Overview

Steven Feldman, MD, PhD, and Jonathan Silverberg, MD, PhD, MPH, provide their clinical insights into the burden of disease experienced by persons with atopic dermatitis and strategies for management. They discuss how improved understanding of pathophysiologic mechanisms has led to the availability of new topical and systemic therapies that, when integrated with other therapies, can reduce patients' disease burden. They also discuss 6 medications in late-stage development for atopic dermatitis.

Content Areas

- Burden of disease
- Pathophysiologic mechanisms
- Basic management
- Topical therapies
- Systemic therapies
- Emerging therapies

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CE Statement

Target Audience

The target audience is dermatologists, pediatric dermatologists, allergists, along with nurse practitioners and physician assistants within those specialties who manage patients with atopic dermatitis.

Learning Objectives

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

- Recognize essential and important signs and symptoms that should be considered in the diagnosis of atopic dermatitis (AD)
- Develop treatment plans that address both symptoms and patient concerns
- Integrate newly-approved AD therapies into treatment plans
- Describe emerging AD treatments in late-stage clinical development

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Novartis: Clinical area: Psoriasis

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Regeneron: Clinical area: Atopic Dermatitis

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Glenmark: Clinical area: Atopic Dermatitis

Kiniksa: Clinical area: Atopic Dermatitis

Leo: Clinical area: Atopic Dermatitis

Lilly: Clinical area: Atopic Dermatitis

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Module 1: Burden of Disease

Steven R. Feldman, MD: In this module we will characterize the burden of disease experienced by persons with atopic dermatitis, and risk factors for atopic dermatitis. We review recommendations for assessing disease severity, as well as comorbidities that are common in patients with atopic dermatitis.

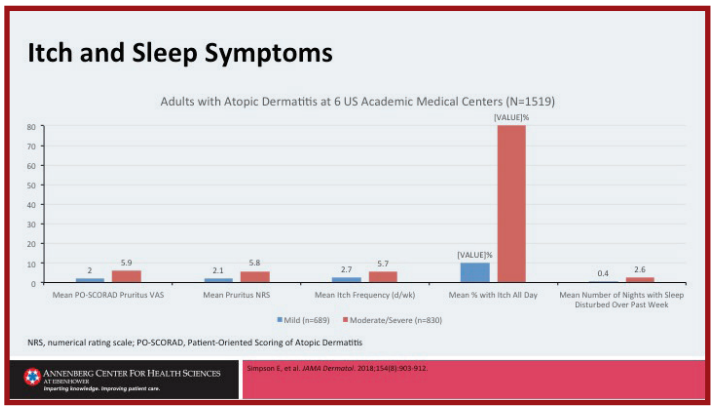
Let us start with a case scenario. Luis is a 9-year-old male seen in clinic with a complaint of worsening pruritus causing difficulties in school and sleep. He first complained of dry, itchy skin on the flexural areas of his arms and legs about 2 years ago. His symptoms are worse in the wintertime.

There is a family history of a father with asthma and rhinitis. On physical exam he's got diffusely dry skin. There is redness, dryness, and lichenification in the flexural areas of both the upper and lower extremities, with increased scaling on his legs. Jonathan, let us discuss the impact of atopic dermatitis on a patient like Luis.

Jonathan I. Silverberg, MD: There is a wide range of impacts of atopic dermatitis on the patient.

There is a component where we understand the direct impacts on sleep disturbance and daytime fatigue, which is directly related to both the itch and the skin pain. That in and of itself can have a number of indirect effects in terms of absenteeism, presenteeism, workplace productivity, etc, and impact on job performance.

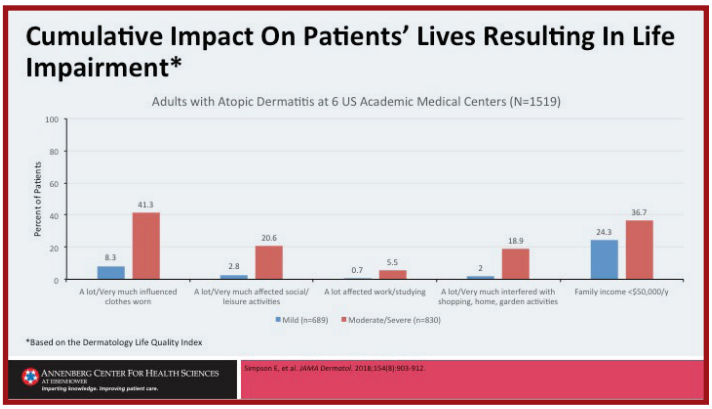
In the pediatric realm, and even within the adult realm, there is an impact on education, leading to potentially poor qualifications impacting career trajectory and financial problems. There is also a component of mental health symptoms. And that is probably multifactorial, related to both the sleep disruption and the itch. But they may even have other components driving it, but we see symptoms of depression, anxiety, low self-esteem. There are even associations with chronic headaches that have been shown. And then, even, potentially suicidality, across different studies.



Then there is that impact that happens on activities of daily living, and just the entire aspect of what patients might like to do, in terms of poor tolerance for—for heat, as an example—or challenges with clothing, which can impact family time, it can impact daily activities, limiting business trips. A variety of different impacts.

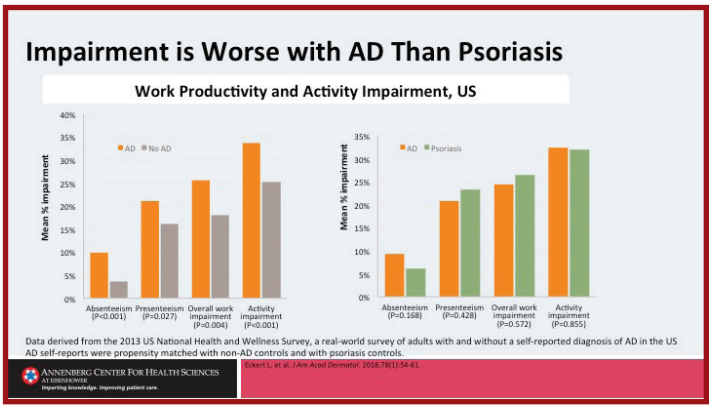
The hallmark of atopic dermatitis is the itch and, consequently, the impact that itch has on sleep, on those other downstream manifestations. These are data from a multicenter study that examined the burden of atopic dermatitis in a treated population and found that, not surprisingly, the more severe the disease in that moderate-to-severe patient population, that there is a higher average intensity of itch.

There is a greater frequency of itch that happens. More patients reporting, that persistent itch throughout the day. And then, of course, that sleep disturbance as well, being more prominent in moderate-to-severe disease.



There is a cumulative impact that happens on patients' lives in terms of quality of life impairment. And again, these are data from that same multicenter study that showed that even in mild patients, you can see considerable impacts in terms of quality of life.

Limitations in terms of clothing worn. Limitations in terms of social and leisure activities, work study, even just shopping and garden activities, which are all different domains of the Dermatology Life Quality Index. But, as expected, with more severe disease you have an even



stronger impact on those aspects than in the patients with mild disease. And, you know, interestingly enough, those patients with more severe disease actually having, on average, a higher proportion with lower household or low family income, which suggests that this may be impacting income generation because of those cumulative effects.

How does atopic dermatitis compare with other inflammatory disorders? We are certainly very familiar with psoriasis. This is one that has gained a lot of attention over the past decade. It appears that atopic dermatitis is at least as bad as psoriasis, and from some studies may even be worse in terms of its work productivity impact and activity impairment.

These are data from a US population-based study that examined work productivity and activity impairments in patients with atopic dermatitis and found that, not surprisingly, higher rates of absenteeism, higher rates of presenteeism. Even when they are able to go to work there is a loss of work productivity, overall work impairment, and activity impairment. And we would expect that, of course, compared to healthy controls.

