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EXPERT perspectives

Shifting Paradigms, Emerging Treatments in Moderate to Severe Atopic Dermatitis

A CE/CME Activity

Overview

David Bernstein, MD, and **Amy Paller, MD,** combine their expertise and discuss emerging concepts, treatment advancements, and critical issues associated with the management of patients with atopic dermatitis (AD). The discussion focuses on real-world patient management and includes case studies to facilitate integration of new knowledge into clinical practice.

Content Areas:

- Epidemiology and pathogenesis of AD
- Long-term disease management
- Prevention of flares
- Efficacy and safety data for emerging therapies

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http://annenberg.net/Atopic-Dermatitis-CME

CE/CME Information

Target Audience
This activity was developed for dermatologists, allergists, pediatricians, primary care physicians, nurse practitioners, nurses, pharmacists, and other health care professionals who have an interest in atopic dermatitis (AD).

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

- Examine the epidemiology and pathogenesis of AD and the relevance to the management of patients with AD
- Integrate a proactive approach to long-term disease management in AD, with a focus on prevention of flares, assessment of disease activity, and patient education
- Discuss the mechanisms, efficacy, and safety data for emerging biologic therapies and which patients are likely to benefit

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The estimated time to complete the activity is 2.0 hours.

This activity was originally released in February 2017 and is eligible for credit through February 28, 2018.

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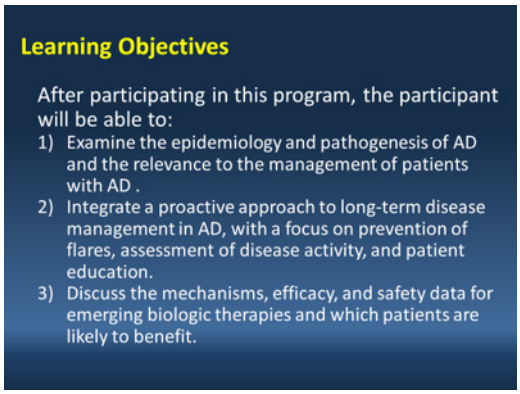
1 *Atopic Dermatitis: Epidemiology*

Dr. Bernstein: Hi. Welcome to this educational program, Shifting Paradigms, Emerging Treatments in Moderate to Severe Atopic Dermatitis. My name is David Bernstein. I'm professor of medicine and my specialty is allergy/immunology, and I have a faculty appointment at the University of Cincinnati College of Medicine. I'm sharing this program today with my colleague Amy Paller.

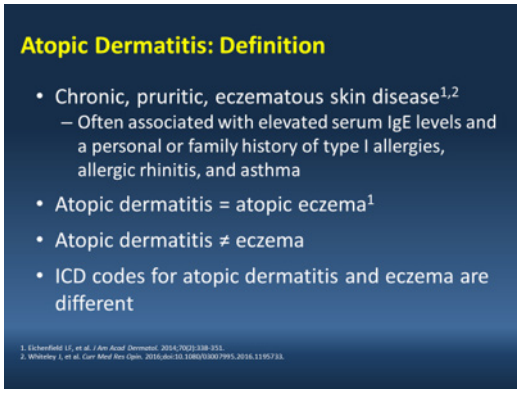
Dr. Paller: Hi. I am the professor and chair of dermatology and professor of pediatrics at Northwestern University Feinberg School of Medicine in Chicago, and I specialize in the care of children with atopic dermatitis.

Today we're going to be covering several aspects about atopic dermatitis ranging from epidemiology, to pathophysiology, to the clinical assessment, medical management, prevention of flares, and also emerging therapies.

Participants in this program should be able to examine the epidemiology and pathogenesis of atopic dermatitis and the relevance to the management of patients with atopic dermatitis, integrate a proactive approach to long-term disease management in atopic dermatitis with a focus on prevention of flares, assessment of disease activity, and patient education. Finally, we hope that you'll be able to discuss the mechanisms, efficacy, and safety data for the emerging biologic therapies and which patients are likely to benefit.



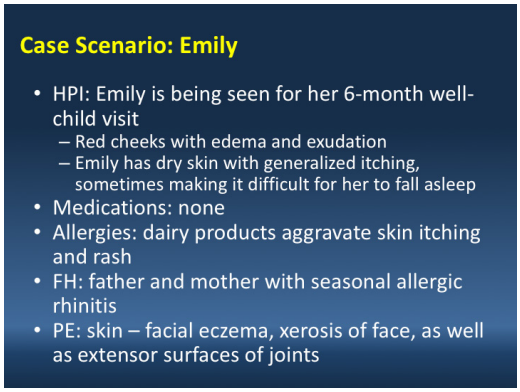
Dr. Bernstein: Today, we'll begin with a discussion of the epidemiology of atopic dermatitis and we'll begin by defining what is atopic dermatitis. Atopic dermatitis is a chronic, pruritic, eczematous skin condition that affects adults and children—particularly children—and often associated with elevated total IgE levels in the serum and a strong personal history of atopy, be it a family history of allergy, or a personal history of allergies including food allergies, allergic rhinitis and asthma.



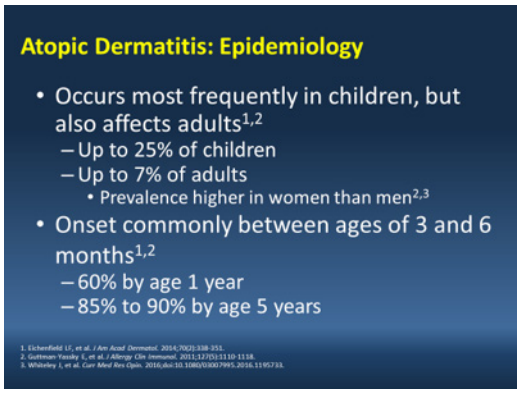
We would like to make the point that atopic dermatitis, in the medical literature, is often used synonymously with the term "atopic eczema"; and this is fine, although in the US we like to use the term "atopic dermatitis."

Dr. Paller: I'd like to also emphasize, David, that the term eczema should really not be used for atopic dermatitis. Eczema is a broad term that encompasses many eczematous disorders such as dyshidrotic eczema, nummular eczema, and in fact the ICD code for eczema is different from the one for atopic dermatitis. We need to make sure that physicians, when coding for atopic dermatitis, use that specific code. In this day of electronic medical record, it's really going to be important—as we use that to understand the epidemiology of the disease—to get that coding right.

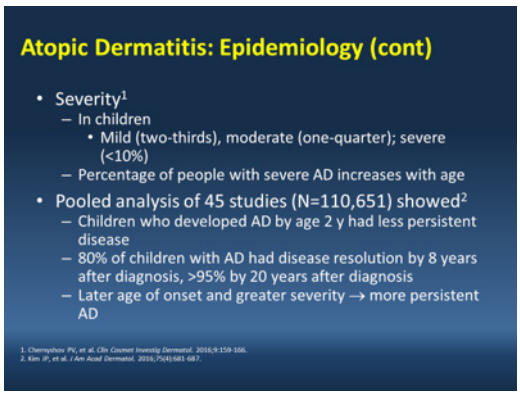
Dr. Bernstein: Emily is our patient who's being seen for a 6-month, well-child visit. She presents with a rash, she has red cheeks, and she has swelling, edema and exudation on her face. Emily seems to have dry skin—generalized dry skin and itching all over—which really makes it difficult for her to sleep at night, and the parents really are concerned about this. She is on no medications when we see her. There is a history suggestive of allergy to dairy products. She has an intolerance to dairy products, and often this seems to aggravate her skin itching or her rash. Both her dad and her mom have a strong history of atopy that is seasonal allergic rhinitis during appropriate pollen seasons. We look at her skin, and she has eczema on her face; her face is dry, and she also has eczematous involvement of the extensor surfaces of her joints.



Let's talk a little bit about the epidemiology of what Emily has—and that's atopic dermatitis. This occurs most frequently in children, but also affects adults. It has been estimated in some studies to affect up to 25% of all children, and in other studies, up to 7% of adults. The prevalence may be higher in women than men. The beginning, the onset of this disease, this condition, most often begins between the ages of 3 and 6 months. By the age of 1, of those who are going to get atopic dermatitis, 60% will already have had manifestations of the condition, and by the age of 5, 85% to 90% will already have shown signs of atopic dermatitis.



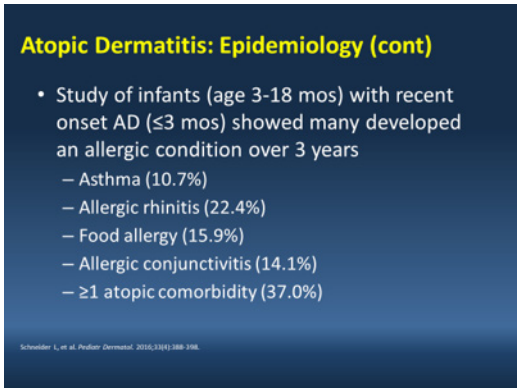
Dr. Paller: Now when we look at severity, that varies by age as well, so when we look at children, about two thirds have mild disease, about one fourth have moderate, and less than 10% have severe disease. But what we know is that as we look at increasing age, we see greater severity of the disease. Now, certainly, one of the important questions is how long does it last, especially in those kids? There have been many studies with some very different results, but a recent analysis of 45 studies showed, first of all, that the children who developed atopic dermatitis by age 2 tend to have less persistent disease. Secondly, that 80% of the children with atopic dermatitis had disease resolution by 8 years after diagnosis, and more than 95% within childhood. What it did show, as well, was that the later age of onset, and the greater severity, were associated with more persistent atopic dermatitis.



Dr. Bernstein: Well this is really useful information for Emily's parents to know about because the fact that Emily has developed this problem at an early age would mean that she's likely to no longer have her atopic dermatitis by the time she turns 8 years of age.

Dr. Paller: Yes, absolutely. Now we know that atopic dermatitis in infancy often is associated with later development, in particular, of asthma, allergic rhinitis, and conjunctivitis, and that's been called the atopic march.

Dr. Bernstein: Yes, we know that this is something that's been observed for many years, and studies of infants and prospective studies, have really shown that those infants that develop atopic dermatitis between the ages of 3 and 18 months—certainly at a very early age—are very likely to develop other allergic conditions as they age, even beyond 3 years of age. Recent studies seem to show that asthma developed in about 11% of children who had early onset atopic dermatitis, and allergic rhinitis eventually developed in 22% of these infants who had early onset disease. Food allergy is also a common manifestation as these children age, as is allergic conjunctivitis.



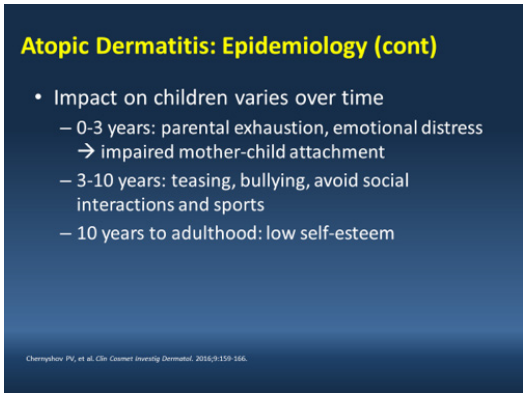
Dr. Paller: The numbers that you just showed actually were from a recent trial that we participated in and, interestingly, were lower than what's been traditionally in the literature. I want to point out that that was interesting because in that trial the children in both arms were treated very early on and at the first sign of a flare, so that possibly that early intervention may be making a difference in the numbers.

Dr. Bernstein: Very interesting.

Dr. Paller: I think we need to emphasize also when talking about epidemiology, that the quality of life is tremendously impacted, not only for the children, but also for their families. Associated with the itching is this decrease in sleep duration. A decrease in quality of the sleep, that's not only for the children, but also for the family. One study showed that, on average, parents get 1 to 2 hours less sleep with a child that has atopic dermatitis and sleep disruption. One of the dangers is also co-sleeping. One of the easiest things for parents to do is to take that child into the bed, and that's not healthy behavior, we certainly discourage that.

In general, there's less productivity, whether we're talking about issues in school with children, or whether we're talking about adults and their jobs, and absenteeism from both of those activities, and there certainly also is psychological distress. Studies have shown an increase of depression, anxiety, even suicidal ideation, in this set of patients.

Now the impact does vary over time. If we're talking about the young children, that huge effect has a big burden on the parents. The parents are exhausted and, in fact, not only can there be psychiatric issues in parents, particularly anxiety and depression, again, but also an impaired parental-to-child attachment. At 3 to 10 years of age, then we're talking about kids getting into school and preschool, now we're seeing teasing, bullying, avoidance of social interactions, avoidance of sports as well, because that can make the atopic dermatitis more uncomfortable. Then finally when we get to the older children and the adults, we see that low self-esteem from years of having issues with interactions with others, and worries about themselves.



