open-label phase 3 extension study.

This analysis reported by Dr. Lebwohl et al is a post hoc analysis of this extension study. Patients in the extension study were evaluated every 28 days, using an Investigator's Static Global Assessment or ISGA score. If their disease was still mild or worse, in other words, if their ISGA score was 2 or more, they continued on topical crisaborole for another 28 days and were then reevaluated. If their atopic dermatitis was clear or almost clear, that is an ISGA score of zero or 1, the treatment was stopped until the reevaluation 28 days later.

The investigators then reported the data of 4 groups, 4 cohorts, and this is a little complicated, but each cohort is based on the number of initial, consecutive, on-treatment cycles. One, 2, 3, or 4. So, for example, cohort 3, received 3 continuous months of topical crisaborole and were clear or almost clear of atopic dermatitis at the evaluation, at the end of those 3 months.



Here were the key findings: 517 patients entered the extension study, the average age ranged from 11 to 14 years among the 4 cohorts, the body surface area involved ranged from 16% to 20%, so these were patients with bad disease.

The patients who achieved ISGA zero or 1 declined across the cohorts. For example, 78% of patients in cohort 1 achieved ISGA of zero or 1 at the end of the first treatment cycle, compared to about 15% in cohort 2 and 5% in cohorts 3 and 4. While about 15% of patients in cohort 2 achieved ISGAs of zero or 1 at the end of the first treatment cycle, this increased to 76% at the end of the second treatment cycle. And while less than 5% in cohort 3 achieved ISGA of zero or 1 at the end of the second treatment cycle, this increased to 59% at the end

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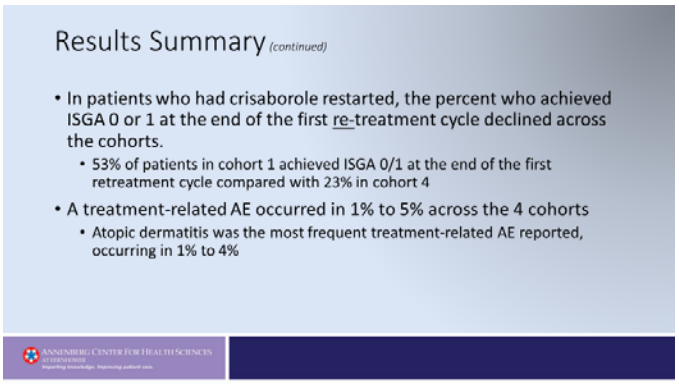
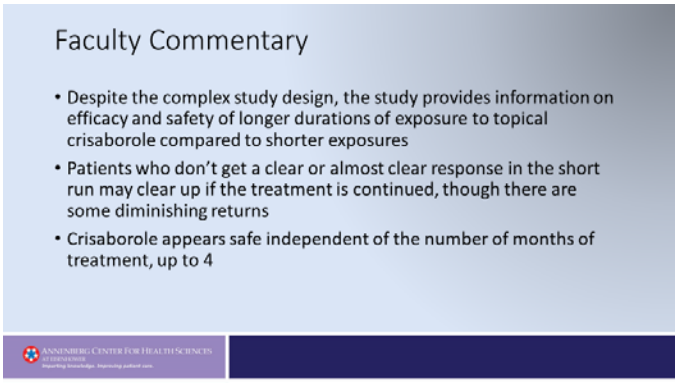
of the third treatment cycle. And then in the fourth cohort, again, only about 5% achieved ISGA of zero or 1 at the end of the third treatment cycle, but increased to 43% at the end of the fourth treatment cycle.

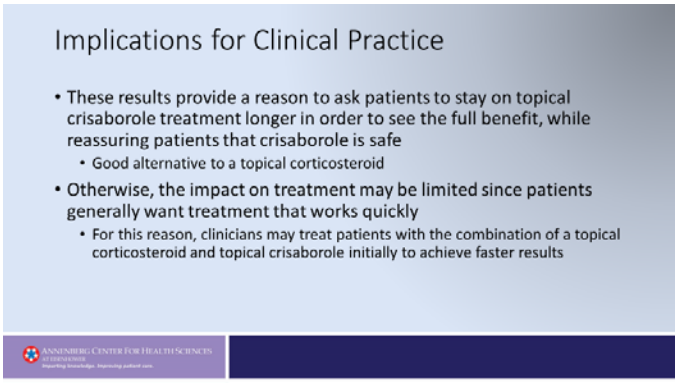


So, recall the patients who achieved ISGA of zero or 1 at the end of a 28-day treatment cycle had their crisaborole held until their ISGA score increased to greater than or equal to 2, at which time the crisaborole was restarted. In these patients who had crisaborole restarted, the percent who achieved clear or almost clear at the end of the first re-treatment cycle declined across the cohorts. So, for example, 53% of patients in cohort 1 got to ISGA of zero or 1 at the end of the first treatment cycle compared to 23% in the fourth cohort.

In terms of safety, the percentage of patients who achieved a treatment-related adverse event ranged from 1% to 5% in the different cohorts. Atopic dermatitis was the most common, most frequent treatment-related adverse event reported, occurring in 1% to 4% of the patients.



Well, this is a very complicated study and here's my thoughts and analysis. First, it's such a difficult study design to follow, but it does give us information on efficacy and safety of longer durations of exposure to topical crisaborole, compared to studies that only looked at shorter exposures. What we find is that patients who don't get clear or almost clear response in the short run may clear up if the treatment is continued, though there's some diminishing returns. The drug appears safe, independent of the number of months of treatment, up to 4 in this case. There were more colds and things the more time patients were on drug, but of course the longer you keep an eye on people, the more likely they are to have a cold or some other adverse event over time.



This study may give doctors the confidence to ask patients to stay on topical crisaborole treatment longer in order to see the full benefit of the drug, while reassuring patients that the treatment is safe. In terms of its impact on how we manage patients, I don't think this study is going to have a big impact on treatment. Patients

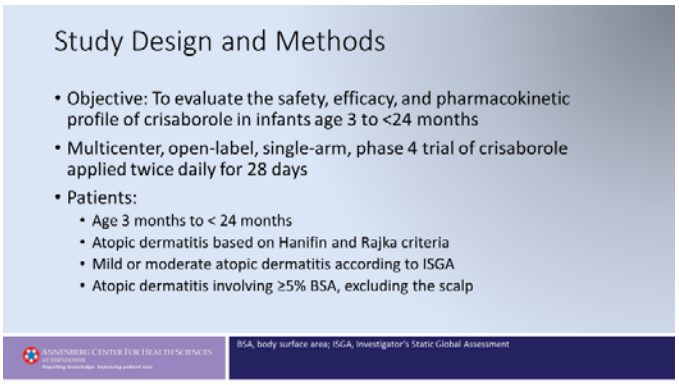
tend to want treatments that work faster, but for patients who don't want to use a topical steroid, this study may be used to encourage patients to stick with the treatment, to see the full potential benefit. It may be that doctors will recommend doubling up and using topical crisaborole with a topical steroid initially to get faster results and then switch to the topical crisaborole for long-term safer maintenance.

There's always unanswered questions. I think it's fine to tell patients the drug will work slowly and stick with it, but it's hard to get patients to do it. Adherence to topical treatment can be abysmal. Adherence tends to be better in studies than in real-life patients, too. So if a drug like this works slowly in the study, unless we find ways to get our patients to use the drug, at least as well as it was used in the studies, we're likely to see worse outcomes in our real-life patients.

Safety, Efficacy and Pharmacokinetics of Crisaborole Ointment 2% in Infants Age Three to Less Than 24 Months with Mild-to-Moderate Atopic Dermatitis

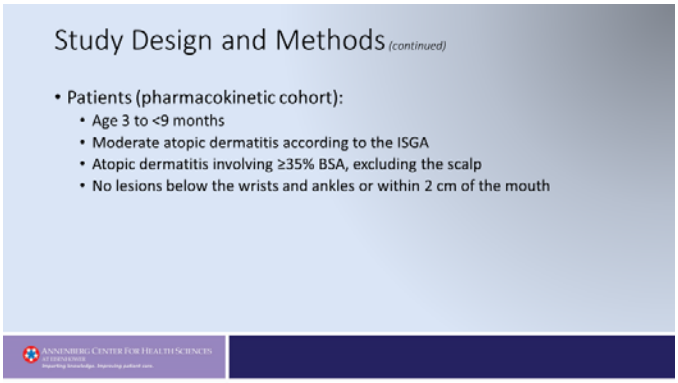
Presented by Dr. Schlessinger and colleagues at the 2020 American Academy of Dermatology virtual annual meeting.

Steve Feldman, MD: This study was conducted to meet a post-marketing requirement of the US Food and Drug Administration, to investigate the safety, efficacy, and pharmacokinetics of crisaborole in children age 3 months to 2 years with mild- to-moderate atopic dermatitis.