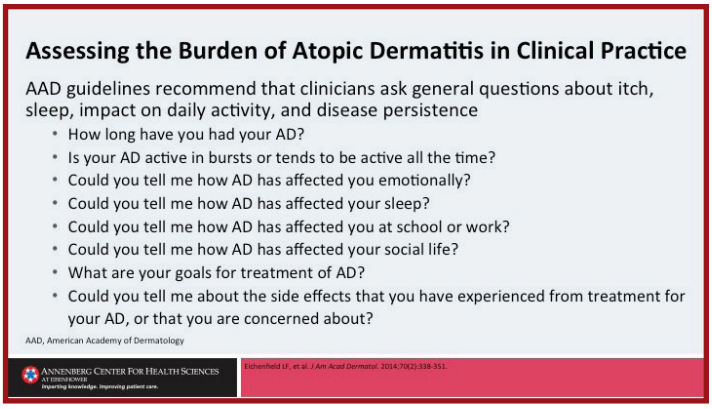
What was fascinating was when they compared it to those patients with psoriasis, you actually had similar impacts as psoriasis. And in some respects, in the case particularly of absenteeism, it looks like there is a higher impact, although not statistically significant, but, overall, a very similar burden to psoriasis. And we see that, in fact, atopic dermatitis is a highly burdensome disorder, comparable to some of our worst disorders.

One of the questions that comes up is, we understand this is a very heterogeneous disease, we understand that it can impact many different aspects of patients' lives, how do we best assess the disease severity? How can we sort of parse out and figure out when a patient will have these impacts? There are a lot of different ways in doing that, and a lot of different assessments that exist.

Some of the common assessments that are used in clinical practice would be body surface area, so just how extensive the disease is. The location, the distribution of the lesions. There are sites on the body which are going to be more problematic for patients than others. For example, hands and feet, in terms of their functional significance. The face, head, and neck area in general, potentially, because of its aesthetic component and the visual aspects of that.

There are other tools, as well, that can be used to assess disease severity, and even just directly assessing quality of life, such as the Dermatology Life Quality Index. Many of these are used in clinical trials but are not routinely used in clinical practice. The best practice here, and our guidelines, suggest that, at the very least, you should be asking about a bunch of these, whether you're using these formal, structured assessments or not. At the very least, build into the patient interviews, questions that will assess the impact of atopic dermatitis on patients' daily living and quality of life.

And it's critical to have that understanding of the symptom burden, of the impact on quality of life, in order to understand the burden of disease. Because for many patients, you may not be able to fully appreciate the severity by visualizing the skin alone.



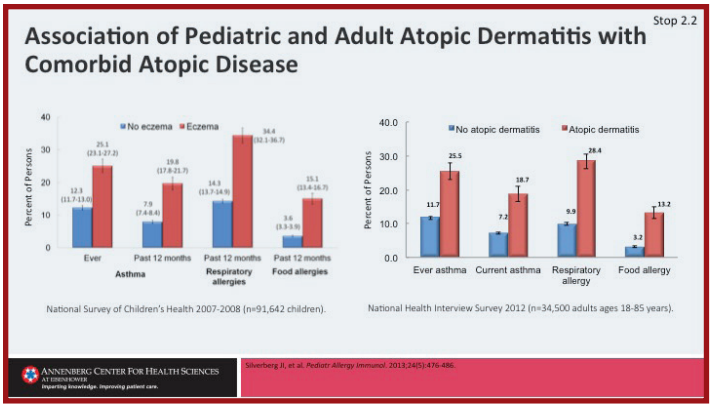
What are some ways that we can do it in clinical practice? Well the AAD guidelines, American Academy of Dermatology guidelines, recommend that clinicians ask general questions about itch, sleep, impact on daily activity, and disease persistence. These are some examples of questions that can be asked. Certainly, you'd want to know how long they've had their atopic dermatitis. Does it tend to come in bursts? Or does it tend to be active all the time? How does it impact patients emotionally, on their sleep, activities? These are all things that can be asked as open-ended questions.

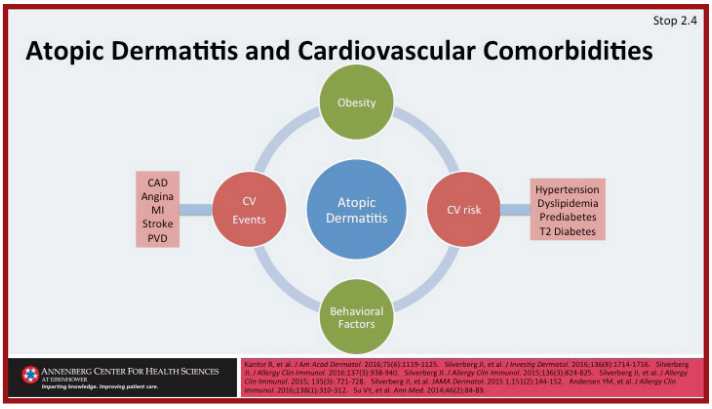
I personally find it much easier to use some of those structured assessments and questionnaires because you often get that rich information that you need without necessarily having these long conversations. These are things that are simple questions that we can build into our routine clinical practice for all patients. Maybe it doesn't mean all questions, but at least a few of these can tell us a lot about patients' experience.

Module 2: Comorbidities

Jonathan I. Silverberg, MD: Atopic dermatitis is associated with a wide variety of comorbidities. Among these are other atopic diseases, as well as neuropsychiatric and cardiovascular diseases. Atopic dermatitis is also associated with osteoporosis, injuries, developmental issues, and several types of infections.

In terms of the atopic comorbidities, these are data both from 2 US population-based studies both in children and in adults—in children, it's the National Survey of Children's Health—and found that for children who reported having, or for caregivers who reported their children as having eczema, about 25%, or 1-in-4, had a lifetime history of asthma; about 20%





had a history of asthma in the past 12 months; about one-third reporting respiratory allergies or hay fever in the past 12 months.

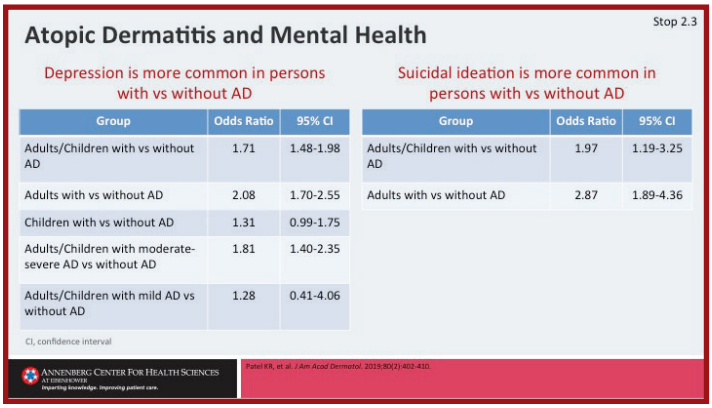
And food allergies being reported in higher numbers, as well, in the past 12 months. The food allergy numbers are a little bit debatable, because sometimes patients will report food insensitivities that may not be true allergies. But the point being that there are clearly dramatic increases of these comorbidities in the atopic dermatitis pediatric population.