Dr. Bernstein: As physicians, we can have a huge impact if we can successfully manage these children with atopic dermatitis that seems to be impacting their quality of life and all these other functions that you just mentioned.

Dr. Paller: A lifelong impact because of the improvement in their psychological state.

Dr. Bernstein: Yes, absolutely. From what we've discussed so far, this is a considerable health problem. It affects a high proportion of children, and some adults, and we know that this condition—atopic dermatitis—is extremely common, and we also know that there are unmet needs in terms of managing patients with atopic dermatitis, even in the adult population. Recently, a study was published that seemed to indicate that—in about 400 adults—this was a big problem for adults who have this condition—moderate or severe atopic dermatitis. These patients really suffered from daily itching, many of them more than 18 hours a day, and sleep disturbance, unable to get through the night, unable to have a restful sleep. This is a major impact in adults, as well, in terms of their quality of life.

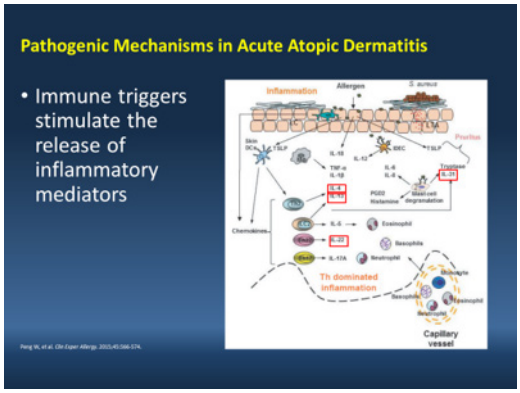
Dr. Paller: Absolutely. We need to think not just about their quality of life, but also the impact on society. There's much greater health care resource utilization, more provider visits, more emergency department visits, greater risk of hospitalization. The indirect costs are even greater than the direct costs, time missed from work, childcare issues, school issues.

Dr. Bernstein: If we go back to our case, Emily. Emily has atopic dermatitis, she has problems with sleep and this has had an effect on her school performance and her ability to interact with her peers and other children, and also has impacted her family. What happened to Emily is that she was managed well and she responded very nicely in terms of reducing her atopic dermatitis clinical manifestations. We're going to talk now about how you approach management of somebody like Emily, in future modules, and this hopefully will facilitate and enable primary care physicians, as well as specialists, to treat people like Emily.

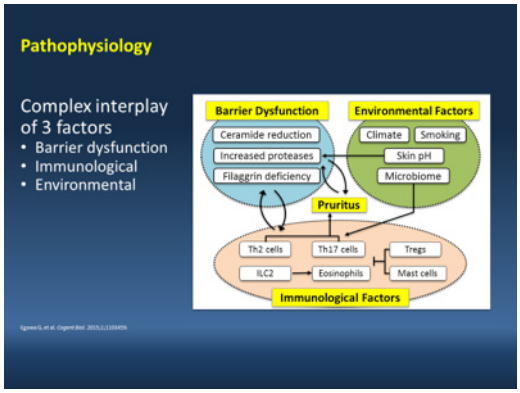
2 *Atopic Dermatitis: Pathophysiology*

Dr. Paller: Now let's talk a little bit about the pathophysiology of atopic dermatitis. In atopic dermatitis, immune triggers stimulate the release of inflammatory mediators, and the whole process involves the barrier and its interplay with these various immune factors. We can start at the epidermal barrier where we can have anything from an allergic trigger to nonspecific inflammatory trigger, *Staphylococcus aureus,* or even scratching itself, disrupting the barrier, passing through the barrier, and triggering the immune response.

The epidermal barrier itself is comprised of a variety of proteins and lipids. The most famous of these, of course, is filaggrin, which is known to be deficient in some individuals with atopic dermatitis, but there are a large variety of other proteins that are important, as well as lipids known to be deficient, like ceramides and long-chain fatty acids. The epidermis is also the site of innate immunity. For example, the epidermal cells or keratinocytes produce antimicrobial peptides, which are very important in reducing the risk of infection. The immune system in atopic dermatitis is fairly complex. Very important are dendritic cells and the T-cells, as well as a variety of other immune cells, all of which elaborate cytokines and chemokines that drive the atopic dermatitis response.



Most prominent among these cytokines are interleukin 4 and interleukin 13. These are Th-2 cytokines. Interleukin 31 is another prominent cytokine that has been specifically related to the itch. Then, of course, interleukin 22, and in adults, interleukin 1, seen in more chronic disease, also are thought to play a major role. It is the interplay of the barrier dysfunction, the immunologic response, but also environmental factors that are involved in triggering and sustaining the inflammation of atopic dermatitis. Among these environmental factors are climate and climate change, smoking, increases in skin pH, and certainly the microbiome.



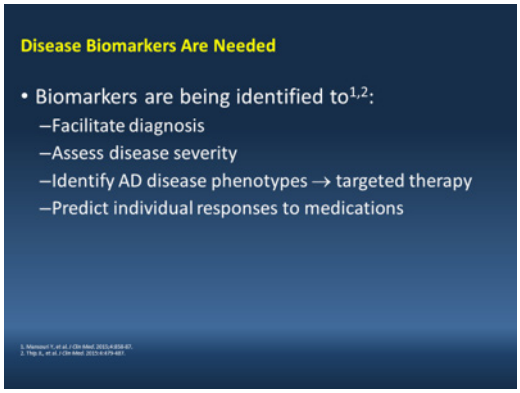
When we're talking about the microbiome in atopic dermatitis, what we know is that with flares, there is a shift towards increases in *Staphylococcus aureus* and concomitantly a reduction in the diversity of the microbes on the skin in these active areas of atopic dermatitis. We know that *Staphylococcus aureus* in itself produces factors that can trigger or exacerbate the atopic dermatitis, increasing the cytokines that drive it and also decreasing the expression of some of the important factors that make up the barrier. There's been increasing attention paid, as well, however, to the reduction of some of the normal flora that are seen on skin with flares of atopic dermatitis, and there is increasing evidence that some of these microorganisms that are normally on our skin produce factors that reduce *Staphylococcus aureus* and in themselves may be helpful in suppressing the inflammation of atopic dermatitis.

Dr. Bernstein: Amy, it looks like the barrier dysfunction may represent the key factor for why somebody might or might not develop atopic dermatitis, and there's been a lot of attention paid to filaggrin deficiency or genetic abnormalities in filaggrin in these patients with atopic dermatitis. An interesting publication from your group actually recently showed, however, that filaggrin protein, and RNA in gene expression in tissue of kids with atopic dermatitis, appear to be normal, so this story is yet to be written, I think, in terms of some of the other contributors to this barrier in terms of what other components of this barrier are important.

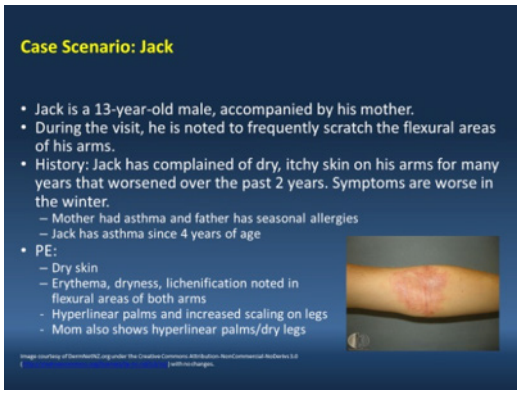
Dr. Paller: That was a big surprise to us to see that the levels of filaggrin were normal in children in the first 5 years of life who were within their first 6 months of atopic dermatitis when we took biopsies from regional areas that showed barrier dysfunction, but normal levels, and we have a lot to learn.

Dr. Bernstein: Stay tuned!

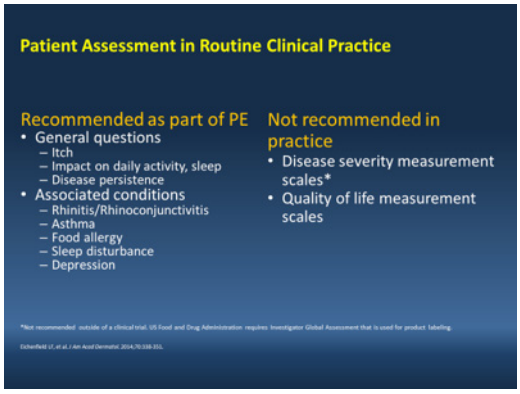
Dr. Paller: That brings us to biomarkers, and biomarkers, of course, are looking at levels of things like filaggrin, and also some of the immune cytokines and chemokines. It's important to mention biomarkers because this is an evolving area of interest. We expect that in the future, as these are better sorted out, they will guide us in diagnosis, in assessing the disease severity, and identifying subsets within atopic dermatitis that will allow more targeted therapy, and will also help us to develop more targeted therapy as we learn what's important in subsets with atopic dermatitis. Ultimately, we're going towards personalized medicine and the ability to predict individual responses to medications based on the profile of an individual.



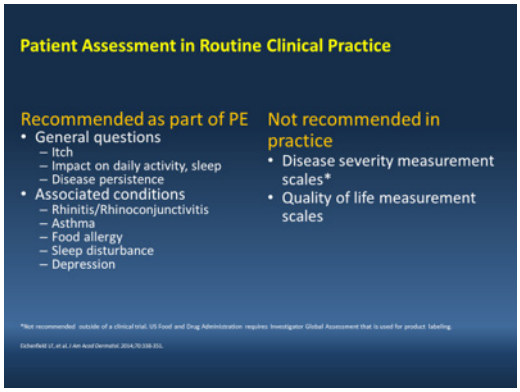
3 *Atopic Dermatitis: Clinical Assessment*



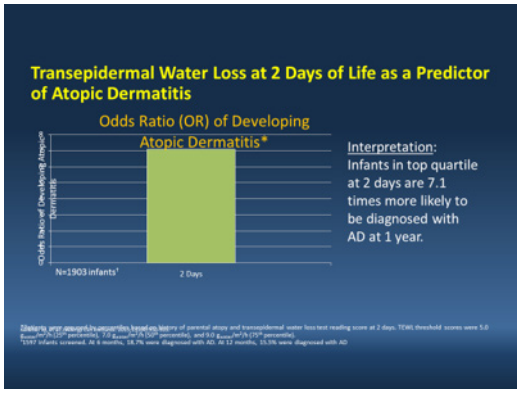
Dr. Paller: Now let's talk about clinical assessment. We can start with Jack. Jack is a 13-year-old boy who comes in with his mother. During the visit, we note that he's frequently scratching the flexural areas of his arms. He's had dry itchy skin on his arms for many years, but in the past 2 years it has worsened considerably and he notes that his symptoms are worse in the winter. His mother had asthma and his father experiences seasonal allergies. In fact, Jack has had asthma since 4 years of age. On examination, we note generally dry skin with erythema, dryness, and some lichenification in the flexural areas of both of his arms. Further examination shows hyperlinearity of his palm, and some increased scaliness of his legs in addition to involvement in his popliteal area. In fact, his mom, who is with him, also shows hyperlinear palms and tells me that throughout the winter she's putting lots of moisturizers on her legs because they're so dry.



Dr. Bernstein: Let's talk a little bit about how we assess a patient who comes to the office with what we think may be atopic dermatitis. Obviously, it's very important to get a good history in terms of itching. How persistent is the itching? Does the itching involve daytime activities as well as sleep? How does the itching and scratching impact the patient's daily activities and sleep? How long has this been occurring, or how long has the duration of this disease been noticed? We also ask about, because this is atopic dermatitis and it helps us to at least categorize this condition, to know what the family or personal history of atopy is. We ask the patients whether they've had seasonal symptoms during pollen season, or they're allergic to dust or indoor allergens. We also get a good family allergic history. We ask about early symptoms of asthma, which may be coming to the fore and actually follow the onset of atopic dermatitis. Is there any history of a food allergy, particularly milk and eggs, in the early years of life? Again, we ask about sleep disturbance, and we also try and probe to see whether there've been any issues with adjustment disorders or mood disorders, looking for signs of depression.



What we don't recommend, generally, is using scales to actually measure severity and routine clinical practice. These really should be reserved for clinical trials and studies. We also explore the history for evidence of risk factors that may predispose our patient to develop atopic dermatitis. We already mentioned the family history of atopy, which is very important. If you have 2 parents, for instance, with an atopic history, your chance of developing atopic dermatitis is 3- to 5-fold higher. We also are aware that there are certain genetic mutations in the filaggrin gene, which was already mentioned, that would be significant risk factors for more severe or persistent atopic dermatitis that has earlier onset of the disease. This only really involves a minority of all patients, perhaps 10% or less. These patients may also be more predisposed to develop herpes eczema herpeticum or herpetic infection of the skin. There's only moderate association—with raised, slightly higher, association—with African Americans, and there seems to be a signal that patients with parents of higher educational status may have a greater risk. We don't have any clear evidence that exposure to indoor pets or urban living environments, or daycare environments, predispose to development of atopic dermatitis.