Crisaborole is a topical nonsteroidal medication that was approved for the treatment of adults and children age greater than or equal to 2 years at the time of the study. The results of this study confirmed that topical crisaborole is safe and effective in children less than 2 years of age, with results similar to those observed in patients age greater than or equal to 2 years. The approved labeling for crisaborole was subsequently revised to include use in children aged 3 months to 2 years.

This study was a multicenter, open-label, single-arm, phase 4 trial of crisaborole applied twice daily for 28 days. The following were required for a patient to be eligible for the study. First, age 3 months to less than 24 months, a diagnosis of atopic dermatitis based on Hanifin and Rajka criteria, mild or moderate atopic dermatitis according to Investigator's Static Global Assessment or ISGA, atopic dermatitis involving 5% or more body surface area, excluding the scalp.



In addition to assessing the safety and efficacy, the study also investigated the pharmacokinetics of crisaborole. Inclusion criteria for that cohort included age 3 to less than 9 months, moderate atopic dermatitis according to the ISGA, atopic dermatitis involving a lot of body surface area, they had to have 35% or more of body surface area, excluding the scalp affected, and no lesions below the wrists or ankles or within 2 cm of the mouth.

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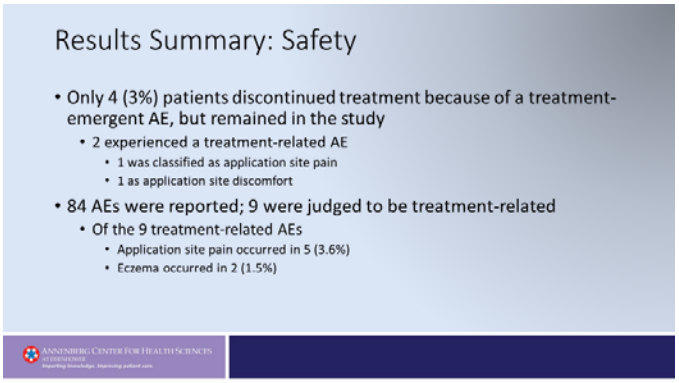
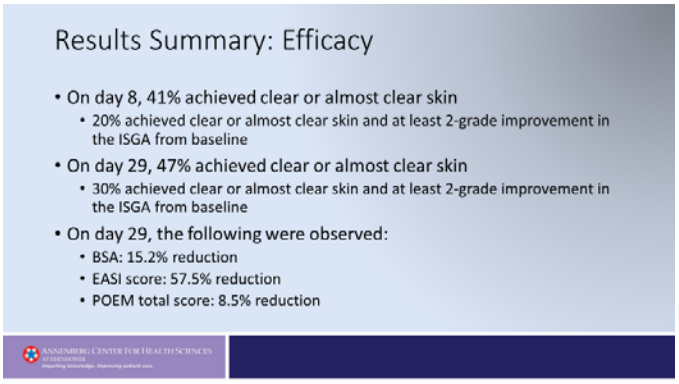
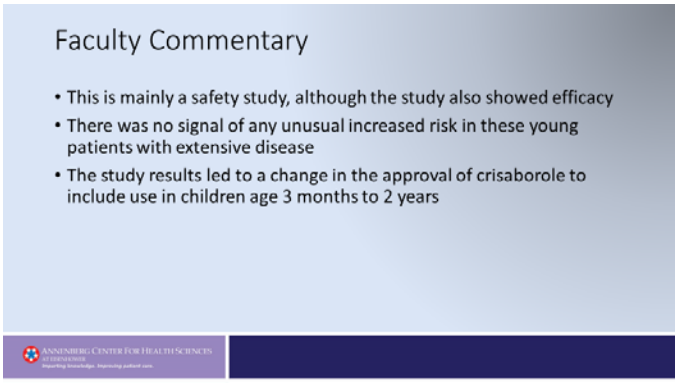


The safety results first. Only 4, which is 3% of the patients, discontinued treatment because of a treatment-emergent adverse event, but remained in the study. Of these 4 patients, 2 experienced a treatment-related adverse event. One was classified as application site pain, and the other as application site discomfort. Eighty-four adverse events were reported, but only 9 were judged to be treatment-related. Of the 9 treatment-related adverse events, application site pain was the most common occurring in 5, which is 3.6% of the patients. Treatment-related eczema occurred in 2 patients.

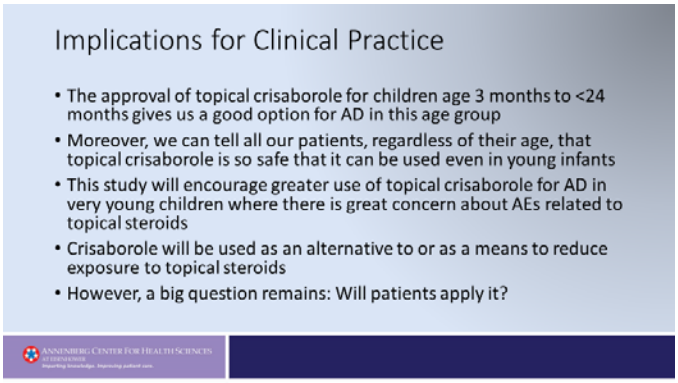


Let's move on to the efficacy results. On day 8, 41% of patients achieved clear or almost clear skin, with 20% achieving clear or almost clear skin and at least 2 grade improvement in the ISGA from baseline. On day 29, 47% achieved clear or almost clear skin, with 30% achieving clear or almost clear skin, and at least a 2-grade improvement in the ISGA from baseline. On day 29, the following mean percent changes were observed: the body surface area at a 15.2% reduction, the EASI score a 57.5% reduction, and the POEM score an 8.5% reduction.

The key pharmacokinetic parameters were measured, and that showed systemic exposure similar to what you see in patients age greater than or equal to 2 years.



So here's my thoughts. The main points of the study are that this is primarily a safety study. The study also showed efficacy. Patients with extensive areas of involvement were enrolled. If the drug is safe in these patients, it's probably safe. Sure enough, there was no signal of any unusual increased risk in these young patients. Thus, the approved age of topical crisaborole was dropped to include children age 3 months to 2 years.

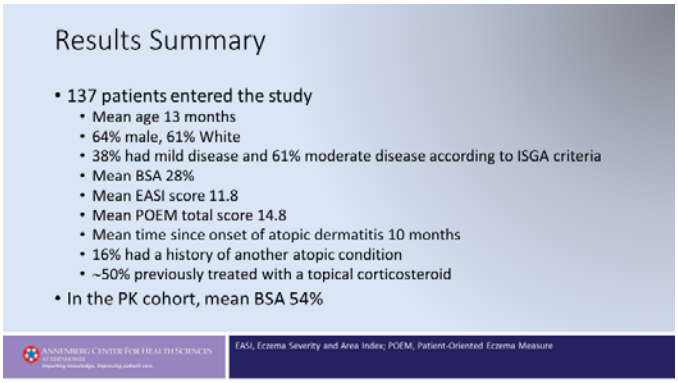


How will this affect our management of patients? The approval of topical crisaborole down to the age of 3 months gives us a good option for atopic dermatitis in patients 3 months and older. Moreover, we could tell all our patients, regardless of their age, when using topical

crisaborole, that topical crisaborole is so safe that it can even be used in young infants.

How about the future? I think this study will encourage greater use of topical crisaborole in atopic dermatitis in very young patients. In that population, we're more concerned about steroid side effects than we are in older kids and these data support using topical crisaborole instead of, or as a means to reduce, steroid exposure.

In my mind, the biggest unanswered question that remains with topical therapy is, will our patients apply it? Parents love their children. They love their children the world over, but they aren't always particularly compliant with topical therapy even when their kids are suffering with atopic dermatitis. Knowing that this drug is safe and effective in very young children may help to some extent, but it's still a high hurdle to get people to use topical treatments in the long run.



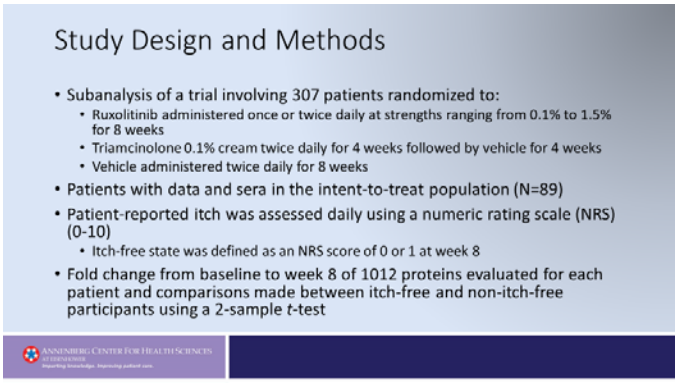
Let's discuss the key findings of the study. There were 137 patients entered into the study; 64% were male, 61% were white, 38% had mild disease, and 61% moderate disease according to the ISGA criteria. The disease was pretty horrible in these patients, with a mean body surface area involved of 28%. The mean Eczema Severity and Area Index or EASI score was 11.8. The mean Patient-Oriented Eczema Measure, the POEM, total score was 14.8. The mean age was 13 months and the mean time since onset of atopic dermatitis was 10 months. Sixteen percent of the subjects had a history of another atopic condition. Approximately half had been treated with a topical corticosteroid. In the pharmacokinetic, the PK cohort, the average body surface area was a bit over 50%.