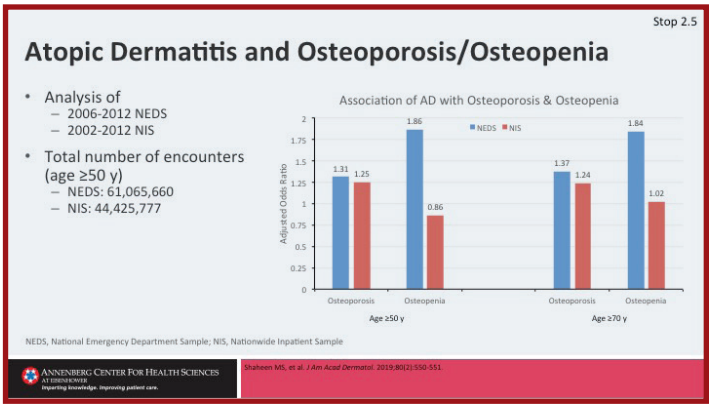
When you look at the National Health Interview Survey for the atopic dermatitis adult population, you actually find remarkably similar numbers in the adults as well. Where approximately 1-in-4 adults will report a lifetime history of asthma; about 19% reporting current asthma; almost one-third reporting respiratory allergy; and then about 13% reporting food allergies. It is very consistent prevalences of these atopic comorbidities in both children and in adults.

of depression, suicidal ideation, and a variety of other mental health symptoms, or mental health diagnoses that led to mental health hospitalizations.

In terms of the cardiovascular connections, this is one that is a little bit more complex because atopic dermatitis has multiple impacts on the patient's well-being. It may directly lead to more sedentary behavior, poor health behaviors, in general, in terms of more smoking, alcohol consumption, etc. Those behavioral factors are certainly going to have their own downstream effects.

Connections have been shown between atopic dermatitis and obesity, as well. And, of course we know the role of obesity in cardiovascular disease. But there may even be other connections where atopic dermatitis somehow directly leads to hypertension, or dyslipidemia, or diabetes. This is an area that we need to further study.





With respect to the mental health symptoms, there are more and more studies that are developing or have come out recently on this topic. This is a recent study where we examined the mental health hospitalization rates within the atopic dermatitis patient population and compared that to the general population to understand not just do patients have depressive symptoms, but does it lead to psychiatric urgencies or emergencies that would lead to hospitalizations?

And in fact, that children with—and adults with—atopic dermatitis, did have significantly higher odds

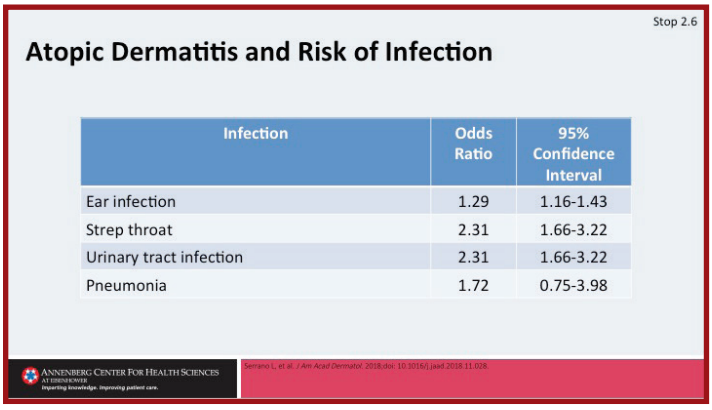
When you put all that together, what you see is now, more and more across studies, increased associations with atopic dermatitis, somewhat, and cardiovascular disease. Somewhat similar to the psoriasis story that we are familiar with. It's not clear if it's quite as strong of a signal. It may be a little bit less. But it appears to be there, nonetheless, in the atopic dermatitis population, and something that we want to be cognizant of, and potentially screening for.

The connection with osteoporosis and osteopenia is a fascinating one with atopic dermatitis. And this is one

that now we have several studies done internationally that have confirmed these findings. And this probably is also multifactorial for, in terms of what are some of the mechanisms or reasons for this.

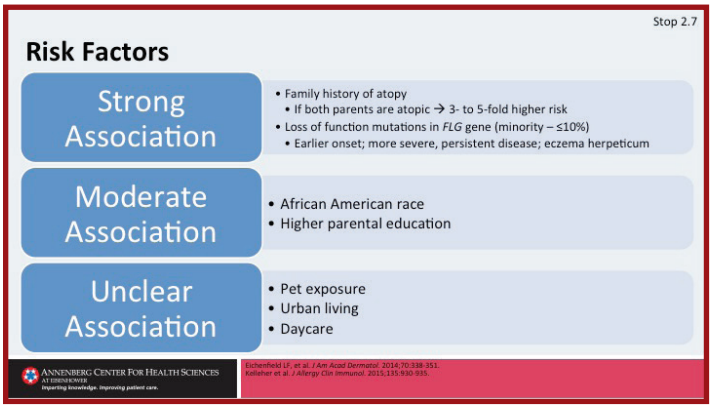
In fact, across multiple cohorts, this is a study that was recently published that examined multiple nationwide cohorts throughout the United States of middle-aged and older patients age 50 and up, and found that, overall, significantly higher odds of osteopenia in the age 50 and up age group for atopic dermatitis. Whereas, in the emergency department setting then, when you go to age greater than 70, you also see that signal.

In the osteoporosis signals, you see that for both the outpatient, for the emergency department setting, and the inpatient setting in both the age greater than 50 and in sensitivity analysis that looked at age greater than 70. This is something that we need to learn more about. And we need to figure out how to best prevent and treat. But this is another emerging comorbidity in the world of atopic dermatitis.



Infections are a fascinating one. We've long known about the connection between atopic dermatitis and skin infections. And it's something most clinicians are well aware of. But increasingly, now, there are studies that have shown higher rates of other types of infections, things that go beyond the skin.

A recent meta-analysis published in the Journal of the American Academy of Dermatology, showing significantly higher odds in a pooled meta-analysis of



ear infection, strep throat, and urinary tract infection. Not a significant association overall for pneumonia, but also keeping in mind that this is an early area of inquiry and research, and, hopefully, we'll see even more studies coming in the future to better understand this.

In terms of what some of these risk factors are, there are a number of things we have to think about when it comes to atopic dermatitis. These are things that are academic discussions, but sometimes these are directly relevant to our ability to diagnose and counsel patients and caregivers as to what they should expect for their family member or for their own disease.

We know there are strong associations with family history of atopy. If one parent has atopic dermatitis or atopy, there is a significantly increased risk of their child having it. But if both parents have it you get a 3- to 5-fold higher risk of their child getting atopic dermatitis. We know about the loss of function mutations in the filaggrin gene and that is the one that has been most consistently shown across studies and may be associated particularly with earlier onset or more severe persistent disease. And potentially even with some comorbidities such as eczema herpeticum.

But even then, the majority of patients don't have the filaggrin mutations. There are other genetic mutations that likely occur, but not nearly as well reproduced across studies. It seems like atopic dermatitis is fairly monogenic in a small subset, but is probably polygenic in the larger population.

In terms of associations, we've seen, in the United States, associations in kids with African American race where African American children may have up to double the prevalence of atopic dermatitis as their Caucasian counterparts. And then we also know that across many studies, internationally, there seems to be an association with higher parental education, for reasons not fully understood, that may be in part confounding due to metropolitan living. And urban living certainly has been something that has shown associations with atopic dermatitis.

There are other things that have been shown, as well. Patients who live on farms may have lower rates of atopic dermatitis. Some studies have shown protective effects of pet exposures, some have shown potentially harmful effects of pet exposures. There is still a lot of these different risk factors that we need to sort out when we are thinking about how to properly prevent the disease.

I'm curious, Steve, which of these do you encounter the most and incorporate into your clinical decision-making the most?

Steven R. Feldman, MD: I'm not sure how much I take them into account or address them when I'm seeing these patients. If we think of our case scenario, Luis, who has this atopic dermatitis and clearly it itches. It's

going to impact his sleep, therefore, his school, his life, his family's life. Still, I focus on treating the skin lesions and getting them cleared up. And hopefully in doing so, I've addressed a lot of those issues. But certainly, all these issues speak to the importance of getting these patients' disease under control. Should I be doing more than that?