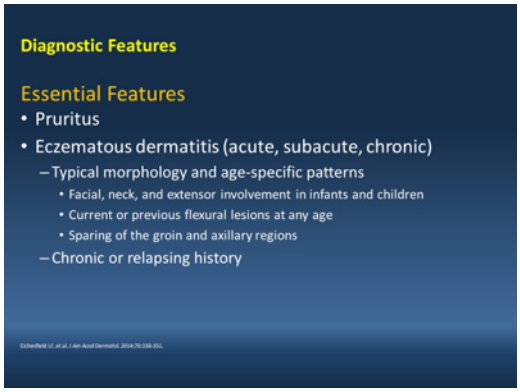
Dr. Paller: There was an interesting study that I just want to mention, that came out of Ireland, where they're prospectively analyzing a broad group of children without any increased risk of having atopy or atopic dermatitis. In prospectively analyzing these children, they looked at transepidermal water loss, which is a great functional measure of how well the epidermal barrier was working. They measured this at 2 days as well as at 2 months and 6 months of age, and followed these babies to see if they would develop atopic dermatitis. What they found is that those babies that were in the top quartile in their transepidermal water loss at 2 days of age, were more than 7-fold more likely to have atopic dermatitis at 1 year of age. In fact, they've now followed this group of patients out for a longer period of time and find, similarly, that those that have the greatest transepidermal water loss at 2 days of age are at a higher risk of developing food allergy at 2 years of age. Some very interesting data, really reinforcing the importance of that very early barrier function with the risk of developing atopy.

What's interesting is that actually this transepidermal water loss at 2 days of age was not dependent, for example, on having a decrease in filaggrin because of a filaggrin mutation. It wasn't reflective of that, but does raise the question as to whether we can seize this information for a way to intervene and maybe prevent the development of atopic dermatitis. Perhaps the atopic march. In fact, there have been 2 studies recently. One out of the US and the UK, and the other from Japan, that have shown us that if, in the first weeks of life, one starts a daily emollient in those children at higher risk, that if there's a first degree relative with atopy, there is a decrease in the risk of atopic dermatitis. In the study from Simpson and Williams from the US and the UK, for example, that was a decreased risk, at 6 months of age, by 50%, by just starting, in the first 3 weeks of life, the use of a daily emollient.

Dr. Bernstein: That sounds like a great idea for a large primary prevention study in the future.

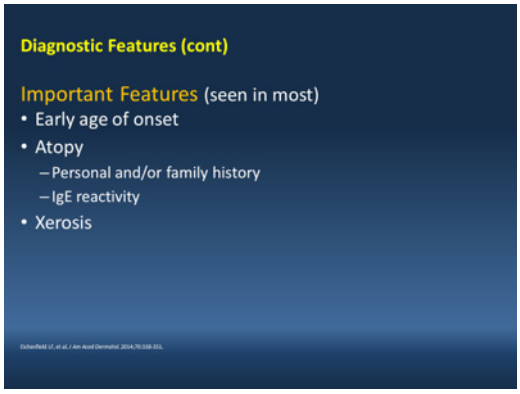
Dr. Paller: In fact, they're doing that right now!

Dr. Bernstein: Well let's talk about some of the essential diagnostic features of atopic dermatitis. We know that of course pruritus is the most predominant feature that really brings the patients to see us most of the time. We look at the skin and we see this eczematous dermatitis. We can see differences in whether these are acute, subacute, or chronic lesions which have secondary changes. The typical, though, morphological patterns we look for may vary with age. We know that in infants and children we generally will see… more likely see, skin involvement in the face and the neck, and extensor areas. At any age we might see flexural fold lesions or changes. We generally will see sparing of the groin and axillary regions in patients with atopic dermatitis. Of course, this is a chronic condition. It can come and go. It can get worse and better depending on certain factors, but it is also important that we again recognize that this is an early age of onset. This occurs primarily in young children, and that atopy is a very important factor that we need to document in our history.

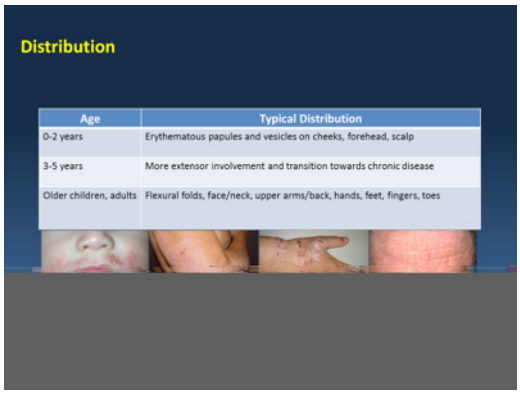


Of course, dry skin is almost a universal feature we see in all affected patients, both adult and children.

Dr. Paller: You mentioned the differences in the appearance and distribution of the skin based on age. Just want to spend a little more time mentioning that, because that's important to recognize. When we see babies who are affected, we see a lot of facial involvement, particularly on the cheeks and the chin. Of course that becomes exacerbated by the fact that as they start teething and they're drooling a lot, the saliva is a tremendous irritant and probably is contributing to the fact that we see that distribution at that age. We also can see so much swelling and oozing in association with the tremendous inflammation that's going on on the face that it can be mistaken for infection, when, in fact, it's just that exuberant inflammatory response.



Babies can have involvement of the scalp. In fact, it's common to see an overlap of seborrheic dermatitis or cradle cap in atopic dermatitis at that age. There's often quite a bit of truncal involvement then too. As we evolve into the age of toddlers, and even towards the end of that early infant age, we tend to see more involvement on the extensor surfaces. I've always thought that may relate to the friction of crawling, for example, but we tend then to see—as these children then get to school age and adolescence and adulthood—really more of what we typically think of as the distribution in those flexural areas, particularly the antecubital areas and the popliteal areas. We think of the neck involvement, and we can see facial involvement, but that facial involvement really tends to be more periorbital around the eyes, around the mouth. Not so much the cheeks and chin that we saw in babies. Of course, once babies get out of diapers and that diaper area is a spared area, one of the good signs early on of atopic dermatitis is that sparing of the diaper area; we can see really the entire body being affected at that point.



Let me also mention 2 other very common features of atopic dermatitis in children, in particular. One is keratosis pilaris. That is the plugged hair follicles that we commonly will see on the lateral aspects of the face and the extensor upper arms and thighs. The other is this association with ichthyosis vulgaris. You mentioned this earlier in talking about the filaggrin deficiency that's genetic. Almost 10% of particularly those of northern European or Asian descent will have ichthyosis vulgaris from this deficiency of filaggrin, and that manifests with hyperlinear palms. We see more lines on the palms and also with drier skin, and particularly on the lower extremities, and particularly in colder weather. It can just disappear during the warmer weather and when there's humidity. Keratosis pilaris, ichthyosis vulgaris, 2 other factors to look for in the examination.

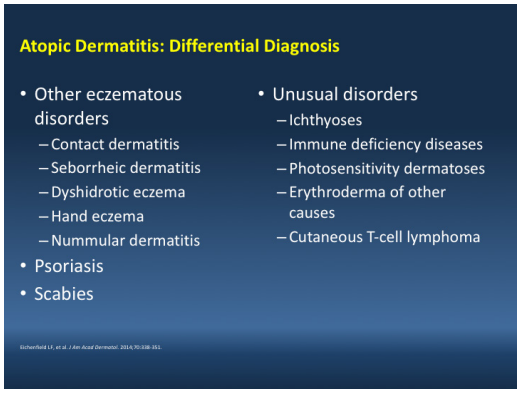
Dr. Bernstein: Keratosis pilaris, is it an acneiform appearing lesion sometimes?

Dr. Paller: Well it can look like acne, but tends to be much drier.

Dr. Bernstein: Drier? Yes.

Dr. Paller: It is a follicular process.

Dr. Bernstein: Yes, okay. Thank you.



Dr. Paller: Now there are things to consider in the differential diagnosis for atopic dermatitis. I think we'd be remiss not to talk about that a little bit. The first and most important of these are other eczematous disorders. We stressed before not just calling this eczema, because that is a broader term. Some of these eczematous disorders can occur as differential diagnosis, but they also can occur concomitant with the typical atopic dermatitis. For example, seborrheic dermatitis, I mentioned earlier, can be seen, particularly in babies, on the scalp. Dyshidrotic eczema, seen on the hands and feet, sometimes just manifesting as what looks like severe atopic dermatitis, but sometimes also showing very tiny papular lesions, vesicular lesions, sometimes it's been likened to tapioca pudding appearance on the palms and soles, sometimes lining the fingers and toes. Hand eczema in general, particularly on the palmar areas, although we so commonly will see irritant hand dermatitis on the dorsal aspect of the hands because of that exposure to cold weather and particularly to excessive hand washing. Then nummular dermatitis—those well-defined plaques of dermatitis, often with secondary infection, that can be scattered on the trunk and on the extremities in particular.

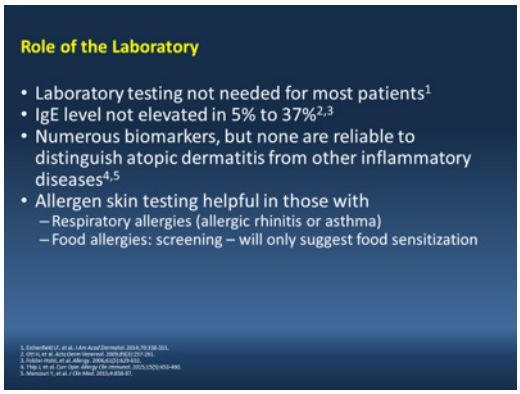
We can't forget about contact dermatitis in the differential diagnosis. Contact dermatitis can be irritative, and of course these individuals with atopic dermatitis have very sensitive skin and are more easily irritated. We talked about that with saliva and the propensity towards having cheek and chin involvement in those young babies, but we can also see this with exposures to a variety of irritants. Then there's allergic contact dermatitis. That's something that we can often suspect from distribution and then confirm with patch testing, but nevertheless it's something that you have to think about because it can occur exactly in the areas of the atopic dermatitis if it's a response to something that's being applied topically to treat.

Then there are other disorders in the differential diagnosis. Psoriasis, particularly in children, can be somewhat indistinct and can often be misdiagnosed as atopic dermatitis. Scabies of course, when it occurs, causes a lot of scratching and can look eczematous. It can be mistaken to be atopic dermatitis, or can be on top of atopic dermatitis and lead to exacerbation. Then more unusual disorders. For example, the infant with ichthyosis or an immune deficiency may present with an atopic dermatitis-like picture.

Dr. Bernstein: Absolutely.

Dr. Paller: Sometimes photosensitivity dermatoses. The distribution will help with that. Erythroderma is where there's extensive redness and dryness everywhere from a variety of causes; and in adults with atopic dermatitis, we always need to think about cutaneous T-cell lymphoma. Very commonly misdiagnosed as atopic dermatitis, but is unresponsive to traditional therapy.

Dr. Bernstein: Well we also need to think about how the laboratory can help us in evaluating our patients with atopic dermatitis. In general, we'd have to agree the laboratory testing is not needed for most patients. The serum total IgE is a strong marker of atopic dermatitis seen in the majority of patients. There have been numerous biomarkers that have been studied, and many research studies, but at this time none are really reliable to help us distinguish atopic dermatitis from other skin disorders you mentioned, for instance.



Now if you have a patient, though, with a strong atopic history that coincides or follows atopic dermatitis, it is important to consider respiratory allergies. There are some patients in whom their skin condition may actually aggravate during a pollen season, and you can get that from the history. In that case, testing may be helpful. In terms of food allergens—generally to do this food allergy testing in all patients is not helpful—but if you have a good history suggestive of the skin getting worse after ingesting milk or eggs, or some other food, this may certainly be worthwhile to test the patients for food allergy either by serum specific IgE or skin testing if that's possible.

Dr. Paller: Of course laboratory testing can be helpful in looking at the differential diagnosis. For some of the conditions that I mentioned a biopsy of skin may be helpful in distinguishing those.