Association Between an Itch-Free State in Atopic Dermatitis Treated with Ruxolitinib Cream and Systemic Inflammatory Mediators

Presented by Dr. Owens and colleagues at the 2020 American Academy of Dermatology virtual annual meeting.

Steve Feldman, MD: To summarize, patients who achieved an itch-free state with topical ruxolitinib mostly experienced greater decreases in inflammatory mediators than those treated with triamcinolone 0.1% or vehicle. More patients in the ruxolitinib twice daily cohort achieved the itch-free state followed by the once daily cohort.

The importance of this is that atopic dermatitis is a chronic inflammatory skin disease characterized by substantial pruritus. Topical ruxolitinib offers therapeutic benefit, and this study confirms that the reduction in itch is correlated with reductions in the inflammatory process.



This study involved the subanalysis of a trial involving 307 patients randomized to ruxolitinib, administered once or twice daily at strengths ranging from 0.1% to 1.5%, for 8 weeks, or to triamcinolone 0.1% cream twice daily for 4 weeks, followed by vehicle for 4 weeks, or to vehicle administered twice daily for 8 weeks. The subanalysis

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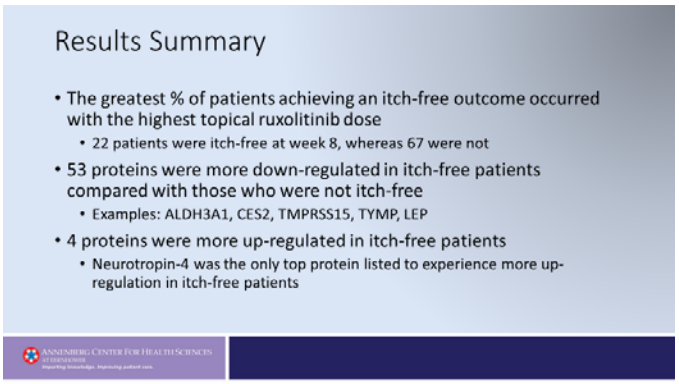
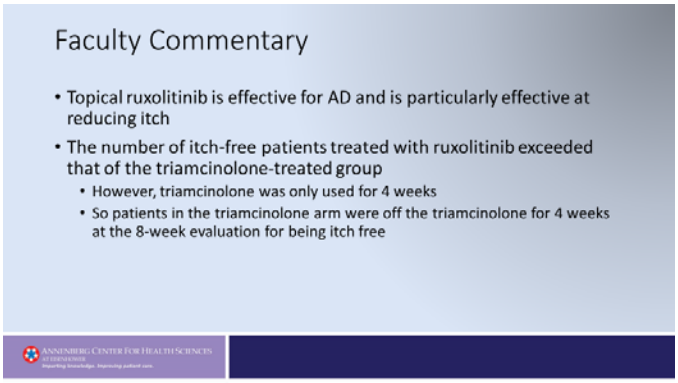
involved 89 patients with data and sera in the intent-to-treat population. Patient-reported itch was assessed daily with a Numeric Rating Scale or NRS, which went from zero to 10, and itch-free state was defined as an NRS score of zero or 1 at week 8.

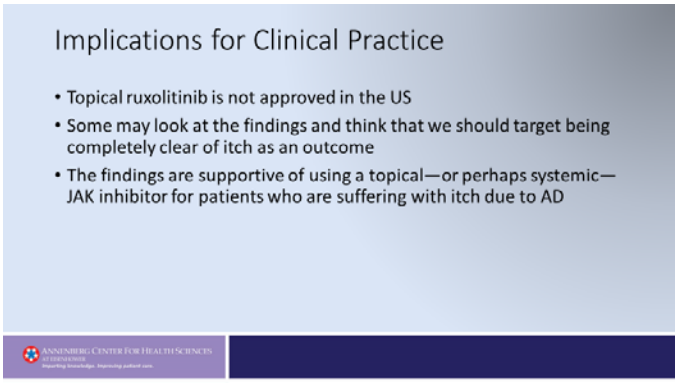
The fold change from baseline to week 8 of 1012 different proteins was evaluated for each patient and comparisons were made between the itch-free and the non-itch free participants using a 2-sample *t*-test.



Here are the key study findings. The greatest percent of patients achieving itch-free outcome occurred with the highest topical ruxolitinib dose. Twenty-two patients were itch free at week 8, whereas 67 were not. Fifty-three proteins were more down-regulated in the itch-free patients compared to those who were not itch free. Some of those down-regulated proteins where the ALDH3A1, CES2, TMPRSS15, TYMP, and LEP. Four proteins were more up-regulated in itch-free patients. Among these, neurotropin-4 was the only top protein listed to experience more up-regulation in the itch-free patients.



Here are my thoughts and analysis of the study. Let's talk first about the main points of the study. First, topical ruxolitinib is effective for AD and is particularly effective at reducing itch. The number of itch-free patients exceeded that of the triamcinolone-treated group, but as I understand it, we have to keep in mind that the triamcinolone was only used for 4 weeks. So patients in the triamcinolone arm were off the triamcinolone for 4 weeks at the 8-week evaluation for being itch free.



How will this affect our current management? Well, until topical ruxolitinib is available, this study won't have a big impact on management. Some people may look at the findings and think that the results support the idea that we should be targeting getting patients completely clear of itch as an outcome. How will this affect our future management? Well, I think these findings are supportive of using a topical or perhaps even systemic Janus kinase (JAK) inhibitor for those patients who are suffering with itch due to atopic dermatitis.

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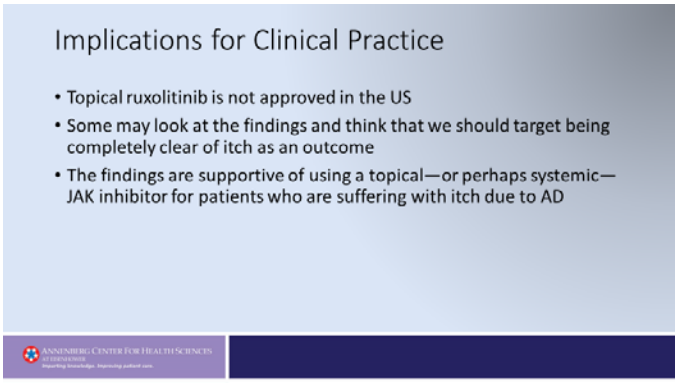
What questions remain unanswered? Well, one of the unanswered questions is quite practical. Will insurers cover the product if it's approved? If insurers were to only approve topical ruxolitinib when patients have failed a topical steroid or 2 first, the patient population that would be receiving this drug might be highly selective for patients who have resistant disease. And that could mean resistance to good treatment compliance. And that might mean that the drug in real-life practice might not be as effective in the people in whom we use it as it was in the clinical trial.

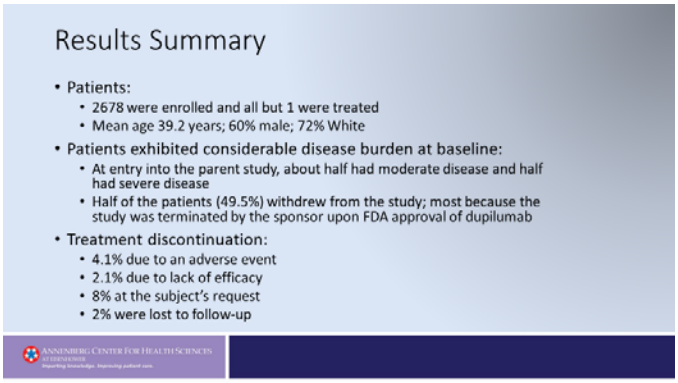
Dupilumab Treatment for up to Three Years Demonstrates Sustained Efficacy in Adult Patients with Moderate-to-Severe Atopic Dermatitis: Results from Liberty AD Adult Open Label Extension

Presented by Dr. Blauvelt and colleagues at the 2020 American Academy of Dermatology virtual annual meeting.