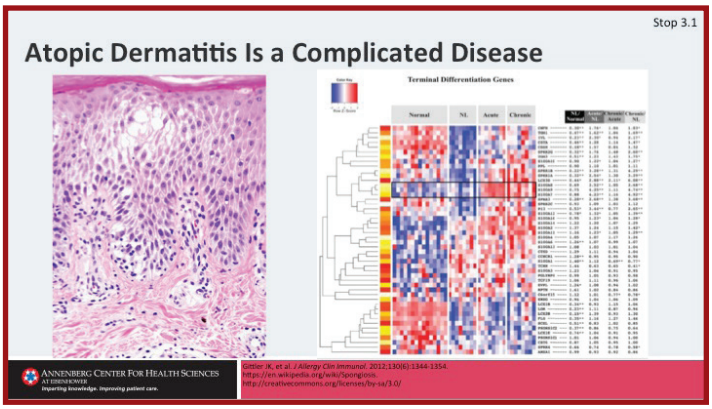
Jonathan I. Silverberg, MD: That is a great question. To your point, the first thing is to recognize that these are the downstream consequences that occur in our atopic dermatitis patients. Because if you don't recognize that, then you don't realize how important it is to get tight control of their disease.

Above and beyond that, there are scenarios where, yes, recognizing these comorbidities can be quite helpful. It is not always easy to address these things. And some of these are going to be beyond our practice scope in the standard dermatology setting.

There are opportunities for us to at least be able to screen our patients, and potentially refer them to the appropriate provider. You know, just as an example, when patients have refractory hay fever and allergic conjunctivitis, that is not just an isolated thing. That is actually going to impact our ability to control their skin disease, because as long as their eyes are itchy and they are rubbing them nonstop, that is going to lead to lichenification, and eczematous lesions there.

There are scenarios where we don't feel comfortable working up that hay fever and understanding what those aeroallergens are, but if we refer them to the right provider, as an allergist for example, that may actually impact and improve their overall disease severity.

There are also some studies now that have shown, in the pediatric population, that by actually just using something like melatonin to improve sleep, that you can improve the atopic dermatitis disease severity as well. We don't believe that that is an anti-inflammatory effect, but if patients are not sleeping well and they are scratching all throughout the night, that is going to impact things. There are opportunities, certainly, for us to think beyond just the limitations of the skin. And those can also have direct effects on the skin.



there is any perturbation of normal skin, all kinds of things can happen.

Let's look at the histology. You see a spreading apart of the skin cells with edema fluid. You see inflammation, dilation of blood cells. There are probably thousands, if not tens of thousands, of changes happening in skin, and alterations of the barrier function. If you look at the genes affected, you can find tens of thousands of genes whose expression goes up or down.

And one wonders, is this telling us something about the pathogenesis of the disease? These kinds of studies are not helpful for telling us the cause. They tell us that when you have atopic dermatitis you have tremendous perturbation, but what's causing those perturbations is much more difficult to get at.

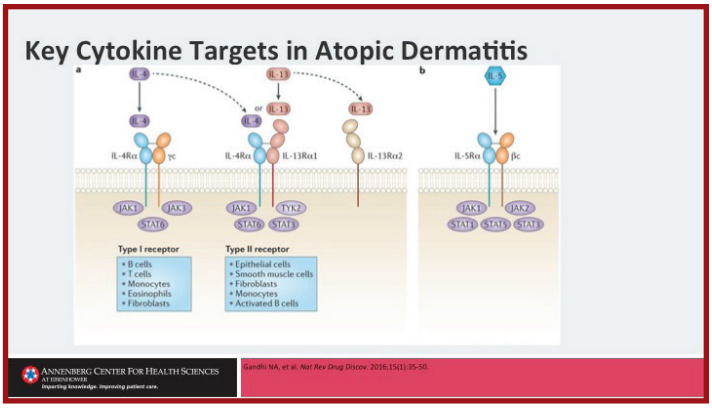
The genetics of atopic dermatitis have been studied. And there have been many, many studies of the genetics of atopic dermatitis. And in many of those studies you find filaggrin gene mutations. Filaggrin mutations are clearly a critical aspect of atopic dermatitis. In addition, many of the studies find genetic abnormalities in interleukin-13, interleukin-4, and the interleukin-4 receptor through which both interleukin-13 and interleukin-4 work. And then you have other studies that have found a host of other genes associated with the immune system that are related to the disease.

Given that interleukin-13, interleukin-4, and the receptor that modulates the effects of those cytokines are genetically abnormal in patients with atopic dermatitis, these are key cytokine targets for the disease. Here

Module 3: Pathophysiology

Steven R. Feldman, MD: In this module we review our current understanding of the pathophysiology of atopic dermatitis. We discuss the role of cytokines, genetics, and immunologic pathways, and how these serve as treatment targets.

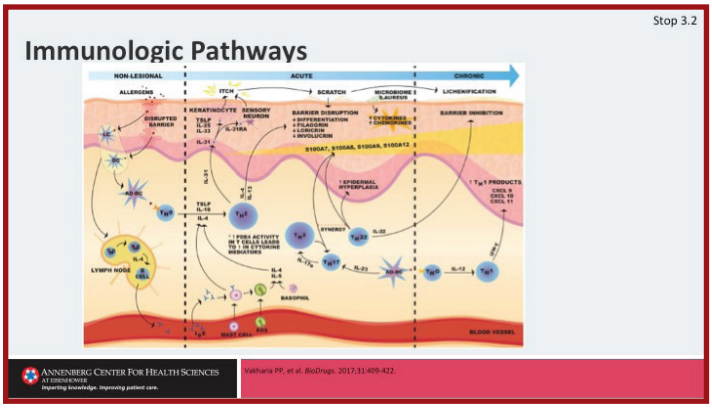
Atopic dermatitis is a complicated disease. If you think of human physiology and the complexity of normal skin and all it does to serve as a barrier between us and our environment, then it's pretty quick to see that when



we see interleukin-4 and interleukin-13, and how they bind to the interleukin-4 or -13 receptor, which shares a similar subunit, the interleukin-4 receptor-alpha subunit. Blocking interleukin-4, blocking interleukin-13, or blocking both by blocking the receptor, would be key targets for approaches to improve atopic dermatitis.

You could do that with antibodies, with biologics that would either bind the cytokine or block the receptor.

And if you look, the signal from the interleukin-4, interleukin-13 receptors are mediated through the cell through JAK-STAT proteins. Those intracellular targets, which might be addressable through small molecules, would be additional targets for improving atopic dermatitis.

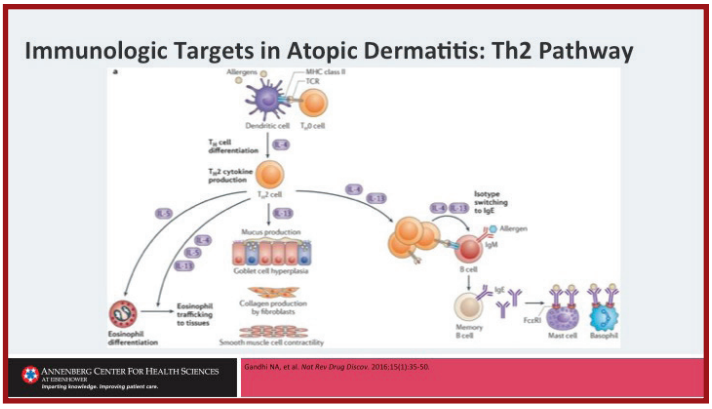


The immunologic pathways in the skin are, not surprisingly, complicated. Because your skin is your primary immune organ. I mean it is separating us from the environment. It is what faces the outside world. It is what faces infections and irritants. In the nonlesional skin of atopic dermatitis, the disrupted barriers and allergens can cause activation of the immune system.