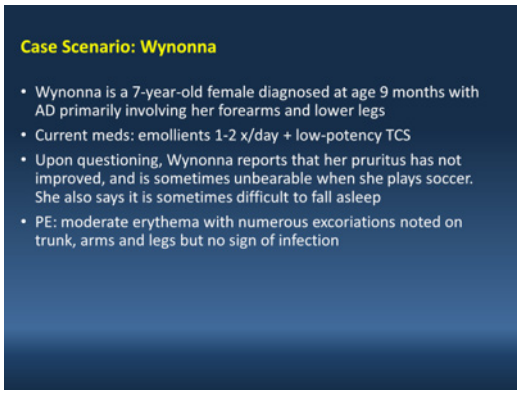
Dr. Bernstein: Absolutely.

Dr. Paller: Well let's go back to Jack, with his comorbid ichthyosis vulgaris and atopy.

Dr. Bernstein: Well Jack has a strong family history of allergy and atopy. He's developed asthma. He developed a pretty significant case of atopic dermatitis, pretty severe at a very early age. His parents also have a positive history of atopic dermatitis and they had some of the manifestations that might even want us to consider ichthyosis vulgaris in the differential diagnosis of this family. This again is a strong genetic risk factor. We don't know if he has it or not, but it's something to at least think about. We know that Jack follows that pattern of the atopic march. He's developed early-onset atopic dermatitis. Now he has asthma, and we expect that his condition of asthma will persist as he gets older. Let's talk about management of Jack, and patients like Jack, in the upcoming management module.

4 *Atopic Dermatitis: Medical Management: Overview*

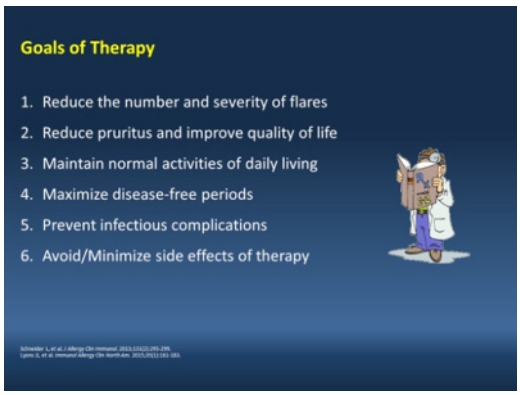
Dr. Bernstein: We're going to discuss management, and we're going to begin with a case. This is Wynonna. Wynonna is a 7-year-old girl, a young girl who was diagnosed with atopic dermatitis at the age of 9 months. This has involved primarily her forearms and lower legs. She has been managed to date with moisturizing agents or emollients which have been administered 1 to 2 times per day, and she has also been treated with low-potency topical corticosteroids for treatment of her lesions.



We questioned Wynonna. She is really not happy. Her itching has not improved dramatically. This really affects her when she plays sports. She plays soccer, and she says it's very difficult for her to get to sleep or to get good quality sleep at night.

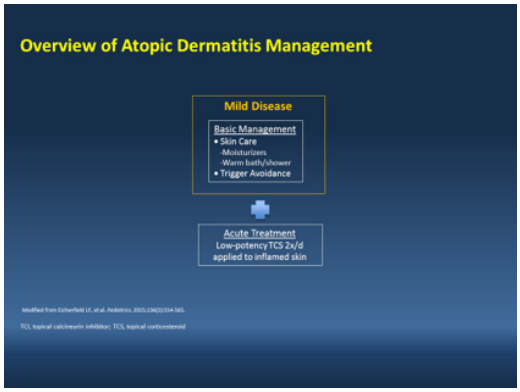
We look at her on physical exam; she has some of the stigmata of moderate atopic dermatitis. She has redness, and you can see she has excoriations that we see on her trunk. We see this on her arms and legs. Fortunately, no signs of infection.

Dr. Paller: Well our goals of therapy then are going to be first of all to reduce the number and severity of flares; of course to reduce the pruritus and thereby improve her quality of life; to try to maintain the normal activities of daily living that she already finds can exacerbate her disease; to maximize her disease-free periods; to prevent infectious complications; and to avoid or minimize the potential risk of side effects from the therapy itself.

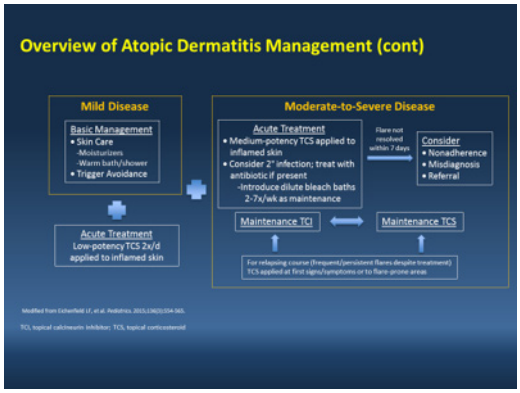


Now when we think about how to do this, we can talk about mild disease vs moderate to severe disease, and it becomes an algorithm of treatment that allows us to build on what is basically management, and then add other elements.

The basic management of skin care is, of course, the vigorous use of moisturizers, to take a warm bath or shower as long as you do use moisturizers, and to avoid triggers. Now, with acute treatment, then we can add to that, generally, a low-potency topical corticosteroid for milder disease, applied to inflamed skin. Alternatives are some of the nonsteroidal agents like topical calcineurin inhibitors or the new crisaborole. Then as we advance to the more moderate to severe disease we tend to need stronger therapy. We might use a medium-potency topical corticosteroid to the inflamed skin to try to quell a flare. We would look for secondary infection and treat it with a systemic antibiotic, if present, and then use dilute bleach baths 2 times a week, to daily, as needed, for maintenance treatment to help both reduce infections and also to decrease the inflammation itself. In those individuals who don't respond to that, then we have to consider, is it because there is not adherence to what we have prescribed, which is very common? Is it perhaps there's a misdiagnosis, we're missing something that needs to be treated in a different way? Is it just that it's too severe and we need to think about next steps?

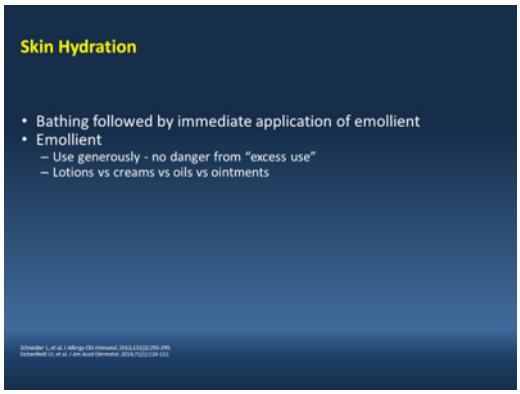


For those who have milder to moderate disease we can get under control relatively easily, then we need to figure out maintenance. Maintenance can be very tricky because really the risk of treatment is in continuing chronic use, for example, of stronger topical steroids. How do we use maintenance corticosteroids, how do we use maintenance nonsteroidal agents, and how do we turn that into a regimen that is able to quickly quell the flares but allow safe continuing treatment?

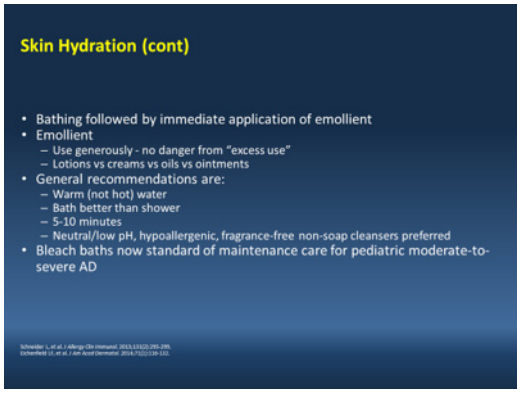


5 *Atopic Dermatitis: Medical Management, Part I*

Dr. Bernstein: Well the first step in treating any patient with atopic dermatitis is hydrating the skin. Patients like to bathe. We all like to bathe and so do patients with atopic dermatitis. We recommend that it's okay to bathe once a day, for instance, but it's so important when you finish your bath to apply a moisturizing agent or emollient before the skin really dries to really try and hydrate the skin as much as possible. We advise using these emollient agents often and very generously. There's really no danger from overusing emollient moisturizing agents.

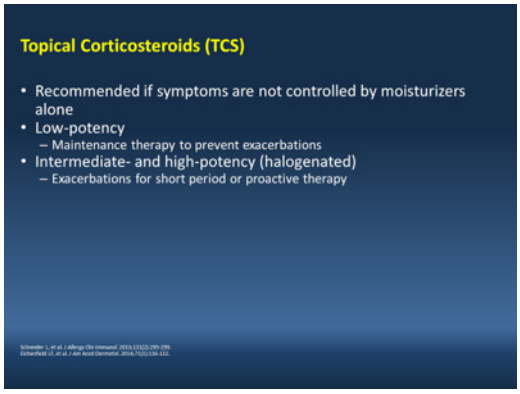


There are a variety of products that are available. The best functioning ones—the ones that do the best job in terms of hydrating the skin—are oils or ointments, but most patients don't like these. We often settle for lotions or creams. I think any of these would be reasonable, depending on what the patient's preference is. The general recommendation is to use warm water, not necessarily hot water, don't want to dry the skin out any more than we need to, better to bathe than to shower. Only bathe for 5 to 10 minutes, don't have a prolonged bath, and very important when you choose a soap or cleansing agent, to avoid fragrances; to avoid strong soaps with agents like surfactants, for instance, that can really irritate the skin and perhaps aggravate the disease.



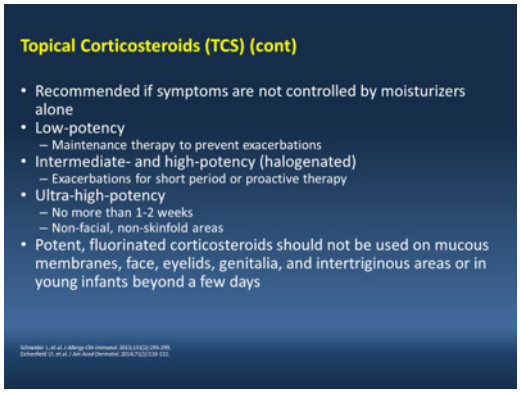
We really prefer non-soap cleansers in terms of what you use when you take a bath. Now bleach baths, as we already mentioned, are very important, now standards of maintenance care for pediatric patients with moderate to severe atopic dermatitis. This may have an effect as you mentioned, Amy, on reducing inflammation, as well as preventing and treating infection.

Well what topical corticosteroids do we use? How do we select these? Of course, we recommend initiation of topical corticosteroids if intensive moisturizing or emollient treatment is not effective alone. Of course, we begin with a low-potency topical corticosteroid. We advise use of maintenance therapy to prevent exacerbations. If you're using a low-potency topical corticosteroid, you perhaps need to do this every day as opposed to a few times a week. You can also choose to use an intermediate or high-potency topical corticosteroid which would usually be a halogenated product. This is very effective, as we said, for treating acute exacerbations if that's necessary. It can also be used as maintenance proactive therapy but used less often, perhaps 2 to 3 times a week as opposed to daily because the concerns about potential adverse effects of chronic use of these stronger topical corticosteroids.



Ultra high-potency topical corticosteroids are generally not used unless there's a very severe acute exacerbation. We use these for very short periods of time. We like to really avoid using these on the face where you know there's greater potential for absorption and skin changes in thin-skinned areas such as the face and other skinfold areas.

Dr. Paller: Do you ever use a halogenated steroid on the face?



Dr. Bernstein: At times. I think we would use for a very severe exacerbation and again for very short durations until we can get the inflammation and the skin under control and switch to a lower potency topical corticosteroid.

Dr. Paller: Yes, I would agree. I think sometimes it can be very useful to just use for a few days, but the one area on the face I worry more about is that periorbital area because of the easy traversal through the lids and we know of the dangers of steroids for the eye.

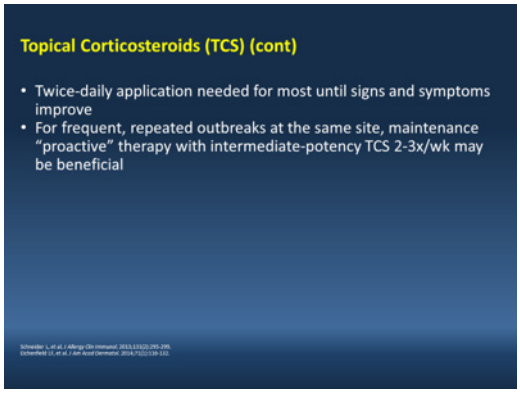
Dr. Bernstein: We're concerned about skin atrophy too.

Dr. Paller: Absolutely. I should add that one thing in my treatment regimen is aggressive therapy when I first meet children. So many of them come in and they've tried many different agents and aren't getting any better. The first thing I will do is I will hit them hard. I'll have them go 2 weeks on nonfacial areas with a class II, pretty potent topical corticosteroid and just knock it out. On the face, I'll even go for a few days with that and then dial down to a lower strength topical steroid or a nonsteroidal agent.