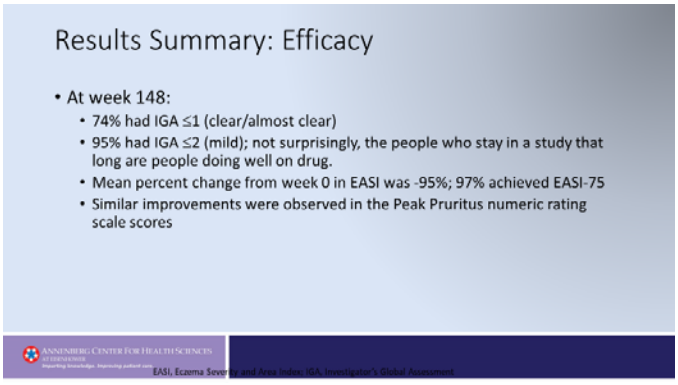
Steve Feldman, MD: To summarize, treatment with dupilumab was safe and effective for up to 3 years in patients with moderate-to-severe atopic dermatitis. Moreover, incremental improvement over time was observed on multiple measures of disease assessment. The safety profile was found to be consistent with observations from shorter controlled studies. This study extends observations from previous trials and demonstrates that dupilumab is safe and effective for up to 3 years in patients with moderate-to-severe atopic dermatitis.



This study is an ongoing phase 3, multicenter study assessing the long-term safety and efficacy of repeat doses of dupilumab 300 mg weekly in adults with moderate-to-severe atopic dermatitis. Patients were treated with dupilumab for up to 148 weeks. Patients who previously participated in any dupilumab study or had been screened for a phase 3 study, but were not randomized because of randomization closure.



The key findings of this study: 2,678 subjects were enrolled and all but 1 were treated. The mean age was 39.2 years, 60% were male, 72% were White. Patients exhibited considerable disease burden at baseline. At entry into the parent study, about half had moderate disease and half had severe disease. Half of patients, 49.5%, withdrew from the study. but most of them because the study was terminated by the sponsor when the FDA approved the dupilumab. Only 4.1% withdrew due to an adverse event and 2.1% due to lack of efficacy. Eight percent withdrew at the subject's request and 2% were lost to follow-up.



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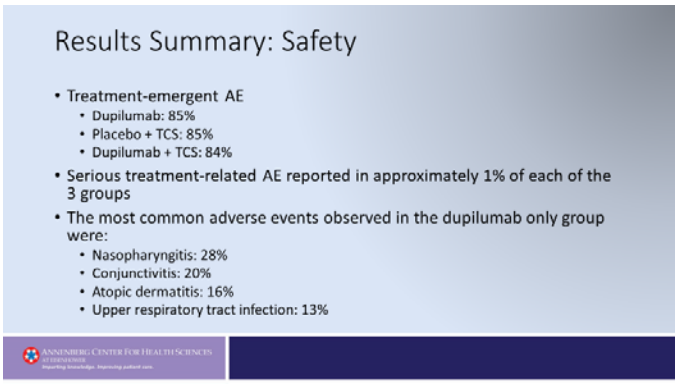
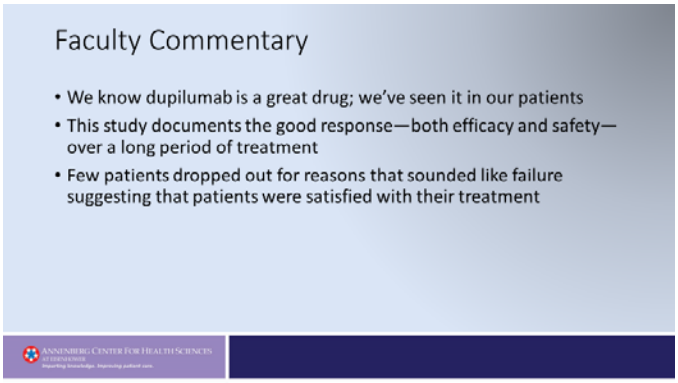
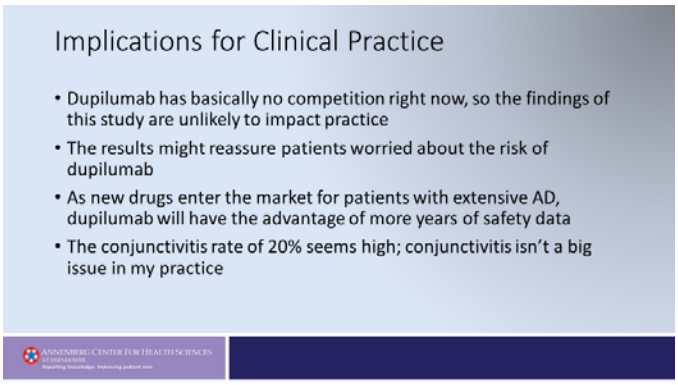
At week 148, 74% had IGA of less than or equal to 1, which means they were clear or almost clear. Ninety-five percent had an IGA of less than or equal to 2, which is mild, almost clear or clear. Not surprisingly, the people who stay in a study that long are people doing well on the drug. The mean percent change from week zero in EASI was 95% improvement. Ninety-seven percent achieved an EASI-75 score and similar improvements were observed in the Peak Pruritus Numeric Rating Scale scores.



In terms of safety, a treatment-emergent adverse event was reported by 85% treated with dupilumab and which may sound high, but it was all 85% reported an adverse event in the placebo group plus topical steroid group as well, and 84% treated with dupilumab plus topical steroids. A serious adverse event related to steady treatment was reported in 1% of each of the 3 groups. The most common adverse events observed in the dupilumab-only group were nasal pharyngitis in 28%, conjunctivitis in 20%, atopic dermatitis in 16%, and upper respiratory tract infection in 13%.



Here are my thoughts and analysis of this study. The main points are, we know dupilumab is a great drug. We've seen it in our patients. This study documents the good response, both efficacy and safety over a long period of time. When I look at long-term data, the thing I want to know more than anything else is whether patients stay in the study. If they stay in a long-term extension study, I presume they are happy and here, few patients dropped out for reasons that sounded like failure.



How will this impact our current management of patients? Dupilumab has basically no competition right now. So I don't think the findings of this study will change things much. If we had patients who were worried about the risk or especially the long-term risk of a drug, we might be able to use the results of this study to reassure them.

How did the results of this study impact the future state of patient management? As new drugs enter the market

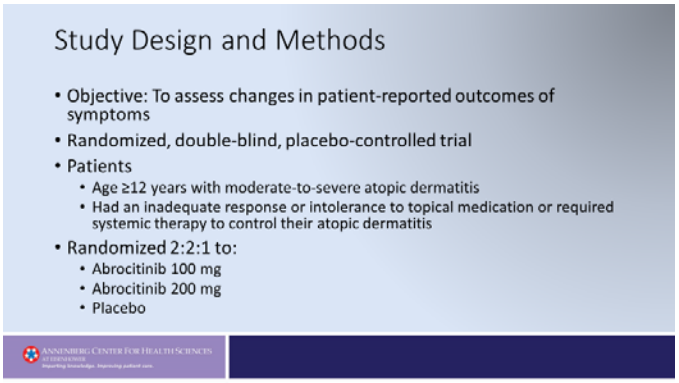
for patients with extensive atopic dermatitis, dupilumab will have the advantage of many more years of safety data available. And I think that will encourage us to continue using dupilumab well into the future.

What questions remain unanswered? Well, we can always wonder if something strange happens after 3 years of follow-up, but it seems unlikely. The conjunctivitis rate of 20% seems pretty high. I haven't noticed conjunctivitis being a big issue in my practice, but it will be interesting to see if similar issues are observed with other new systemic treatments for atopic dermatitis.

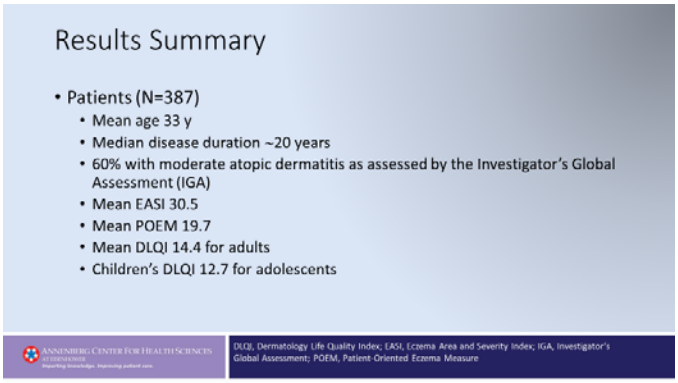
Patient-reported Outcome, or PROs, with Abrocitinib Treatment in Patients with Moderate to Severe Atopic Dermatitis

Presented by Dr. Silverberg and colleagues at the 2020 American Academy of Dermatology virtual annual meeting.