And if we could think again about the histology that we saw, the histology of atopic dermatitis, to me, as a dermatopathologist, looks identical to the histology that I would see in contact dermatitis, allergic contact dermatitis, or even perhaps in an irritant reaction. I suspect that the primary immune pathways are going to be very similar.

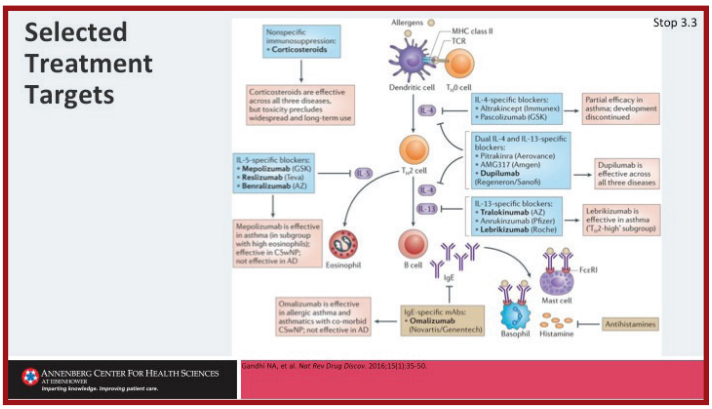
In the acute phase, you have inflammation and resulting itching. Some people believe the itching comes first, and that disrupts the barrier. People scratch and that causes the inflammation. But I believe that it's the inflammation that comes first. At least, in part, because we see so many immune molecules in the genetics of atopic dermatitis.

The other reason is because I see these patients who have pityriasis alba and they are not scratching. They are having a change in their pigmentation due to, I believe, underlying inflammation. It seems to me it's the inflammation that comes first, and not the itching. But certainly, the itching is important.



And you have cytokines involved in the itch, like interleukin-31. The cytokine cascade activates T-cells. And then you move on to a more chronic phase where other cytokines may be involved, creating the lichenification and the thickening of the epidermis, and the long-term changes that we see in atopic dermatitis.

The T-helper 2 pathway that gets activated is a key target for improving the disease. You have allergens that are being picked up by dendritic cells, and they are activating T-helper 2 cells. And these cells are producing interleukin-4 and interleukin-13, which have an array of secondary effects on the immune system and the skin, ultimately leading to B-cells and IgE, which potentially could be another target. Although, as we'll discuss, late-phase targeting of IgE does not seem to be nearly as effective as targeting earlier cytokines like interleukin-4 and interleukin-13.



With the growing understanding of the immune system, we've developed an array of potential targets. So, the interleukin-4 can be targeted by specific interleukin-4 antibody drugs. Interleukin-13 can be targeted by specific drugs. And these drugs are of interest not just in atopic dermatitis, but also in those other atopic conditions like asthma.

You can block both interleukin-4 and -13, and we already have a drug, dupilumab, that does that. And that is clearly a highly effective way of treating atopic dermatitis. This pathway eventuates in IgE production

and we have a drug that can target IgE, but it doesn't seem to be particularly effective in atopic dermatitis, even though it may work in asthma.

To summarize: We have a lot of potential targets; and with our growing understanding of the immune system, we are developing more potential targets all the time. Jonathan, do you have any different insights or thoughts on these pathways?

Jonathan I. Silverberg, MD: These illustrate the complexity and how much is going on. We have so many different animal models, and different ways of studying these diseases, and, in particular, atopic dermatitis. Sometimes, we don't know how relevant these are in humans. And the punchline, or the way we learn the most is, ironically, from the clinical trials.

To your point, while we fought so much about IgE as a possible mechanism in atopic dermatitis, the clinical trials probably show us that IgE is not that main causal pathway. It may have an accessory role, but it leaves us lacking. And we start looking more and more at the Th2 pathways and see how impactful they are in terms of targeting. And we recognize more that it's probably the upstream of the IgE and the Th2 inflammation. But there could be something even further upstream. It's an exciting time. We are learning so much in the field.

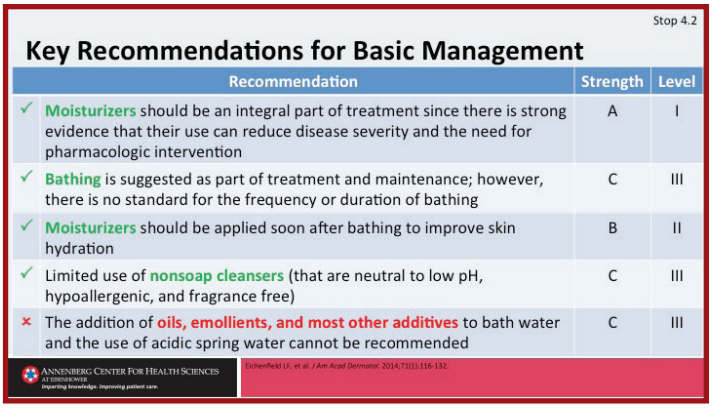
Module 4: Basic Management

Steven R. Feldman, MD: In this module, we discuss the goals of therapy, and key recommendation for basic management, such as skin hydration, trigger avoidance, and patient education. We'll review possible factors that contribute to the suboptimal patient adherence that we often see, and strategies that can be employed to promote adherence.

The goals of therapy include reducing the number and severity of flares, reducing the itching, and improving patient's quality of life, maintaining normal activities of daily living, maximizing disease free periods, preventing the infectious complications, and, of course, minimizing the side effects of treatment. Sometimes even just minimizing the perception of the side effects of treatment may help.

There are a number of key recommendations that have been made for basic management of atopic dermatitis. I'm going to present things that came from the American Academy of Dermatology guidelines on the treatment of atopic dermatitis. One of the strongest recommendations was that moisturizers should be used. They are an integral part of the treatment since there is strong evidence that their use can reduce disease severity and the need for drug management.

This makes sense because these patients have dry skin, and because we know that filaggrin mutations are important in the disease, and barrier function is



probably an issue for these patients. Bathing has been suggested as a part of treatment and maintenance, although there is no standard recommendation for the frequency or duration. And I've heard some dermatologists recommend lots of bathing to hydrate the skin and others recommend less bathing to avoid removal of the natural oils in the skin. Either way, a moisturizer should be applied after bathing to improve the skin hydration.

Also, limiting the use of non-soap cleansers that are neutral to low pH, hypoallergenic, and fragrance-free, may be sensible. Avoiding the use of detergent cleansers which would strip the skin of its oils would be a reasonable recommendation. And the addition of oils and other additives to bathwater has not been recommended. There is not data to support it. And if you put oil in the bathtub it doesn't mix with the water. It just sits on the surface anyway.

The American Academy of Dermatology guidelines gave an "A" evidence rating supporting the use of moisturizers, topical corticosteroids, and topical calcineurin inhibitors, the latter often used to avoid the side effects of topical corticosteroids. The AAD guidelines strongly advised against the routine use of topical antistaphylococcal treatments, unless the atopic dermatitis is actively infected.

The guidelines had specific advice on skin hydration, including bathing followed by immediate application of emollient. The emollient used could be generous. That you don't have to worry about excess use. You could use the emollient in the form of a lotion, a cream, an oil, an ointment. I believe one vehicle works better than all the others, and it's the one that that patient that you're taking care of at that moment wants to use.