I often find that the majority of these kids just get dramatically better. Some of them rarely have to use much after that from doing that more aggressive initial therapy because this is such a process that cycles and gets exacerbated by not getting in there and treating aggressively.

Dr. Bernstein: Oral steroids are rarely needed for those severe exacerbations but sometimes you do have to use them.

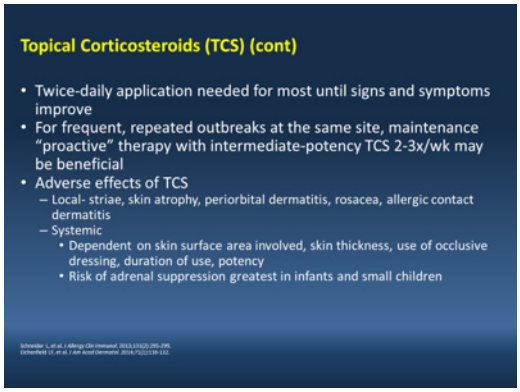
Dr. Paller: Well I never use them in children.



Dr. Bernstein: Never use them in children, in adults we do. So that's the name of the game, do intensive therapy with twice daily application of a topical corticosteroid, if you're treating acute atopic dermatitis, until signs and symptoms are improved. That should be as long as it takes until you see resolution of the inflammation of the skin and the lesions for at least 3 to 4 days before dialing down on the dose. For repeated outbreaks that occur of the same type, of course we already said that maintenance proactive therapy is a reasonable strategy. You can use, for instance, an intermediate-potency topical corticosteroid 2 to 3 times per week in those areas you know that are problematic. That's a reasonable thing to do in long-term maintenance therapy.

Dr. Paller: That's particularly helpful, for example, for the child who has that recurrent antecubital or popliteal involvement and every time we stop the steroid it comes back. You can do the proactive therapy there, keeping it up 2 to 3 times weekly when it looks clear or almost clear, and they do pretty well.

Dr. Bernstein: Absolutely. We also worry about adverse effects of topical corticosteroids. We know that using higher potency topical corticosteroids can cause localized effects in the skin: the common stigmata or striae you can get, and unfortunately, in time, skin atrophy, if you're not careful. Periorbital dermatitis is a name we've already mentioned. Rosacea can be a complication, and of course allergic contact dermatitis if our patients become sensitized to the corticosteroid itself or an additive in the products. You have to be careful if they're not getting better as we might expect—it may be due to the fact that they have an allergy to something we're giving them. That could be an iatrogenic factor that may make things worse.

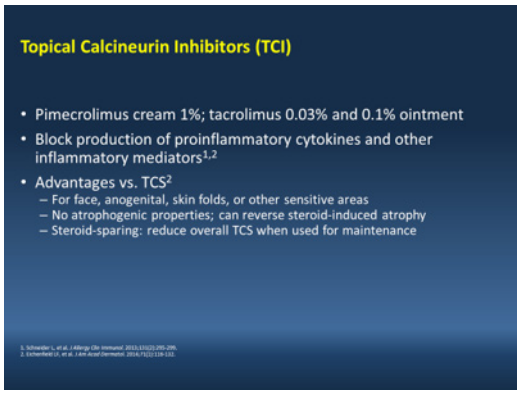


Systemic use of steroids—we know that we don't necessarily recommend that, particularly in children—but we do know that there can be systemic corticosteroid effects with prolonged use and we occasionally are concerned about the risk of adrenal suppression, particularly in younger children where this can be a problem if you use a higher potency or medium potency topical corticosteroid on a long-term basis. This is relatively a rare event that we see in clinical practice.

Dr. Paller: I think this is really important to stress that so many parents come in with steroid phobia and in fact a lot of doctors have steroid phobia as well, and perpetuate this by telling families to limit the use to just a few days and of the dangers of topical steroids. It should really be stressed that when used properly it's really quite unusual to even see the local side effects like thinning of skin, let alone anything systemic. This is really an important piece of our regimen in care. If the parents are so worried about the risks of steroid that they're not using them, and using them appropriately, the children risk not getting better. That impact of not getting better on their quality of life is so much greater than the risk of the local, or certainly the systemic effects, of the use of the topical agents.

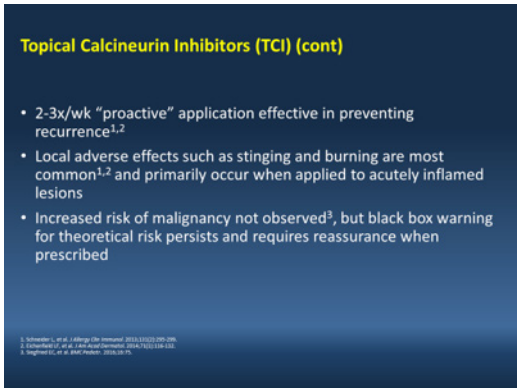
Dr. Bernstein: Very important, very important.

Dr. Paller: Let's move on to talk about nonsteroidals. We do have some options. The topical calcineurin inhibitors came out more than 15 years ago now, in 2 flavors. We've either got pimecrolimus cream or we've got a tacrolimus ointment in 2 different strengths. These are shown to block proinflammatory cytokine expression and not to have some of the other potential risks of topical steroids. They don't have atrophogenic properties, for example. They've actually been shown, when used for more maintenance therapy, to reverse some of the steroid-induced atrophy if it occurred. They are steroid-sparing and particularly important for sensitive areas like the face, the genital area.

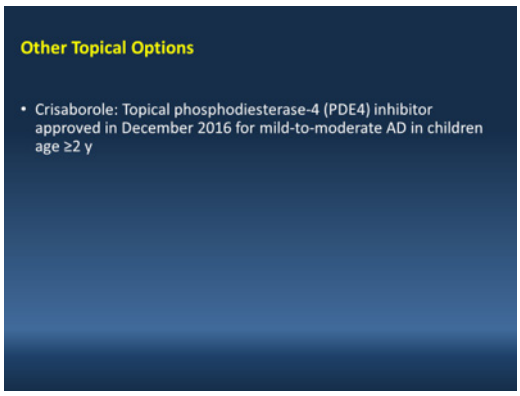


The biggest problem with getting them is that access has been more of an issue. The topical corticosteroids are still considerably less costly and easier to obtain through prescription. Now for the topical calcineurin inhibitors, twice-daily application is recommended. One can also use the topical calcineurin inhibitors for proactive therapy, just as we talked about before, putting this on 2 to 3 times weekly on those areas that recurrently flare.

After getting it into control with possibly either twice-daily use of the topical calcineurin inhibitors, or more commonly with the topical corticosteroids, and the only thing we really see with the topical calcineurin inhibitors are local effects like stinging and burning. In fact, this particularly occurs when you're using it on very inflamed lesions. I'll commonly calm things down with a topical steroid and then if I'm going to use a calcineurin inhibitor I will switch over to that because that markedly reduces the risk of having stinging or burning when you're applying it.

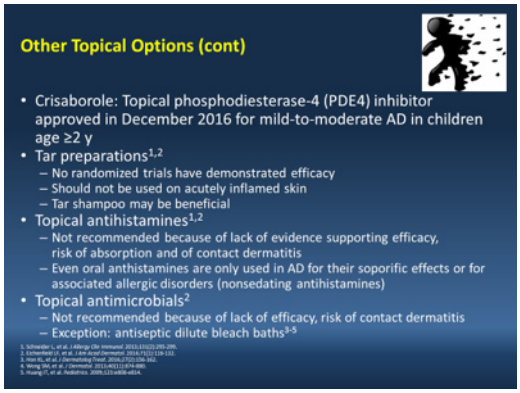


Now, back in 2006, a black box warning was applied to this whole group of topical calcineurin inhibitors. It was the first time a theoretical risk had led to putting on a black box warning and was done because of the known problems with systemically administered tacrolimus for transplant patients. Some very, very high-dose studies in primates that were done preclinically. I'm relieved to say that in the last 15 years there's been absolutely no evidence of an increased risk of malignancy, but should mention that that black box warning still is there which means that pharmacists have to tell parents about the potential risk. Very important for doctors in the office when prescribing these to take one extra minute to warn about the fact that they may hear about the potential increase risk of malignancy but to reassure that there's absolutely no evidence of this clinically.



I also want to mention that we have a new topical inhibitor that is not steroidal and has just come on the market—and that's something called crisaborole. Crisaborole is a phosphodiesterase-4 inhibitor for mild to moderate atopic dermatitis [in children] as young as 2 years of age. We'll talk about that more to come.

Dr. Bernstein: We also have other potential options if a patient is not responding to the modalities we've already described, that is moisturizing agents and topical corticosteroids. There have been a lot of popular preparations that have been used over the years including tar preparations, which themselves may be beneficial in some patients, but not very pleasing. Most patients don't like the aesthetic parts of using tar on their scalp, for instance, and tar shampoo.



There are topical antihistamines which have been advocated, but there's no good evidence to support the use of topical antihistamines in controlling the itch of atopic dermatitis, and they have the potential to cause sensitization in contact dermatitis. We generally avoid using topical antihistamines in our patients. Again, for topical antimicrobial agents—although this was a widely practiced option—now, looking at the evidence, there doesn't seem to be any good evidence suggesting that chronic use of topical antimicrobials is effective in controlling atopic dermatitis or even preventing necessarily infections.

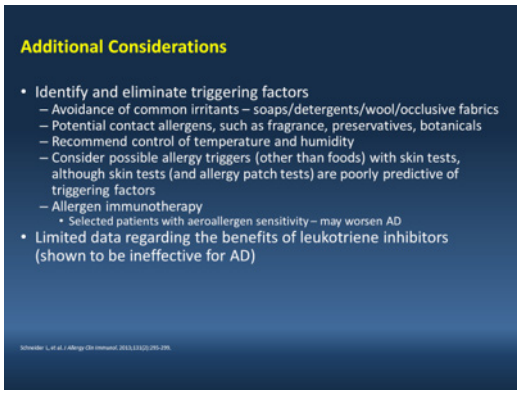
We do sometimes use antiseptic, dilute bleach baths, as we've already mentioned, which could be classified as an antimicrobial approach, but not an antibiotic by any means.

Dr. Paller: Since you mentioned the topical antihistamines, we should add about the oral antihistamines, which, of course, non-sedating, are commonly used for allergies, and many of these children have that. The sedating antihistamines can be very helpful at night because of their sleep-inducing effect. We can still see the kids scratching actively. It doesn't really take away the itch, but they do need their sleep. Sometimes that can be very helpful when used in high doses that make them sleepy, but don't make them so sleepy that they can't go to school the next day.

Dr. Bernstein: You're talking about the first generation antihistamines, say, hydroxyzine or diphenhydramine, or something of that sort.

Dr. Paller: Yes. We should also mention that those are in different classes of antihistamines, so they can be used concurrently or serially during the night, if needed.

Dr. Bernstein: Okay. Well we also need to talk about the importance of being aware of triggering factors in atopic dermatitis. Sometimes, we really lose sight of this. That some of the best ways to really control and prevent flares of the disease, and to help control the disease, is, again, to pay attention. Every time you see the patient at a visit ask whether they're using soaps or detergents to bathe themselves, which can certainly irritate and aggravate their condition.



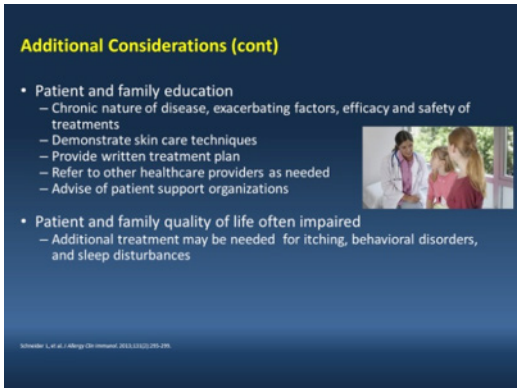
We generally advise against wearing wool or occlusive fabrics. Again, we already mentioned the potential for contact allergens. We have to really pay attention to what they're putting on their skin. A lot of times there are fragrances in some of the emollient products that can be sensitizing. Also, now with the natural products on the market, there's a lot of botanicals, either flower or tree extracts which themselves can be very sensitizing and really cause a real problem beyond what we're dealing with—the patient's atopic dermatitis.

It's really very important to make sure that the patient isn't in a low-humidity environment as much as possible, so reduce exposure to cold and things like that, if possible. We also, if relevant, would recommend that they avoid allergen triggers. If we're able to document, for instance, that during a pollen season, for instance, they have atopic dermatitis and flares, at least we need to be aware of that. I'm not sure that we could actually prevent it, but we know it's coming and we can treat it during the season. Skin testing may actually give us some insight in terms of what are the important allergen triggers.