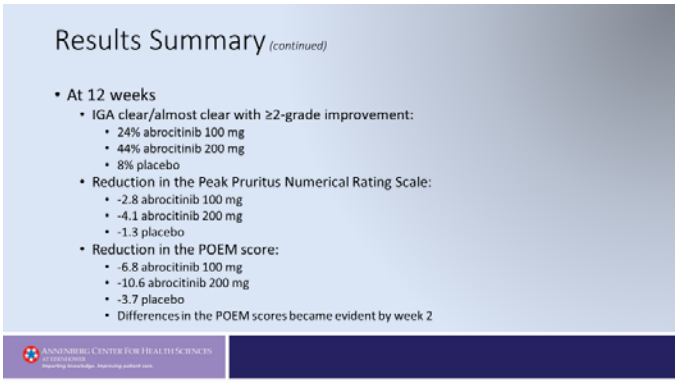
Alan Fleischer, MD: This was a very interesting study. And patient-reported outcomes are important. These are the patient experiences, what they report, not the spots on the skin, but their personal report of what happens to them. And, overall, we saw, in this poster, that patients with abrocitinib treatment reported much greater improvement in patient-related symptoms and quality of life compared with patients who received the placebo.



So, just in brief, this was a large, randomized, multi-center control trial, in which patients received either abrocitinib 100 mg, 200 mg a day, or placebo.



And it was all in those who were 12 years of age and older, so this group of adolescents, as well as adults.

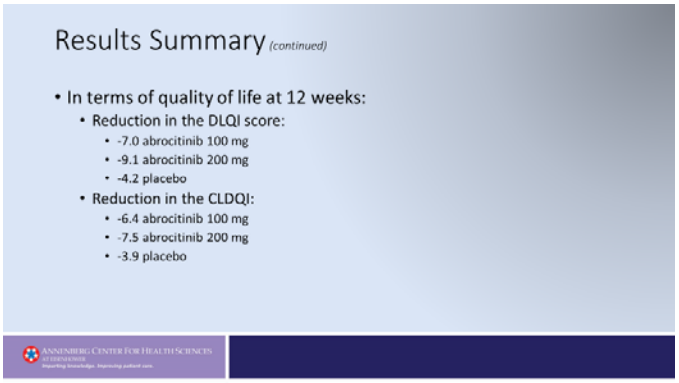


The key finding was that there were several patient-reported outcomes that were really, impressively improved with abrocitinib. At 12 weeks, the IGA response, that is Investigator Global Assessment, of achieving clear or almost clear skin. This is not a patient-reported outcome, but this is a physician-assessed outcome, that in the low dose, 100 mg abrocitinib, 24% achieved clear or almost clear skin. And in the higher dose, 44% achieved clear or almost clear skin. This is in contrast to 8% in placebo patients.

The most common and troubling symptom of people with atopic dermatitis is itch. In this study, itch or pruritus, was measured with the Peak Pruritus Numeric

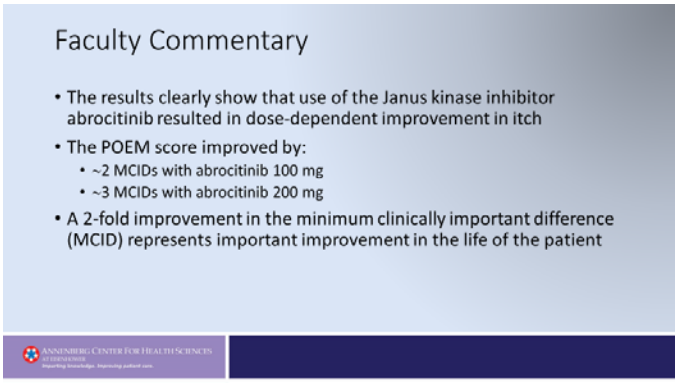
Rating Scale. And what the NRS, or a numeric rating scale is, is a measure that the patient assesses between 0 and 10; 0 is no itch, 10 is the maximum possible itch. And the lower dose of the abrocitinib decreased the Numeric Rating Scale over the period by 2.8 points on this 11-point scale. And the higher dose, the 200 mg, relieved it by 4.1 points compared with only 1.3 points for placebo. So this was a big difference. So, first of all, itch went down remarkably in both treatment groups and in dose-response relationship.

The next measure was the reduction in the POEM score. Now POEM is a measure of the impact of atopic dermatitis on a patient, and it's a validated tool. And the POEM score was dropped by nearly 7 points in the abrocitinib low-dose group, 100 mg, and over 10 points in the high-dose abrocitinib group, compared with only 4 points for placebo. This was a really impressive difference, and differences in the POEM scores became apparent at week 2.



In terms of overall skin-related quality of life, it was exactly parallel to this, that the Dermatology Life Quality Index, the DLQI, or the suitable one for the 12 to 17 group, the children's DLQI, it was actually greater for the 100 mg group and then even greater for the 200 mg group, either way, than placebo.

So the long and the short of it is, no matter how you measure the patient-reported outcomes, that is, their itch severity, their POEM, which is their experience, their overall Dermatology Life Quality Index, it was improved with abrocitinib in a dose-response relationship.



So here are my thoughts about this study. Abrocitinib is what's called a "JAKnib" or "Janus kinase inhibitor," and there's no question that, according to the patients themselves, they experienced a dose-dependent improvement in the sensation of itch, in their experience in atopic dermatitis, as well as their overall Dermatology Life Quality Index.

One of the interesting things is just the amount of improvement, and so, if we look at the POEM score, it turns out there's a measure called the "minimum clinically important difference." How much difference is it that makes a real difference to patients? And the POEM score improved by about 2 minimum clinically important differences, that is MCIDs, in the 100 mg group, and 3 in the 200 mg group. The same is essentially the same in the DLQI. And in 2018, Finley, who developed the DLQI, reported that a 2-fold increase in the MCID for the DLQI really means something. So we're at the point of a drug that makes a huge difference in the life experience with patients with atopic dermatitis.

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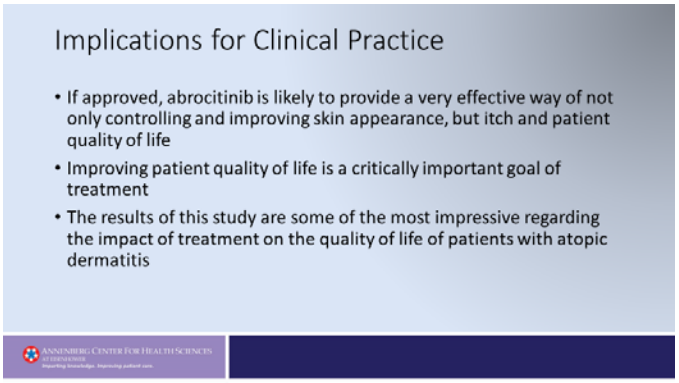
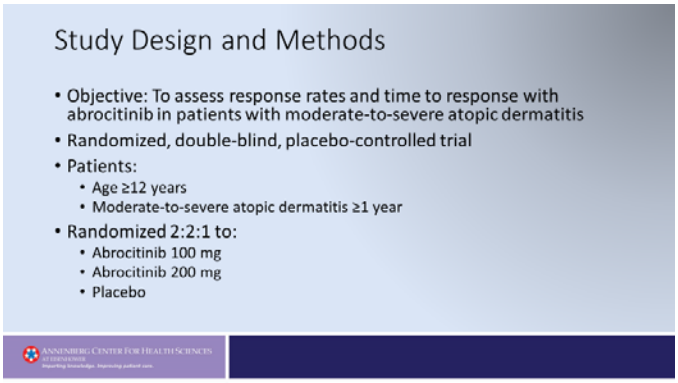




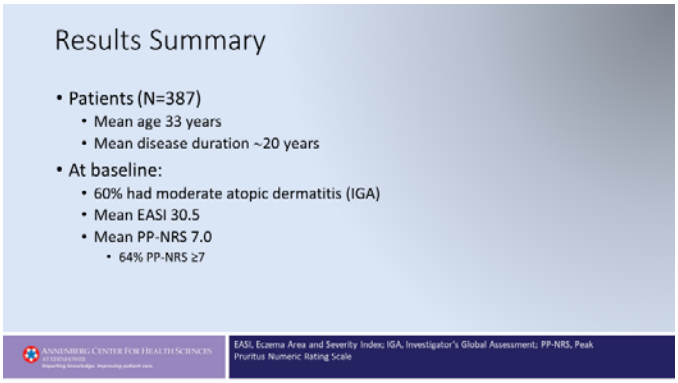
When we have oral JAKnibs approved, this will be a very effective way of not only controlling and improving the appearance of the skin, but the itch and how patients perceive their quality of life. Ultimately, as doctors, our job is not just to make spots get better, but to make patients feel better about themselves and more comfortable in their own skin. And we need great tools to help us to do so. These results are very impressive and some of the most impressive ever published and presented when it comes to atopic dermatitis improvement.