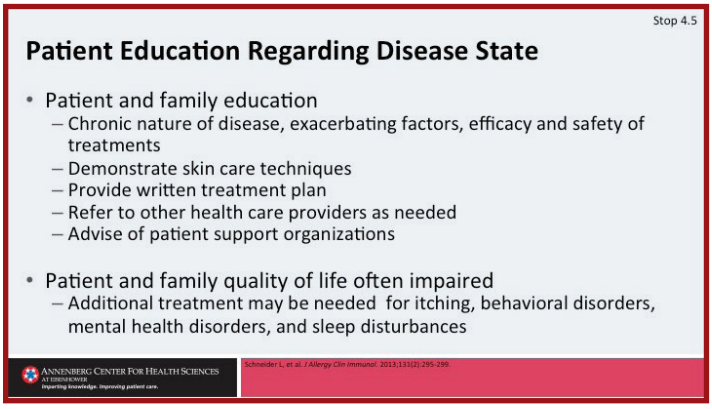
The general bathing recommendations included warm, not hot water. Baths being better than showers. Use a bath duration of 5 to 10 minutes, and use neutral to low pH, hypoallergenic, fragrance-free, non-soap cleansers. Bleach baths, according to the guidelines, are now the standard of maintenance care for pediatric moderate-to-severe atopic dermatitis, although personally, I wonder if there isn't some data suggesting that the evidence for their use isn't maybe as strong as we thought.

Trigger avoidance is very sensible. If you know it makes your atopic dermatitis worse, avoid those things. Common irritants include strong detergents, wool, occlusive fabrics, potential contact allergens like ubiquitous fragrances, preservatives, and botanicals. It was recommended to control the temperature and humidity to avoid exacerbating the dry skin.

Consider possible allergy testing for triggers other than foods, with skin tests. Although skin tests and allergy patch test things are considered poorly predictive of triggering factors. I like to point out to my students that I don't think I've ever seen a patient who's had allergy testing done by the allergist that resulted in their atopic dermatitis going away.

I like to point out to my students that if the allergist ever did the testing, and found the allergens, and made the atopic dermatitis go away, the patient wouldn't come see me anymore because they wouldn't have atopic dermatitis. If it happens that they improve, I don't see it.

Allergen immunotherapy potentially could be appropriate in selected patients who have aeroallergen sensitivity that worsens their atopic dermatitis. Leukotriene inhibition was thought maybe to be helpful at one time. But the limited data have shown it not to be that helpful.



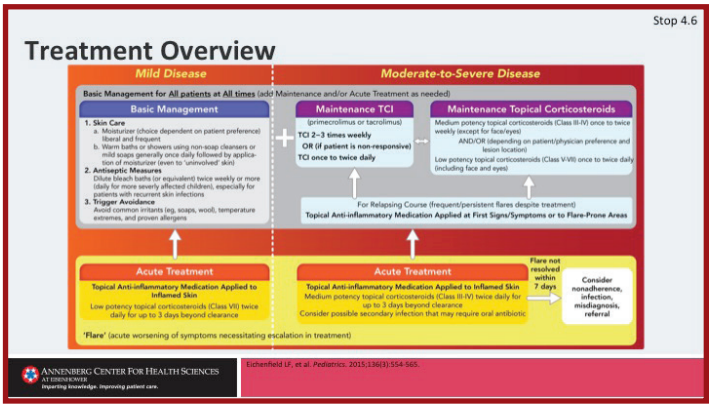
Patient education regarding the disease state is another thing that has been promoted. And you can educate the patient and the family. You can have atopic dermatitis schools for patients. These educational programs can educate patients about the chronic nature of the disease, that we are not going to cure them, that they are going to need to look out for exacerbating factors, they are going to need to know about ongoing management to keep their condition under good control.

These educational programs can educate patients about skin care technique. Critically important, they can provide written educational plans because these treatments that we've discussed get pretty complicated. And if you don't give it in writing it's like not giving it at all.

I had a patient who, the mother, it was a young patient, a year-and-a-half-old, who'd failed treatment from a previous dermatologist, had terrible atopic dermatitis. The child's skin was dry all over. I asked mom, "What are you bathing the child with?" And she mentioned Ivory soap that she was using.

And I said, "Is that what the previous dermatologist recommended." And she said, "Yes. The previous dermatologist recommended Dove or Ivory." I'm quite certain the previous dermatologist probably recommended Dove, not Ivory, but the patient, the mother, just didn't remember that. You know, she's in the office, things are stressful. You have to give information in writing if you want patients to remember it.

The education programs are important because of the impact of the disease not just on the patient, but on the entire family, with sleep disturbance in the patient affecting sleep disturbance in the family. And even just, for example in children, the parental concern that they are good parents when their child is suffering.



When you add up the guidelines, you can put it all into a chart like this. There is basic management with basic skincare that includes information on moisturizers, and how to bathe, antiseptic measures, trigger avoidance. In the acute phase, you're going to use topical corticosteroids. And then, there is a maintenance phase where you might use topical calcineurin inhibitors or intermittent use of the topical corticosteroids.

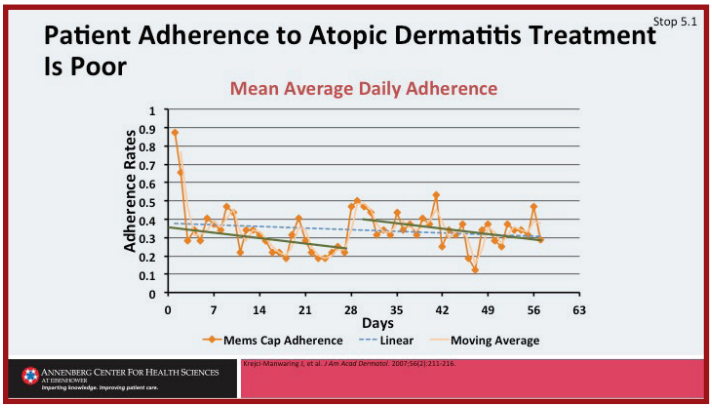
Explain to patients what to do when their disease is quiescent, and when their disease is flaring. And if those things aren't working, then some dermatologists might recommend sauna suits or wet wraps, and possibly methotrexate or cyclosporine. And the treatment gets to be complicated. And the bottom line is that it's hard to get patients to do even simple things.

Module 5: Patient Adherence

Steven R. Feldman, MD: Some years ago, I once proposed to the Human Subjects Committee at my university, that they allow me to do a study where we would take children who have atopic dermatitis and give them triamcinolone in a bottle fitted with a medication bottle cap that contained computer chips that would record the day and time they opened and closed the bottle, so that we could see when they were using the medicine.

I wanted to know what real-life patients did. I asked the Human Subjects Committee to let me do this without telling the children who had the atopic dermatitis, or the parent, that they were even in a study. Because I didn't want to know the behavior of study patients, I wanted to know the behavior of real-life patients. And if I told them they were in a study, it potentially could change their behavior.

When I proposed this to the Human Subjects Committee, the Human Subjects Committee said, "Go ahead. Do it." Fastest study I ever had approved. They didn't even have a single change to the consent form because there was no consent form. And in this graph we see what real-life patients do with triamcinolone when you give it to them.



The medication is applied pretty well the first day you give patients the medicine. And then, within about 3 days, their use of the medicine's dropping like a rock, down by about 70%. Now it continues to go down after that. And then at day 28 something strange happens. We bring them back for a 1-month return follow-up visit, the 4-week follow-up visit, and their use of the medicine jumps up again. And then it starts going down again.

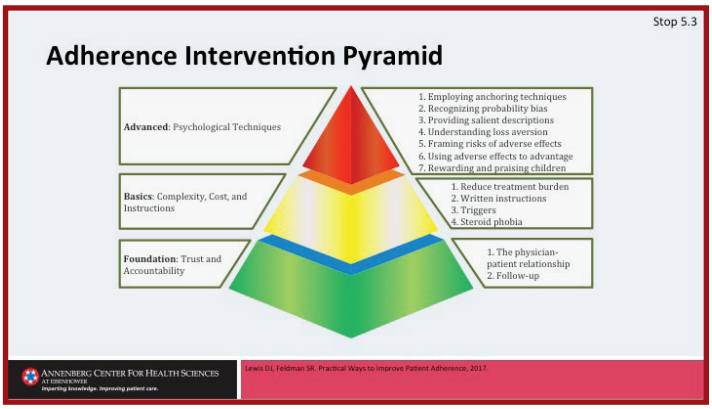
I know that despite what you may have heard, mothers everywhere love their children. All right. You know mothers love their children. But despite that, you cannot count on them to use the medicine on their child. Now this study, we just gave them one simple thing to do, the triamcinolone. We didn't tell them how to bathe. We didn't tell them about bleach, how to moisturize. We just gave them one thing to do and still they don't do it well.