Now there have been a number of studies which have examined the use of allergen immunotherapy—like we use for treating allergic rhinitis or asthma—and its impact on atopic dermatitis. There has been a meta-analysis that put together several studies suggesting that patients, adult patients particularly, with house dust mite allergy may actually benefit from allergen immunotherapy. It's important to select the patient carefully and to make a determination as to whether house dust exposure does aggravate their condition. Personally, we have seen some positive results in such patients.

We talk about leukotriene inhibitors, which we used for other allergic disease like asthma, allergic rhinitis. There really hasn't been any data showing that these are effective in managing atopic dermatitis.

Dr. Paller: We can't talk about management without talking about education. Of course, education is very important if you want your patient to follow the regimen that you've prescribed. We talk to the patient and the family about the chronicity of atopic dermatitis, about exacerbating factors, and about the efficacy and safety of various treatments, but it's important to try to demonstrate skin care techniques, and really important to send families home with a written treatment plan. We all know how we listen to what we're told and promptly can forget when we get home.



Now we have electronic medical records, it's so easy to be able to send home something that someone will have in front of them to remind them of what we said. There are situations where we may want to refer, whether that's to an allergist, or whether that's to a dermatologist, or a specialist, as needed, depending on the complexity. Also, it's very important to let patients know about support organizations like the National Eczema Association that's very helpful with educational materials online.

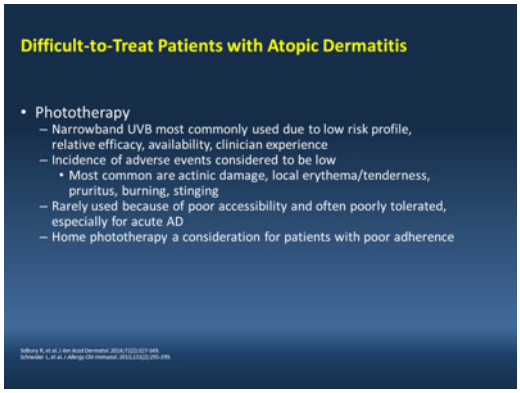
It's always important, as well, to spend a little time talking about the impact of the disease on the patient and the family. You mentioned before how important it is to ask about the itch, and the sleep, and the restrictions that the disease has caused. Sometimes one can discover, for example, that there are psychological impacts. It can be very helpful to address that and to get additional intervention from specialists in that as well.

We sometimes think about itch and sleeping issues and again get referral to specialists who can help with that in addition to the interventions that we can move forward with.

6 *Atopic Dermatitis: Medical Management, Part II*

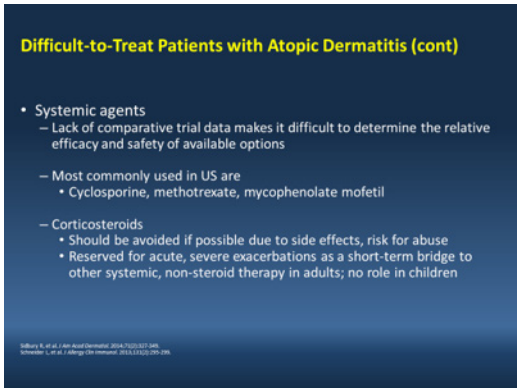
Dr. Bernstein: Let's talk about our case. Remember Wynonna? She comes to us now, has been treated for atopic dermatitis, but is not responding. What we decide to do, based on everything we've discussed, is to go to a stronger topical corticosteroid. She seems to do much better. She's happy, her parents are happy, and her skin looks a lot better. The question is, Amy, what if Wynonna doesn't respond to her stepped-up therapy? What do we do in that scenario, and what options do we have available to us?

Dr. Paller: That's particularly common when you're talking about someone with moderate to severe disease. I think the first thing that we need to do is, obviously, make sure we're not missing something. Is there some staphylococcal infection that needs a systemic antibiotic and, of course we've got to get in that maintenance therapy with the dilute bleach baths. Is there a possibility that she's having a contact allergic response to something that's being applied or something that she just may be in contact with at home that's mimicking the atopic dermatitis and needs to be identified? We know with contact allergies that we may get some mileage out of the topical steroids, but that can be very difficult. What we really need to do is identify the triggers and avoid them, and of course, other possible diagnoses.



But, if indeed, the problem is just that her atopic dermatitis is severe enough that we need to ramp up even further, then we need to think about systemic options. We always think about phototherapy first. Narrowband ultraviolet B light is most commonly used because of its low-risk profile. It's relatively effective. It's pretty easily available in doctors' offices, and we can even try to get home units. There's been a fair amount of experience with it, but for many people it's difficult with respect to adherence. We know that it may be hard, particularly for children who have a tremendous amount of after-school activities, parents often working, to get into the doctor's office for this type of treatment. It's not usually what we choose as our first-line therapy when somebody is very severely involved, because it can be poorly tolerated when the skin is very erythematous. There are some potential adverse events we need to think about, like burning and long-term actinic damage, although the narrowband ultraviolet B is pretty safe. Finally, I did mention home phototherapy for patients who just can't get to the doctor's office, but that's expensive and hard to get these days from insurance companies.

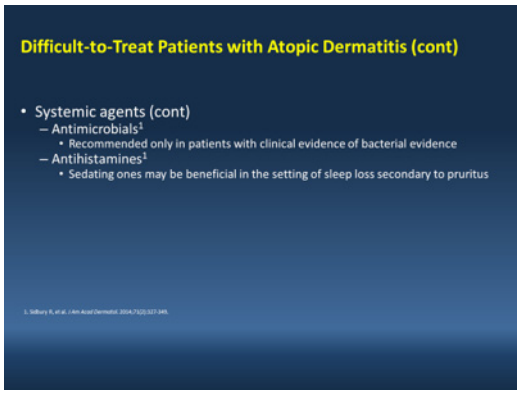
We usually have to think, then, about a systemic immunosuppressant agent and that's all we have to work with. Because of our concerns about these agents, we have a pretty high bar before we get to those, although they can be highly effective and dramatically change the quality of life for these more severely affected individuals. One of the problems we have is that many of these agents have been around for a long time and there aren't really good comparative trial data available to know the relative efficacy and safety of these various options. Now, in the United States, most commonly used are cyclosporine, methotrexate, mycophenolate, in that order. In Europe, azathioprine has also been used. In general, we worry about systemic corticosteroids. I don't use them at all in children. They often lead to rebound when stopped, and we've seen this repeatedly. For example, in our kids with atopic dermatitis who get treated with a burst of steroid and their eczema starts to get better; and then, boom, they stop the medication and it's back with a vengeance.



They're used a little bit more in adults, and they certainly can be a short bridge for severe exacerbations. But you have to have a plan of what to do more long term, or else you're on this roller coaster of use of systemic steroids, which are very dangerous in children, but have many risks, as well, in adults.

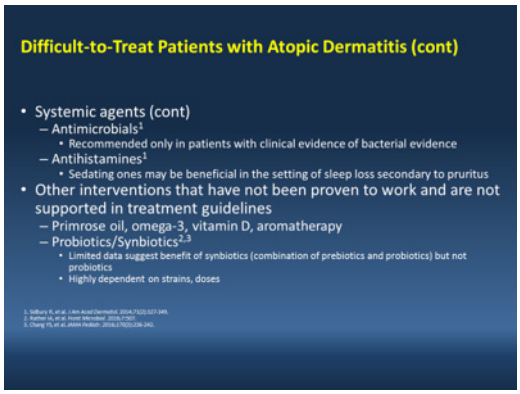
Dr. Bernstein: My experience with adults treated with systemic steroids for acute flares for any dermatologic condition, is that if you choose to do that you'd better be sure you have them on topical corticosteroids as you taper off of the oral systemic steroids to prevent the disease from flaring up again.

Dr. Paller: Absolutely, and in your most severe cases, of course, topical steroids aren't going to hold them. But as a great bridge for those who don't need the systemic agents, that works very well.



Now, I want to remind that we don't use antibiotics except for infection. They really have no role just used empirically unless there is that evidence. As we mentioned before, the antihistamines are largely used for their sedating properties.

Dr. Bernstein: Well, there have been other interventions that have been used over the years. Even when I was in training, we would use things such as primrose oil or omega-3, things of that nature. These are really not supported in treatment guidelines, nor do we use these much anymore because there really isn't good evidence that they have any efficacy for controlling chronic atopic dermatitis. The same could be said for probiotics, which are very much in vogue today. There's limited data, though—suggesting some benefit in some studies—but I think it's still controversial. There's no great consensus on whether probiotics are useful in treating most of our patients.

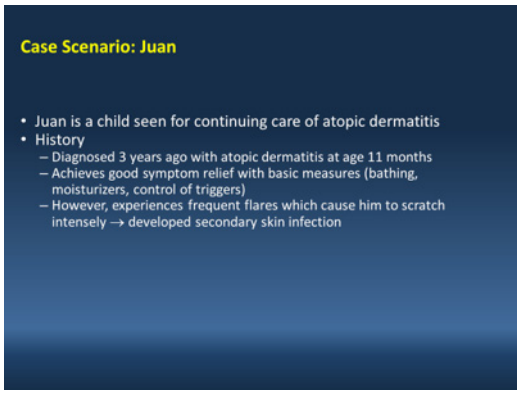


Dr. Paller: So, let's go back to Wynonna who was not responding adequately to appropriate topical steroids, and really didn't have any other reason. We found no infection, we didn't find any other possible exacerbant or alternative diagnosis. She wasn't going to be able to comply with phototherapy, so we advanced her to a systemic immunosuppressive agent. In this case, a 3-month course of cyclosporine brought her into good control, but then there was maintenance, and we don't like to use cyclosporine for long periods of time. There's evidence that if you continue beyond a year you really can have evidence of renal effects, so we like to transition. I generally transition after about 3 months. In this case, we chose to transition her to methotrexate with a little bit of an overlap between the cyclosporine and methotrexate, because methotrexate can take a few months to truly be effective. She's done very well with that. After her initial improvement with the cyclosporine, she was able to maintain that with methotrexate. Her labs have been fine and she's continuing in good control.

Dr. Bernstein: I like to use cyclosporine in these very difficult cases. But I prefer using it as you mentioned, just as short a period of time as necessary, months at a time, because almost always I will see side effects in our patients.

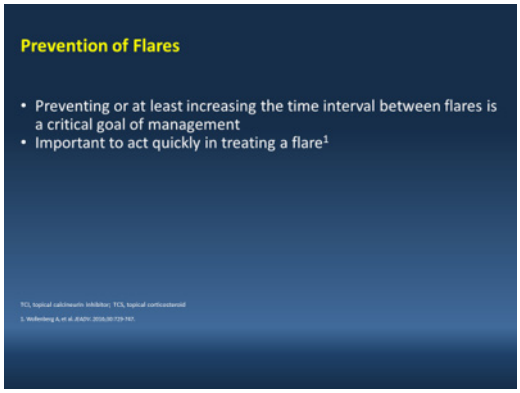
7 *Atopic Dermatitis: Prevention of Flares*

Dr. Paller: Let's talk a little bit about prevention of flares. We'll raise the case of Juan, who's a boy who comes in for continuing care of his atopic dermatitis. He was diagnosed with atopic dermatitis at 11 months of age. Basic measures give him good relief. The bathing, the moisturizers controlling triggers, but he experiences frequent flares. He just scratches tremendously, when that happens, to the point that he develops secondary skin infection.

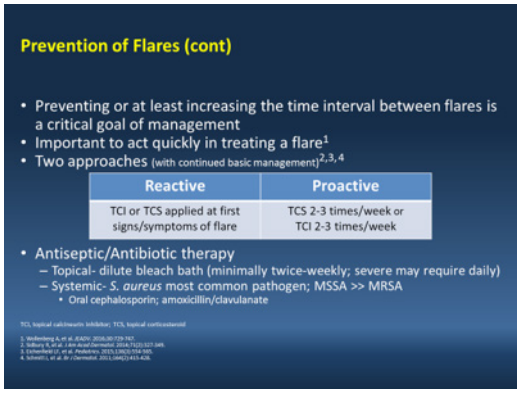


We should talk a little bit about how we might treat Juan and how we might modify his treatment plan.

Dr. Bernstein: It's very important to do something to prevent Juan's flares and we really would like to really reduce the number of flares overall, but also increase the time between each flare, if possible. Of course it's important to treat flares aggressively when they occur. There are 2 approaches, that is: reactive or proactive. Of course, we prefer the proactive approach where once you recognize that Juan is having recurrent and multiple flares, you want to design a strategy to prevent these.