Peak Pruritus Numeric Rating Scale, the PPNRS, Response with Abrocitinib in Patients with Moderate to Severe Atopic Dermatitis: Results from a Randomized Phase 3 Clinical Trial

Presented by Dr. Simpson and colleagues at the 2020 American Academy of Dermatology virtual annual meeting.

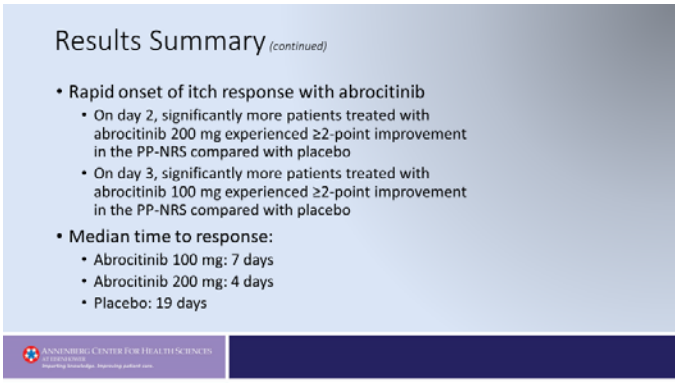
Alan Fleischer, MD: This was a study of the Janus kinase inhibitor, abrocitinib or JAKnib, and this study looked at the most important symptom in atopic dermatitis, that infernal itch. And itch relief is an exceptionally important thing in atopic dermatitis. People say that atopic dermatitis is the itch that rashes. That's almost true, but it's certainly the most debilitating symptom that people have with this condition.

So in this large, randomized, controlled trial of both those who are adolescents, those aged greater than 12 years old, and adults, people were randomized to receive either abrocitinib 100 mg, higher dose abrocitinib at 200 mg, or placebo. And these patients were followed forward and had their overall severity assessed through the Investigator Global Assessment, as well as Eczema Area and Severity Index (EASI) scores. But in addition, the main outcome of this study was the itch reduction.



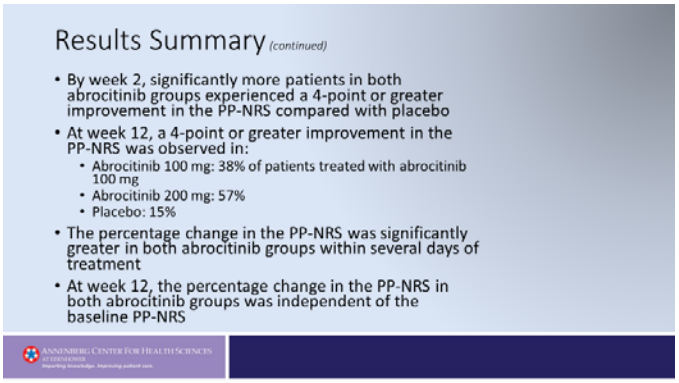
These people started out with a peak pruritus numeric rating scale... that is, how bad is your itch on a scale from 0, which is no itch, to 10, the worst itch you can imagine... of 7, which is exceptionally high. So this is a really impressive and severe itching group. So what happened during the course of the study? It turns out there were 2 outcomes that they looked for.

RESEARCH DEVELOPMENTS IN ATOPIC DERMATITIS

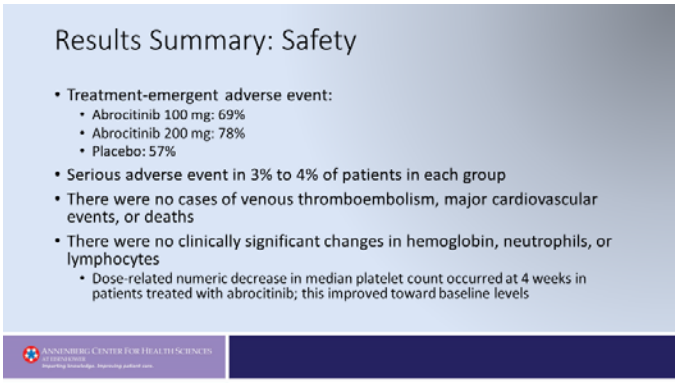


One was the speed with which itch reduction was achieved. So with the higher dose of the drug, the 200 mg, on the second day of treatment, patients began to experience a 2-point or greater improvement in the Pruritus Peak Numeric Rating Scale (PP-NRS) compared with placebo. On the lower dose, it occurred at day 3, and that's actually pretty interesting. So the median-timed response was 4 days for the higher dose, 200, and 7 days for the lower dose, 19 days for placebo.

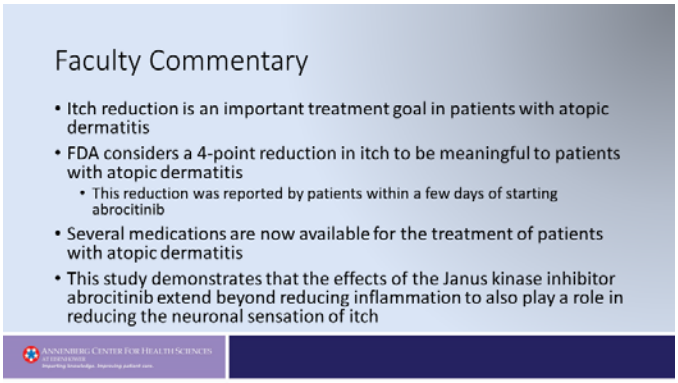
Now, the 2-point reduction is probably meaningful for patients, but we don't know that. It's been established that the smallest amount of itch reduction that is meaningful to patients is a 4-point reduction. Now any itch reduction is probably good, but what convinces scientists that it's a meaningful reduction is the minimum clinically important difference in the NRS, and so that's a 4-point difference.



And it turns out that by week 2, more patients in abrocitinib treatment received a 4-point or a greater improvement in the itch reduction compared with placebo. And overall, at week 12, 38% of patients with lower dose, 100 mg, and 57% in higher dose abrocitinib, had a meaningful clinically important difference in their itch reduction. Only 15% of the placebo patients achieved that. So there was a very rapid response, or what might be called the "kinetics of the response," was rapid.



Overall, there was very good safety in the study, because we're not only interested, ultimately, in the efficacy of the drug. We're interested in the safety of a drug. Both of those have to go together in concert in order for us to feel confident that we're doing the right thing for our patients.



Well, here are my thoughts about this study. In the past, we didn't really even measure itch, but now we have wonderful ways of measuring itch reduction, and worst itch reduction or peak itch reduction, is a meaningful way. So the FDA considers a 4-point reduction to be

meaningful for patients, and this was certainly seen within just days. So it's really impressive.

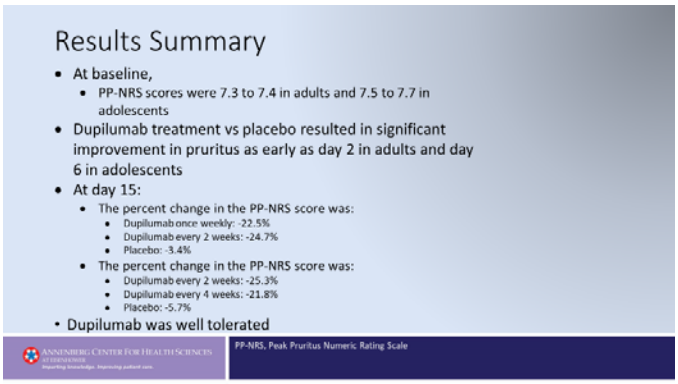
Overall, on the higher dose abrocitinib, a much greater proportion of patients achieved a 4-point reduction than was seen in the dupilumab trials. Now dupilumab is the only systemic drug approved in the United States for treating atopic dermatitis. But one of the really nice things about it is there's really excellent science that exists in the clinical trials for dupilumab, so now we can begin to compare the results between studies. And what I think about, years ago—three decades in fact,—when I started treating psoriasis, the only drug we had that worked was methotrexate. And now we have 11 additional drugs that are clearly more effective. Some drugs are 7-fold more effective than methotrexate. So it's great to have drugs, but how effective are they compared with each other? And that's very important. In this study, we see the single most important outcome in atopic dermatitis, that is itch, being really reduced in a nice, dose-dependent fashion. And this was not just in dose-dependent fashion, but very rapid and in probably a very clinically meaningful way to our patients. We now know that the Janus kinase 1 (JAK1) system is not just important in relief of inflammation, but, as well, there's a direct role of JAK1 on the itch neurons in the control systems. As a result, we see very rapid itch reduction that's marked. Even in this study, we began to see at day 2. So I'm impressed with this class of drugs.