Another thing we learned from this study is that the timing of the return visit has a profound effect on patient's use of the medicine. If I want to get patients to use the medicine well that first week, I don't wait a month to do a return visit.

Why are patients not using the medicine? Most of the focus on trying to learn why patients don't use the medicine have focused on the patients and the reasons they don't use the medicines. That they may be poorly motivated, or they may not trust their doctor, or they may be afraid of the medicine, they may be forgetful.

I like to think of it a little differently, since I don't control patients directly. I only control myself. It's kind of like a Vietnamese philosopher once said, "When the lettuce is not growing well, you don't blame the lettuce. You look at what you can control. You could give the lettuce more light. You can give it more or less water or fertilizer, but you don't blame the lettuce."

When patients are not adherent, it doesn't help to blame the patients. It's only what we can control. It's not that the patients aren't motivated, the question is, did we do enough to motivate the patient? Did we act in such a way that the patient trusts us? Did we reassure them adequately about the medication? Did we build in enough reminder systems? These are all things that we can do.



I like to think of it now as a pyramid. The foundation of getting patients to use the medicine consists of 2 things. Do patients trust us? And do we hold the patient accountable? Without these 2 things, nothing else is going to work. You have to have that foundation in place.

Next, there are basic things that you can do—basic strategies—the usual strategies that people talk about. Like addressing steroid phobia, the triggers, the cost of the medications, written instructions, keeping the treatment simple. All of those things are important. but if the patient doesn't trust us, they may never fill the prescription. If we don't hold them accountable, they may not use the medication, even if we do these other things.

And then, at the top of the pyramid, I like to think of advanced psychological approaches that we can use to get people to use the medication better. Just to prove to you the importance of the foundation, let's just consider piano lessons, for a moment. You know, my kids took piano lessons. The piano teacher gave them some sheet music, had a lesson with the kids once a week, and told the kids, "Practice every day. I will see you at the recital in 8 to 12 weeks."

And the recital sounded pretty good. My kids sounded good. All the kids sounded good. And I believe the reason the kids sound good, they play well because they've been practicing every week. That is what makes them play well. You know, if a new piano teacher said, "Listen, the process that we've used in the past with all these lessons is inefficient. We don't need the lessons. I'm going to give you the sheet music. I want you to practice every day. We won't have weekly lessons. Just practice every day. Practicing is what makes you sound good. I want you to practice every day. I will see you at the recital in 8 to 12 weeks."

We all know that recital would sound miserable because the kids won't practice, because nobody's holding them accountable to practice if you don't have the weekly lessons. The weekly lessons are essential to get people to practice every day. Nobody tells anybody, "Do this every day and I will see you in 8 to 12 weeks," except doctors. Our system is insane. Are we like a piano teacher who gives people the sheet music and tells them, "Practice every day, see you in 8 to 12 weeks?" Not exactly.

We are worse. We are more like a piano teacher who says, "Here's a prescription for some sheet music. Take it to the sheet music store. I have no idea what it's going to cost you. Get the prescription filled. I want you to practice every day. Practicing could cause some side effects, maybe thinning of the skin, maybe rashes, sometimes diarrhea, serious infection. But I want you to practice every day. I will see you at the recital in 8 to 12 weeks. And if things don't sound good, well then, we'll switch to a new musical instrument or something."

In that scenario, all the other things that we are taught to do to get people to use medications, like if the piano teacher without weekly lessons gave written instructions, gave a reminder system, you know, motivated people to practice, I still don't think they would practice. You have to have the foundation in place along with these other factors.

I will share with you my favorite one of these advanced psychological techniques, is just reducing the perception of burden by anchoring patients on something worse first. You know I would do this with injectable medications by telling patients, "I got a great medicine for you. It's very safe, very effective, but you have to take injection medicines once a day. Um, uh, shoot. Did I just say once a day? Uh, no, no, no. I . . . I'm sorry. You don't have to do this once a day. You only have to do it every 2 weeks."

If you tell somebody who's never been on shots, "You got to take a shot every 2 weeks," they are not sure they want to do it. If you accidentally say, "Do it every day," first, and then tell them every 2 weeks, every 2 weeks seems like nothing. Similarly, if I want mom to put triamcinolone on her child twice a day I tell her, "Let's do this 4 times a day."

"We'll have you do it before school. We'll get the school nurse to do it once around lunch time. I will have you do it once after school, and then once at bedtime." "You know, that is probably too much. I don't, that is a lot. Let us do it twice a day, say before school and at bedtime." this is an easy way to make the treatments seem much less burdensome to patients.

Reminder systems sometimes get confused with accountability. Reminding patients to do things is not the same as holding them accountable. And, we tested reminders in our acne patients. We gave acne patients a once-a-day topical medicine to use, with computer chips in the cap that would record whether they used it.

We divided them into 4 groups. Group number 1, shown in black, we bring them back at 6 weeks and 12 weeks, and they don't use the medicine well. Group number 2, we hold them accountable by bringing them back at weeks 1, 2, 4, 6, 8, and 12, like they do in research studies. In research studies they hold the patients accountable for using the medicine. And that does improve the use of the medication.

This also explains why medicines work well in the studies, and then in real life, they don't work as well as they did in the studies because we don't tend to have as many return visits as they do in the studies. The third group, we call the children up every day because we didn't know how to text them at the time. And that didn't seem to help.

But the fourth group, we called their parents up every day and we told the parents, "Don't forget. Remind your child to use the medicine." And as you can see, in this teenage population, that group of teenagers

used the medicine less than all the others. A reminder is very different, and not necessarily nearly as effective as holding people accountable.

Let me share with you my specific, basic strategies to promote adherence. Number 1, make sure you act in such a way that the patient trusts you and you hold them accountable. Then, simplify the treatment. You know, I believe all this talk about moisturizers and bathing and topical calcineurin inhibitors is well and good, but if you make the treatment too complicated it's not going to work.

I know that topical triamcinolone works because if I took a patient with the worst total body atopic dermatitis, and it was refractory to everything, and admit them to hospital and put triamcinolone on them in hospital, they'll clear up in just 2 or 3 days. A simple treatment regimen may be the best treatment regimen.

If I want people to use multiple things, if there are combination products, I kind of like that. They want to be like other teenagers. If I am prescribing therapy to a teenager with atopic dermatitis, I will tell them, "This is the medication most teenagers are using for their atopic dermatitis."

If mom is concerned about risks, and side effects of steroids, I just won't use the word steroid with her. She says to me, "Is this a steroid?" I say, "This is an all-natural, organic, gluten-free anti-inflammatory made in a nut-free facility here in America. The immune system is out of balance in atopic dermatitis, and this medicine will bring the immune system back into balance and harmony, because I like to take a holistic approach to the management of atopic dermatitis in children."

I try to remember to give all the advice I want patients to know, in writing. And then you might think I bring the patient back for a return visit, shortly after starting therapy. And I don't do that. I tell them, the patient, "You know, I want to know how this works. It should work quickly. I will see you back in 1 week." And then I say, "No, then you'd have to miss school or work, you'd have another copay. Let me write down my cell phone number for you. You call me in a week. Or, using the electronic patient portals we have with our records system, send me a message through the electronic portal in 1 week and let me know how this is working."