You really have 2 options in this type of a patient; you could use a topical cortical steroid 2 to 3 times per week. This would probably be a medium potency topical steroid or a topical calcineurin inhibitor 2 to 3 times per week. Both have been shown to be effective on a long-term basis for preventing flares of atopic dermatitis.



Dr. Paller: Another key component to maintenance is the dilute bleach baths. This is an antiseptic approach that of course doesn't increase the risk of resistance as opposed to using antibiotics more frequently. This is an approach that can be used whether children are infected or not. We'll often initiate this when the child comes in with an infection. We treat the active infection but also initiate the dilute bleach baths.

The way that these are used is based on how large the tub is because we want to get to a 0.005% strength, so in a standard tub, if it's filled, we're going to use a half-a-cup and in a tubby I ask the parents to measure it out. So, how much water goes in, we use a scant teaspoon, technically it's 3.8 ccs per gallon or 1 cc per liter when we know that that's how much water is used in the tubby. Even for specific hand or foot treatment, we can similarly create a solution and just have a quick 5–10 minute soak for that.

The studies have suggested, though, that one can use this to continue to reduce not only the risk of infections, but, very importantly, also the severity of the atopic dermatitis itself. When the studies were done, what was very interesting is that those were performed in a randomized, double-blind manner in which one group used the dilute bleach and intranasal mupirocin ointment, and the other just used water in a bleach bottle and bland ammonia on top of the nose.

It was only those areas that were submerged that showed the reduction, and sustained reduction, in the severity of the atopic dermatitis, not the facial area, suggesting that really it's the bleach bath. And that's changed our management to make sure that we get the solution on a cloth to treat areas like the face and neck that otherwise might not get that exposure, and extend that control.

I should emphasize that in these treatments we're not wiping out the bacteria. It may be reducing them, or it may not be doing anything in terms of if you were to culture, but really stresses then that it needs to be maintained or that population will just come up again.

In the trials that were done it was twice weekly, and that looked very good. In my own personal experience, I find that for those who are more severely affected, daily bleach baths are tolerated just fine and do a better job than the less frequent use of them.

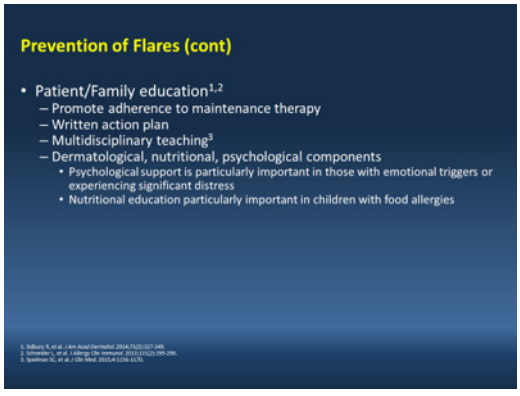
Also, in kids who are actively infected, sometimes sticking them in a bleach bath, even just a plain bath, can be very uncomfortable because of all the open raw areas. I'll often, if I'm using a systemic antibiotic, wait for 5 to 7 days into the course before I'll start that bleach bath and then continue the bleach bath. It's really been an important part of our regimen.

Dr. Bernstein: In terms of—if we have to use a systemic antibiotic—the currently recommended agents would be a cephalosporin or amoxicillin-clavulanate as drugs of choice for treating those obvious infections in patients with atopic dermatitis.

Dr. Paller: Unfortunately, a small percentage of our patients have MRSA, and we should emphasize that the only value of doing cultures in these patients is if you're trying to distinguish MRSA vs methicillin sensitive Staphylococcus aureus, because the majority, especially in the lesional areas, are going to be colonized, so there's no value of finding staph but rather what type of staph.

In those patients who have MRSA infection, then you may have to change based on the sensitivity but I should also mention that the dilute bleach baths are a little bit less effective as a single way to try to maintain in those with MRSA and I often have to go to vigorous means to try to decolonize the entire family as well as, for example, containers of emollients or even their topical products, which can grow out the methicillin-resistant staph.

Thinking about preventing and maintaining control, again, that requires some education of the patient and the family. We want to stress the need to adhere to therapy. It's so common, as things get better, for those families to say, "Oh, well we don't have to use these anymore." We need to stress that of course this is continuing treatment that is required or else it will come back, or we need to be jumping in there rapidly with flares.

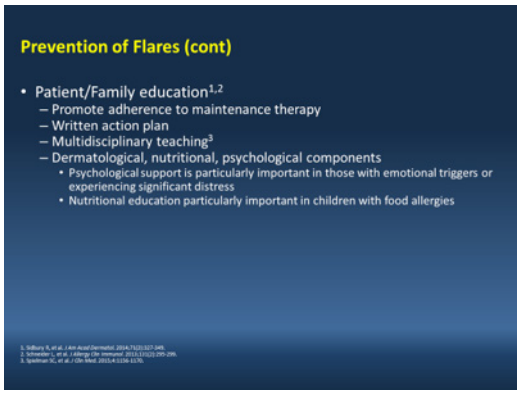


Again, those written action plans, the multidisciplinary approach and sometimes there are some other components that we need to stress. For example, those children who have secondary psychological issues can benefit greatly from seeing a counselor of sorts who can help to sort through that, introduce some behavioral therapy, even medication as needed.

We know that there is an increased risk of attention deficit disorder in individuals who have atopic dermatitis, and recognizing that and getting that intervention, can also be a 2-way street. It can help, as well, with the atopic dermatitis. We have to be careful about food-avoidance diets.

There are some children, a small minority, who have foods that clearly are shown to trigger their atopic dermatitis. But I've seen too many families who decide to introduce their own very limited diets. We've had children come in even with kwashiorkor in to the hospital because the parents have taken them off of things that give them protein, for example. We really need to be stressing that there needs to be physician-directed or nutritionist-directed guidance in order to manage any food-avoidance diets.

Controlling the trigger factors is very difficult. Of course we can more globally talk, as you've so beautifully mentioned, of potential irritants or allergic triggers and of course the staph aureus [inaudible 00:08:27] is a huge trigger, but beyond that it's very hard to find just 1 or 2 factors that may be triggering, that are easily avoided, as opposed to those children who have associated allergies where it then becomes much more important.



Dr. Bernstein: I see in adults often, if they have a job that involves wet work, that can be a particular problem in terms of aggravating their atopic dermatitis or any type of chronic eczematous dermatitis.

Dr. Paller: I'll say that my most common example of that in children is hand dermatitis. It's not really their eczema, per se, it's really more of an irritant dermatitis, but these kids with atopic dermatitis who, in school, are told to wash their hands and wash them very vigorously. We can change that by just pointing out that that top of the hand dermatitis is from excessive hand washing, particularly in the colder weather with reduced humidity and to send soap with cleansers, for example, to the school or even just use soapless cleansers as a wash and not even exposure to water, as well as the vigorous application of emollients and, if needed, the topical cortical steroids to manage that.

Dr. Bernstein: Well, we've talked about Juan and we've actually extensively discussed our treatment options, so what do we do for Juan? We really hit him hard with topical corticosteroids until his dermatitis has significantly improved. Then, we really want to be proactive about preventing future acute flares by treating him with topical corticosteroids on a long-term basis. As we mentioned, perhaps 2 or 3 times per week, selecting a medium potency topical corticosteroid.

Then also incorporate the bleach baths. We can suggest perhaps 3 to 4 times a week that he take a bleach bath and again, continue to educate Juan and his family the importance of really complying with our recommendations because the disease isn't going away and you really have to stick to it.

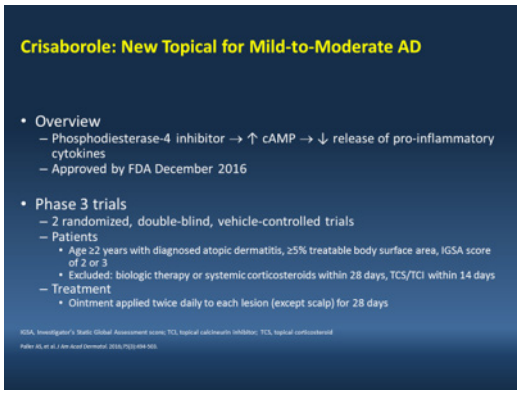
Dr. Paller: I'll mention one other piece about compliance because I think it's just so interesting. There were studies done several years ago in which there was stealth monitoring by putting a sensor in the cap of the tubes of topical medication. What the group found is that overall, over an 8-week period, there was 32% compliance and that it went up in the 2 weeks right before the doctor visit and it was also high in the 2 weeks after the doctor visit.

We need to recognize that this is the reality and really stress the need for compliance.

Dr. Bernstein: Very interesting.

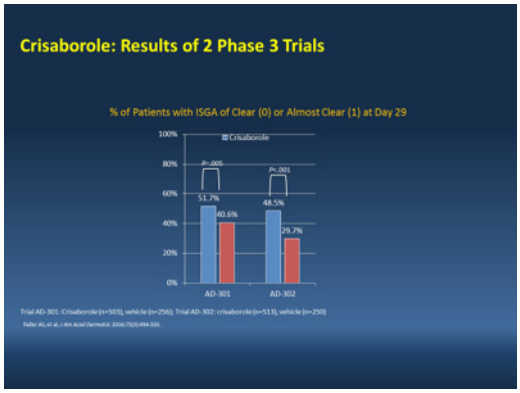
8 *Atopic Dermatitis: Emerging Therapies*

Dr. Paller: Now let's chat a little bit about 2 emerging therapies. The first of these is crisaborole, as mentioned, a new topical for mild to moderate atopic dermatitis. Crisaborole's the first of the phosphodiesterase-4 inhibitors. Phosphodiesterase-4 inhibition works by increasing cyclic AMP and thereby decreasing the release of proinflammatory cytokines.



It was approved by the FDA in December of 2016. There have been several studies supporting its use, including 2 tandem phase 3 studies that were double-blind and vehicle-controlled. These were performed in patients 2 years of age through adulthood, with atopic dermatitis, who had at least 5% body surface area and a score of mild to moderate. These patients had to be off of their topicals for at least 2 weeks and any kind of systemic therapy had to have stopped at least 4 weeks earlier.

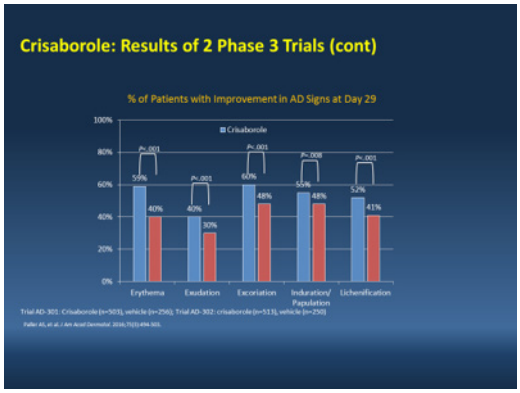
The medication was applied twice daily to lesional skin, excluding the scalp, and was done for 28 days. In these studies, in both groups, there was a statistically significant difference between those who were treated with the crisaborole and those who were treated with the vehicle. Now, interestingly, but not uncommonly, in both of these studies, there was a very high vehicle response rate. That tells you that that's a good vehicle as well.



Dr. Bernstein: Right.

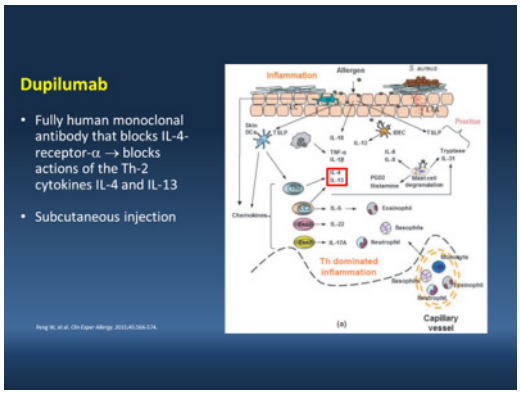
Dr. Paller: But, also is pretty typical of what we've seen in atopic dermatitis studies or just enrollment in a trial with vehicle alone does lead to improvement in a certain percentage that can be a pretty high percentage, particularly in those with mild to moderate disease.

I will add that in this study there were individual features of atopic dermatitis that were also looked at. The erythema, the exudation, excoriation, induration and papulation and lichenification. In each of those sets as well, there was a statistically significant difference between those who had the crisaborole vs those who were using placebo.