Dupilumab treatment results in rapid improvement in itch in adult and adolescent patients with moderate-to-severe atopic dermatitis (LIBERTY AD SOLO 1 & 2, and ADOL trials)

Presented by Dr. Gil Yosipovitch and colleagues at the 2020 American Academy of Allergy, Asthma, and Immunology virtual annual meeting.

Alan Fleischer, MD: In this study, dupilumab treatment demonstrated what the investigators called "rapid improvement" in pruritus, or itch, in adults and adolescents with moderate-to-severe atopic dermatitis. And remember that itch is the most important symptom in atopic dermatitis. Our patients come to us and tell us that they itch terribly. "Please give me something for itch."

So in this study, the itch severity was relatively straightforward and severe. So it was measured with the Peak Pruritus Numeric Rating Scale or PP-NRS. What is that? Well, it's a scale for which you ask study subjects, "How bad is your itch?" with itch of 0 being no itch and 10 being the worst itch they could ever imagine. And, "Where are you on that list?"



And the peak pruritus rating scales in these studies was 7.3 to 7.4 in adults, 7.5 to 7.7 in adolescents. So virtually the same, and, in both cases, severe.

In this study, there was significant improvement is pruritus as early as day 2 in adults, and day 6 in adolescents. Just a note here, significant improvement in the numeric sense does not mean it's significant improvement to the patient. We'll come back to that. And at day 15, the percent change in the itch score, or PP-NRS score, was 22.5% for adults treated with dupilumab once weekly, an unapproved dose; 24.7% every 2 weeks; and 3.4% for placebo. So there was no question that it was far greater. And the same held true for adolescents.

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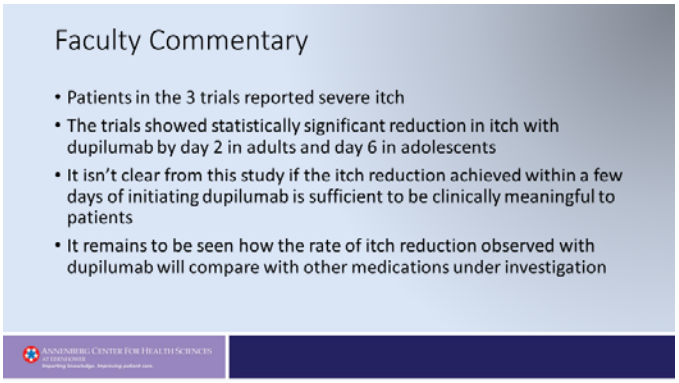
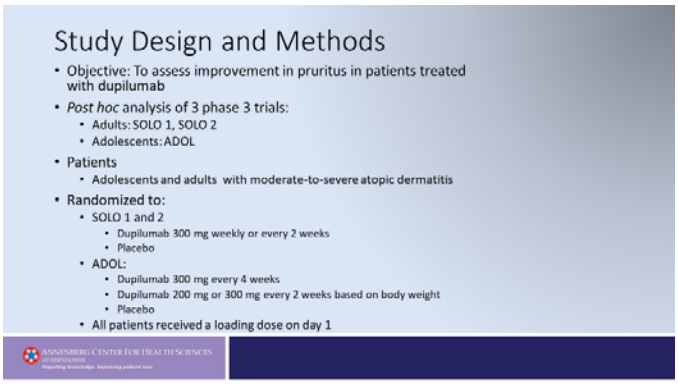


Here are my thoughts about this. So as early as day 2 to 6, there is a statistically significant reduction in the severity of itch. But what we really need to focus on is the word "rapid" and what that means. It's been found with this Peak Pruritus Numeric Rating Scale, the smallest amount of difference that is meaningful for patients is a 4-point reduction, or that's called the MCID, the minimum clinically important difference. So if you have a statistically important difference, but it's not clinically meaningful, does that mean anything to the patient? In my own research group and, so far, unpublished work, we found that, for instance, with dupilumab, it requires about 60 days for half of the population to achieve the itch minimal clinically important difference, the MCID. So, does it do it? Absolutely, and it's a very good drug for achieving that.

By contrast, looking at previously published data, the same occurs in about 10 days for high-dose abrocitinib, 15 days for high-dose upadacitinib. So there's no question that itch relief is achieved through dupilumab; however, whether it's rapid or not remains to be told in a different story because it's about one-sixth the rate that it occurs with the most effective of the JAKnibs. Now, itch reduction does occur with dupilumab. There's nothing new that comes out of this study. And the itch reduction in adolescents is quite comparable to that in adults. This has become the standard of care treatment: Dupilumab for moderate-to-severe atopic dermatitis. And this study and others like it will help us, going forward, to understand the relative effect of 1 drug vs another.

Dupilumab is the gold standard, and now we have drugs that are IL-13 drugs under investigation, lebrikizumab, for instance. We have IL-31 drugs, nemolizumab. We have multiple systemic and even topical JAKnibs under development, and these kinds of wonderful data will help us to be able to compare how patients do. So, in the future, we may need to be a little cautious about the word "rapid." What does "rapid" mean? So, in the title of this poster, clearly, there's no question that some difference was established with dupilumab at day 2; however, is that as rapid as we see with other agents? And that has yet to be seen. So thank you.



This was a study that was based on a post hoc analysis of 3 separate clinical trial programs. The SOLO 1, SOLO 2, and ADOL programs, and involved adults and adolescents with moderate-to-severe atopic dermatitis. Adults in SOLO 1 and 2 were randomized to receive dupilumab 300 mg weekly, or every 2 weeks, or placebo. I was an investigator in this trial. Adolescents in the ADOL study were randomized to receive dupilumab 300 mg every 4 weeks; dupilumab 200 mg or 300 mg every 2 weeks, based upon body weight; or placebo, and all patients received the loading dose.

Treatment Patterns Among Patients with Atopic Dermatitis Using Advanced Therapies in the United States: An Analysis of a Retrospective Claims Database

Presented by Dr. Larry Eichenfield and colleagues at the 2020 American Academy of Dermatology virtual annual meeting.

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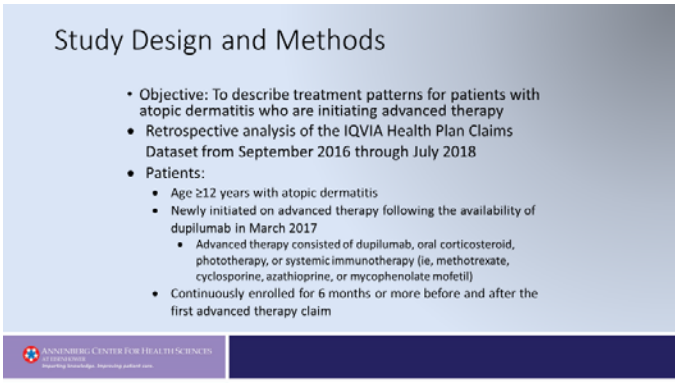
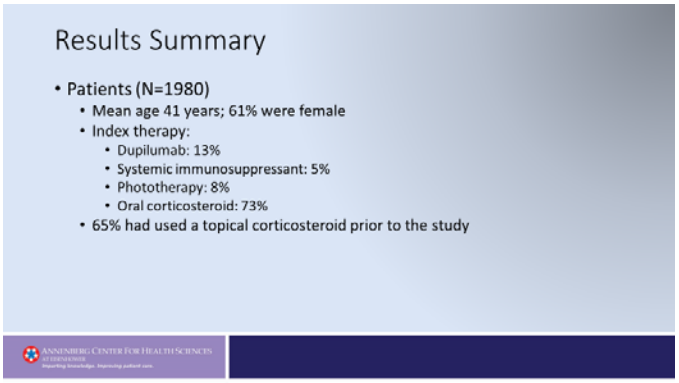
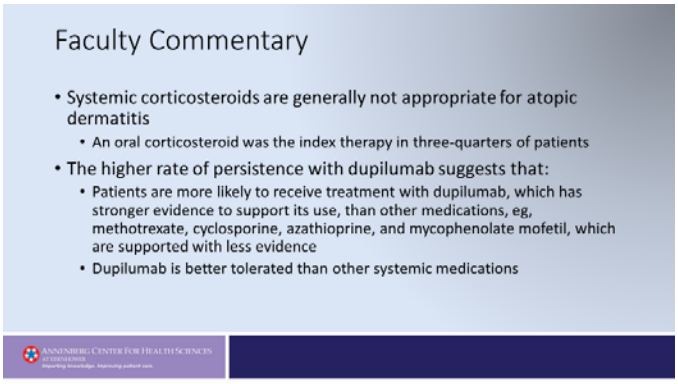
Alan Fleischer, MD: In this study, it was an analysis of US claims database, including nearly 2,000 adolescents and adults with atopic dermatitis. Overall, this was a really interesting study that captures a snapshot of how people are actually being treated in the United States.



How did they do it? Well, it was a retrospective analysis of the IQVIA health plan claims data set from September 2016 through July 2018. And it studied those who are greater than or equal to 12 years old with atopic dermatitis. Advanced therapy was defined as dupilumab, oral corticosteroid, phototherapy, systemic immunotherapy, that is methotrexate, cyclosporine, or other oral small-molecule inhibitors, and patients also had to be enrolled for 6 months or more before they started capturing these patient experiences, because they had to know what was going on.



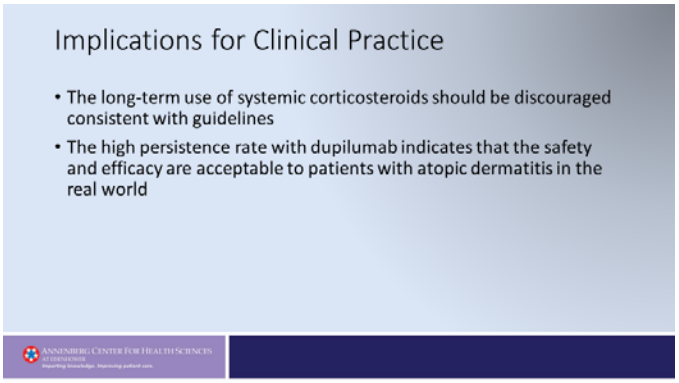
Well, in their analysis, they found that the vast majority of those treated were treated with an oral corticosteroid, that is 73%. Only 13% were treated with dupilumab, and then 5% with systemic immunotherapy, that is oral small molecule treatment, or 8% with phototherapy. In addition, the majority had topical corticosteroids prior to the study.



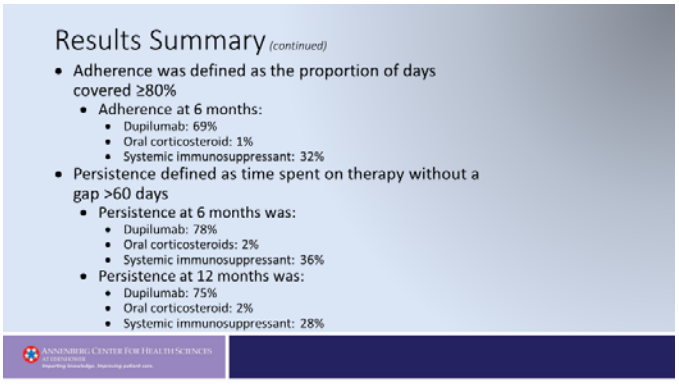
So here are my thoughts about it. The use of long-term systemic corticosteroids is not considered appropriate for the management of most patients with atopic dermatitis. Dupilumab has better 6- and 12-month persistence compared with both the oral small-molecule immunosuppressants, as well as systemic corticosteroids. This implies that, number 1, patients are being pretty appropriately treated. They're not kept on high-dose oral prednisone long term. And the second is that we really have never seen a study, say, comparing long-term dupilumab with long-term azathioprine, but something about azathioprine and mycophenolate mofetil, and similar kinds of drugs, makes it less likely that patients stay on those drugs, that is less than a third of the patients in the real-world population stay on the drugs like those compared with dupilumab, which is much higher.

We never know, examining real-world evidence, why people stop. Could it be they have side effects? Could it be they just did not get appropriate effect? We don't know. All we know is that people did better on the approved treatment than on the nonapproved treatments.

RESEARCH DEVELOPMENTS IN ATOPIC DERMATITIS



So when I think about this study as it relates to patient management, these results clearly support the current guidelines of care that discourage the use of long-term systemic corticosteroids. The comparative efficacy of biologic drugs, such as dupilumab, with oral small-molecule immunosuppressants is not known, but this is a vote in favor of drugs for which we have known safety and efficacy. When we enter an era where there will be multiple drugs approved in this space, we'll be able to more directly compare their long-term use in the community. Ultimately, clinical trials are very important and give us rigid information in our evidence-based world. But what actually happens in the community gives us other insights. When people don't continue on drugs, whereas they do continue on others, it gives us insights into the real-world safety and efficacy. Thank you so much.



Adherence, which was defined in the study as "the proportion of days where they used treatment appropriately greater than 80%" was much higher for dupilumab vs the other treatments. Adherence was 69% with dupilumab, 1% for oral corticosteroids, and less than a third for systemic immunosuppressants. Persistence, that is, did they stay on the drug... Persistence at 6 months was 78% for dupilumab, 2% for oral corticosteroids and 36% for systemic immunosuppressants. Persistence at 12 months, that is 12 months out, was exactly the same: 75% with dupilumab, 2% with oral corticosteroids and 28% with systemic immunosuppressants. So the approved treatment was far more, both persistent, as well as had greater adherence, at 6 and later 12 months, for persistence.

Other posters of interest

Alan Fleischer, MD: There are other points of interest from these various meetings. Much has been learned about atopic dermatitis in recent years that can help us take care of our patients better. And at a basic science level, what do we need to know to help us understand how to target the right medications for the right patients? What do we know about the disease itself? And 2 posters presented at the 2020 American Academy of Allergy, Asthma, and Immunology virtual annual meeting were really worth noting.

The first, which was a study that looked at the role of the human microbiome in the development of a wide variety of disease, was really interesting. It was titled "Alterations in the Composition, Functional Gene Profiles and Metabolites of the Gut Microbiota in Infancy That Determines the Natural Course of Atopic Dermatitis" by Dr. Yoon Mee Park. And this shed some really interesting light on atopic dermatitis. Really, in brief, this study set about to examine the composition and function of the gut microbiome in infancy as it relates to atopic dermatitis. And it involved 132 infants: 84 were healthy, 22 had transient atopic dermatitis, and 26 had persistent atopic dermatitis. The composition of the gut microbiota was analyzed by fecal samples and a whole series of really exotic profiling.

It showed that the gut composition of *Clostridium* species and *Akkermansia* species is lower, and that of gut

Streptococcus is higher, at 6 months of age, in infants with persistent atopic dermatitis. Low levels of *Streptococcus* species and high levels of *Akkermansia* in the gut at 6 months of age were evident in children, with remission of atopic dermatitis at 2 years of age. And the relative abundance of *Streptococcus* and *Clostridium* was associated with the severity of atopic dermatitis. The significance of these findings is likely quite real and important, but certainly not understood by me. I don't think there's one disease atopic dermatitis. I think there are many diseases and how the gut and the skin are related pathophysiologically is a bit uncertain.

Moreover, this work was done in South Korea and was really world class work. At the same time, the microbiome of the gut, as well as the skin, differs all over the world. Does atopic dermatitis in South Korea resemble atopic dermatitis in France or China or the United States? We don't know the answer to this. Does the gut composition of the microbiotic species, does this predict things in 1 group of patients with atopic dermatitis vs another? We don't know that, but it's fascinating that, just by looking at gut species, these investigators were able to sort out differences between atopic dermatitis patients.

The other is a poster by Dr. Mohamed Taki and colleagues titled “Atopic Dermatitis Phenotypes and the Subsequent Development of Atopic Diseases in a High-Risk Birth Cohort.” This study sought to investigate the association between atopic dermatitis phenotypes and the subsequent development of allergic diseases in childhood. In the study, nearly 300 children were enrolled at birth and followed prospectively. They had their occurrence of atopic diseases, including atopic dermatitis, food allergy, allergic rhinitis, and asthma, with annual questionnaires followed forward for 6 years.

The method that they chose to use is latent class analysis. And this is a method that, in a nonjudgmental way, looks to find relationships between various different conditions and relate them statistically, even if it may not be obvious clinically. It's used in many, many different kinds of settings. So this isn't novel use in this setting. These analyses identified 3 separate atopic dermatitis phenotypes: the none or intermittent group; the late onset, that is, late onset in childhood group; and the persistent atopic dermatitis. Persistent atopic dermatitis, but not late-onset atopic dermatitis, was associated with a significantly increased risk of food allergy and allergic rhinitis at age 6 years. By contrast, both persistent and late-onset atopic dermatitis was associated with a significantly increased risk of asthma at age 6 years.

Overall, it appears that the age of onset and the persistence of atopic dermatitis have an impact on other allergic diseases. And I find this really interesting, because in my own daughter, who had pretty severe persistent atopic dermatitis, she went on and developed quite significant asthma. So we don't believe that atopic dermatitis is 1 disease. There are many different phenotypes of atopic dermatitis. Ultimately, we may divide atopic dermatitis into 3 or 10 subtypes. But these kinds of work help us to begin to break down the barriers between different types to help us understand: What are their risks long term? How should we treat them best? Who should we monitor for other concordant diseases? So, this is a really great study. Thank you.