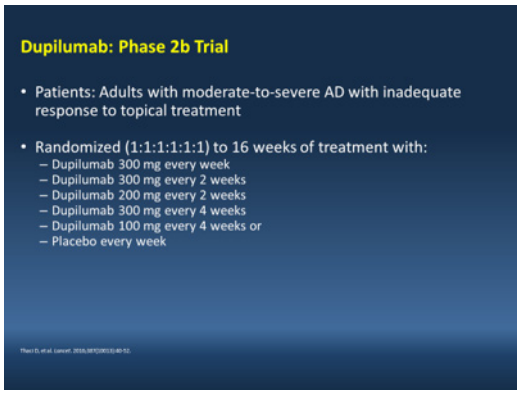


Now, we can consider an adult who has severe atopic dermatitis. Tameka, a 32 year old, who first developed it at 23 years of age. She's been treated with intensive topical therapy as well as systemic medication. She's either gotten adverse effects or she's just not responded. She's been treated with cyclosporine, mycophenolate mofetil, methotrexate. She really couldn't comply with phototherapy. She's been on this constant use of topical corticosteroid. When you try to get her to proactive therapy with a few times a week, she's just flared terribly. She's got poor quality of life. She doesn't sleep well. She's a schoolteacher. It's very hard for her to function.

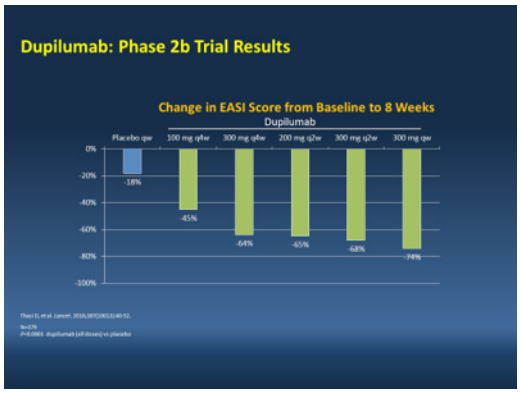
Dr. Bernstein: Yes, I mean, there are obviously unmet needs for managing such patients. Particularly adult patients who really present with very severe atopic dermatitis; who really seem to be refractory to topical therapy and even, as you mentioned, systemic drugs that we're familiar with. We really need new agents to address this unique population. Dupilumab is a monoclonal antibody that specifically blocks the IL-4 receptor alpha which then would block the stimulation of that receptor by IL-13 and IL-4. It blocks the effects of IL-13 and IL-4, which are Th-2 cytokines, which are very, very important in the pro-inflammatory Th-2 directed cascade that we know occurs in atopic dermatitis.



This is a new agent that will be administered through subcutaneous injection. I'm going to discuss an early phase 2 trial, which was done in patients with moderate to severe atopic dermatitis. These patients had inadequate response to topical treatment, topical corticosteroids or calcineurin inhibitors.



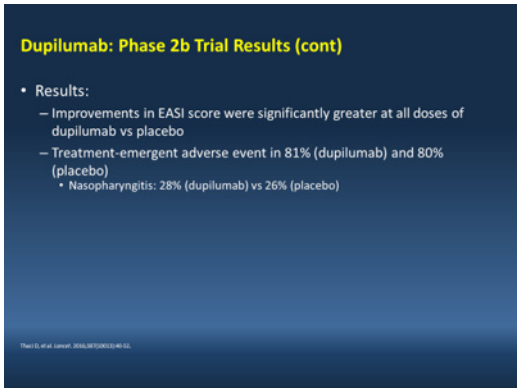
This phase 2 study was done by randomizing patients 1:1:1:1:1:1:1 equally to several arms: dupilumab administered on a weekly basis: dupilumab administered 300 mg every 2 weeks; 200 mg every 2 weeks, as you can see; 300 mg every 4 weeks; or 100 mg every 4 weeks; and a placebo arm was also included in this study. The treatment period was for 16 weeks.



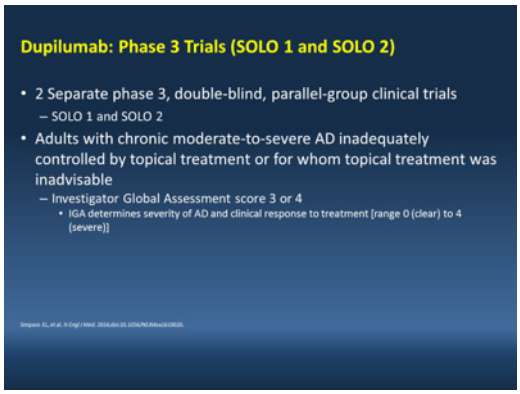
This is some of the data that emerged from this early study. This is a phase 2 dose-ranging study. As you can see, this shows data in terms of what happened during the course of treatment. The change from baseline over the first 8 weeks in the severity index. The Eczema Area Severity Index is EASI, which is a standard index that's used in many of these clinical trials to determine eczema severity. We can see that there was clearly a dose-response reduction in this index, indicating improvement in atopic dermatitis, particularly in the patients that received . . . and you can see the final 2 blocks on the right. Those that received the 300 mg dose on a weekly basis and those that received a 300 mg dose every 2 weeks had nearly an equivalent response ranging between 65-75% reduction in this EASI score index.

The results of this study demonstrated improvement in the EASI score. This was significantly greater than that was observed in the placebo. All doses actually showed improvement, but the greatest improvement, as you can see from the data, was in the 300 mg dose administered weekly or every other week.

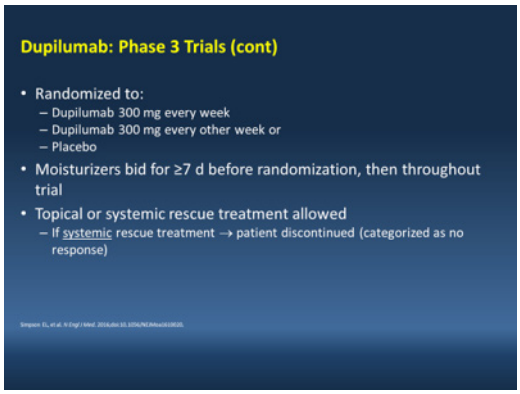
The treatment emergent adverse effects, which were of course evaluated in this clinical trial, seemed to be equivalent in terms of those reported by patients on active dupilumab or placebo. There didn't seem to be any really signals in terms of safety issues related to therapy.



Dr. Paller: There have been some phase 3 trials, too, of course, the studies called SOLO 1 and SOLO 2. Two separate, but in parallel, phase 3 double-blind clinical trials. These trials were, again, just in adults with chronic moderate to severe atopic dermatitis that was inadequately controlled by topical treatment or for whom topical treatment was inadvisable. They had to have an investigator global assessment score of 3 – moderate, or 4 – severe. They were randomized to either every other week 300 mg of dupilumab; or to dupilumab 300 mg every week; or placebo.



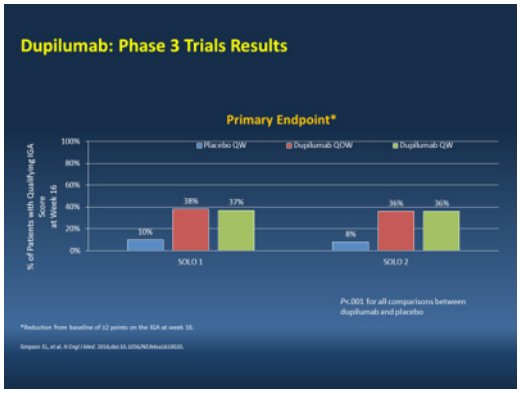
The dupilumab group received 600 mg loading dosage. These individuals were able to get moisturizers twice daily for the 7-day run-in before randomization and then throughout the trial. They were allowed to have topical or even systemic rescue therapy. If systemic rescue treatment, they were discontinued. Otherwise, they were allowed to continue in the trial with the topical.



With this trial, once again, we saw a huge difference between those on placebo and those who were treated with dupilumab. A very similar result in these parallel trials. Interestingly, in the trials, the every other week 300 mg did just as well. Of course, there will be patients who really require the weekly dose but this suggests to us that for maintenance…

Dr. Bernstein: Right.

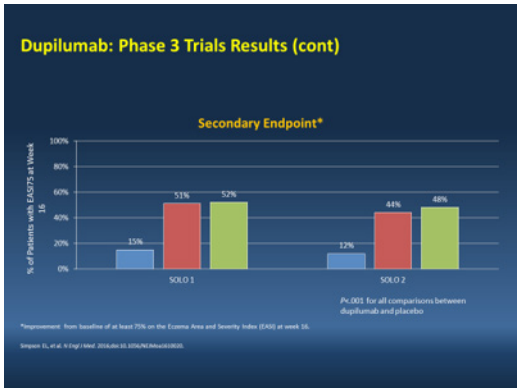
Dr. Paller: …It will probably be likely that these patients can come down to an every other week dosing.



There were secondary endpoints as well, including patients with an EASI 75, so that reduction by 75% at week 16, the endpoint in that, similarly, also showed an excellent separation between those on placebo and those treated with the active dupilumab. In this case, 50% in SOLO 1 and almost 50% in SOLO 2, achieved that very high goal of 75% reduction within that 16-week period. Highly effective medication in the first biologic that's come out.

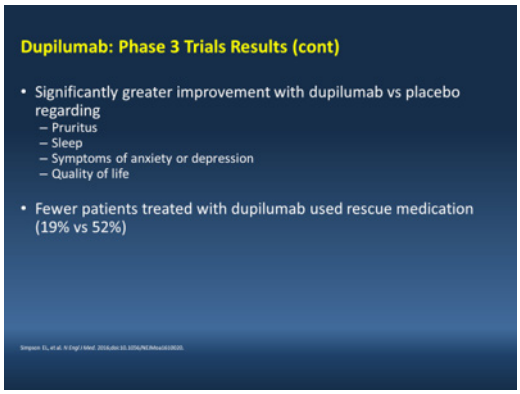
In these studies, there was significantly greater improvement in itch, in sleep, in the symptoms of anxiety or depression and overall quality of life. As you might expect, fewer patients ended up using rescue medications when they were treated with dupilumab. That was only 19% vs 52% who chose to use them at some point on the placebo.

Dr. Bernstein: In terms of adverse effects in these trials, these are listed in this table here. The only one that really stood out was the allergic conjunctivitis or conjunctivitis. As you can see, that this was notable in the dupilumab treated groups vs the placebo. The reason or explanation for this is unclear. Suffice it to say, there was a very low incidence of this effect. But, this will be looked at, I guess, in the future.



Dr. Paller: Absolutely. I want to mention, too, that dupilumab is just the tip of the iceberg here, really.

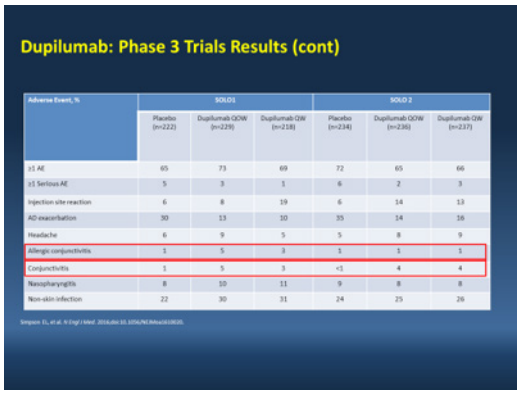
Dr. Bernstein: Right. Right.



Dr. Paller: We're really excited about it being available. It's going to make a huge difference in…

Dr. Bernstein: Absolutely.

Dr. Paller: …our treatment regimen. But, because we understand the pathophysiology, as we talked about earlier, there are other potential targets. They are being very vigorously looked at in phase 1 and phase 2 trials, advancing towards phase 3 trials. For example, dupilumab, of course, as mentioned, is the Interleukin-4 receptor. Interleukin-13, which is the ligand for that receptor, is being vigorously looked at, as well as some other cytokines that we know are increased. Particularly, Interleukin-31 is a potential anti-itch agent.



There are Janus kinase inhibitors, which are looking promising in case reports and are undergoing trials now. And agents, for example, block thymic stromal lymphopoietin, which we know is increased as an early component of that Th-2 cascade. Histamine-4 receptor blockers, looking interesting, and even liver X-receptor agonist, or LXR agonist, coming on the market. As well as more studies, as mentioned earlier, on phosphodiesterase-4 inhibition. We've got a lot of hope now…

Dr. Bernstein: Yes!

Dr. Paller: …for the first time for these individuals with atopic dermatitis for new products.

Dr. Bernstein: Some of these are small molecules, not necessarily monoclonal antibodies that you need to inject. Some may be available, if they're effective, as oral formulations.

Dr. Paller: Right. JAK inhibitors…

Dr. Bernstein: Yes.

Dr. Paller: …the H-4 receptor blockers, for example, are going to be oral agents.

Dr. Bernstein: Yes. Very exciting.

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