Or for a patient who's highly refractory, which means they are very likely nonadherent to treatment, I will tell them, "Send me the message in 3 days," because I want to force them to fill that prescription. I want to get them to use the medicine and get in the habit of using it. By seeing that it works, they get positive reinforcement. And they see a good response, then they know they can clear their disease, when they need to, with the medication.

Jonathan, do you have any other thoughts on basic atopic dermatitis management that we should discuss?

Jonathan I. Silverberg, MD: Adherence is definitely a major issue. Tolerability and the elegance of the topicals that we recommend certainly impact things. But I always tell patients, "If I can't remember to put a medication on twice a day, I have a very hard time recommending to you to put it on twice a day." I try to find ways of simplifying, going to a once-daily regimen, or even less, if possible. But it's not always possible with our available treatment options.

Steven R. Feldman, MD: We are running into a balancing act here. We want the patients to do many, many different things for atopic dermatitis. And if they did it, it might be great for their disease. But at the same time, in the yin and yang of this, the more things we give them to do, the more difficult it is to get them to do it.

Module 6: Optimal Use of Topical Treatments

Steven R. Feldman, MD: In this module we review the efficacy and safety of topical treatments, particularly those with extensive evidence supporting their use, such as topical corticosteroids, topical calcineurin inhibitors, and crisaborole. We also briefly discuss those little or conflicting evidence related to their use in atopic dermatitis.

In this case scenario, we have Anita, a 6-year-old female, diagnosed at age 11 months with atopic dermatitis, primarily involving her forearms and lower legs. Her current treatment includes daily bathing, followed by emollients 1 to 2 times a day, dilute bleach baths once or twice a week, or at least that is allegedly what she's doing.

Upon questioning, Anita reports that her pruritus, her itching, has not improved and is sometimes unbearable when she plays outdoors. She also said it is sometimes difficult to fall asleep. On physical exam there is moderate erythema with numerous excoriations noticed on the neck, arms, and legs. There is no sign of infection. Let's talk about how we would treat a patient like this.

Jonathan I. Silverberg, MD: This is a scenario where we think about moving beyond some of the conservative approaches and we start thinking about our prescription options. Topical corticosteroids are our mainstay today in terms of pharmacological interventions.

Topical corticosteroids are quite effective both to treat the active inflammation, really that idea of reactive therapy and treating an active flare, as well as disease prophylaxis. This idea of proactive treatment and prevention of flare-ups in patients who are prone to those.

For acute treatment, one can use intermediate- or high-potency topical corticosteroids. For prophylaxis, in truth, one can use lower frequency of medium and higher potency topical steroids as well, but often we'll use lower potency corticosteroids to try to reduce the potential for adverse events in those patients.

Frequency is what differs, depending on the approach. When you're treating the acute inflammatory process or the reactive approach, twice-daily application is the general approach. For proactive maintenance, we would typically say once or twice a week on those areas prone to flaring, in order to reduce flairs. On occasion, we can use even 3 times a week for shorter bursts. But once you start crossing beyond the twice-weekly, long-term use, you do run into that potential risk of steroid atrophy.

How much quantity should be put on? Often patients either are counseled, or at least they think that the way to put this on is to take nanogram size amounts and rubbing it in to the point where even a microscope could barely find it. And, in fact, we know that the appropriate quantity and guidance that we should give is the fingertip unit. One fingertip unit of topical corticosteroid would be appropriate for a surface area equivalent to about 2 palms' worth. That is an important aspect. They need to apply appropriate quantities.

We have caution around areas of thin skin, and any part of the body with long-term use. In terms of the adverse events, the things that we are concerned about are mostly local in terms of acneiform or rosacea-like eruptions, potentially focal hypertrichosis.

And then those issues around steroid atrophy or thinning of the skin where one may see more translucence of the skin, striae, greater perception of telangiectasias, and purpura, etc. And we believe that it's fairly rare that systemic adverse events happen. Although some of the older data has suggested that you may have a transient adrenal axis suppression. But it doesn't seem to be a long-standing issue very commonly.

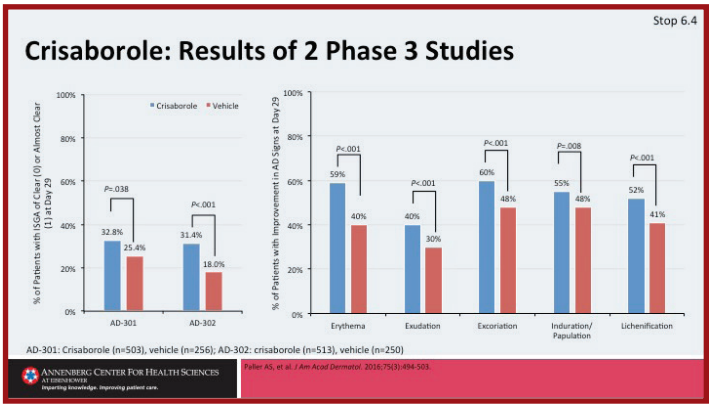
Then we have our calcineurin inhibitors, (that) are non-steroid, but in many respects are very similar in terms of efficacy or what we would expect with a steroid. They are approved for both acute flairs and maintenance therapy in adults and children ages 2 and up. In Europe, they are approved for maintenance, specifically as part of their indication. In the US, it is approved for the acute flairs, but we have lots of data to show that they work well for prevention as well.

These can be used in combination with topical corticosteroids. They can be used on sensitive skin areas while topical corticosteroids are used on other parts of the body. They can be mixed and matched. They can be used as monotherapy. A lot of flexibility here because you don't have those steroid side effects, and because this would be a good steroid-sparing option for patients.

Frequency of use is similar to the corticosteroids, twice daily application for treatment of acute flairs. Two to 3 times a week for proactive maintenance. And here we can often use a little more frequently during the week for maintenance than the corticosteroids, again because we are not worried about the thinning of the skin. The adverse events here are just local, application site reactions, burning, stinging, or itch, which often is transient, but does come up quite a bit and for some patients can be more persistent.

Systemic side effects are thought to be quite rare. We don't recommend any kind of blood monitoring for these patients. And, of course, there is a component of education required for patients with respect to the boxed warning. It is a theoretical black box warning around malignancy, although the manufacturers of both of the topical calcineurin inhibitors have done 10-year post-marketing registries that have shown absolutely no signal for malignancy. It is still something that patients are concerned about, and one that we do need to educate them about, and it takes a little more time.

Our newest kid on the block, topically, is crisaborole, which is a topical phosphodiesterase-4 inhibitor. There were several phase 1, phase 2 studies, but these are the results of 2 identical phase 3 studies done in children and adults with mild-to-moderate atopic dermatitis. And the primary efficacy endpoint for these patients is the proportion of patients who achieved this investigator static global assessment score of clear or almost clear, essentially looking at representative areas and saying have they achieved clear skin.



In both studies, there was statistical significance in the crisaborole group compared to the vehicle group, although you do see substantial vehicle effects, likely because it is a thick, emolliating vehicle in that sense. When looking at the individual signs, one sees statistically significant improvement across all of the individual signs that were examined, erythema, exudation, excoriation, lichenification, induration, papulation.

This is one that is now FDA-approved for mild-to-moderate atopic dermatitis in children and adults.

Safety-wise, we have relatively a well-tolerated and a pretty clean safety profile, although the issue that came up in the studies was treatment-related burning and stinging, which was more common in the crisaborole group than in the vehicle group. Anecdotally, in the real world, we see more burning than in 4% of patients treated, but the question is how commonly in the real world we are seeing this. We still have to sort that out with real-world pharmacovigilance data.

Crisaborole Safety

Adverse Event*	Crisaborole (n=1012)	Vehicle (n=499)	*P*
Treatment-related burning and stinging	4.4%	1.2%	0.001
Infections and infestations	11.7	11.8	–
Gastrointestinal disorders	2.7	2.4	–
Respiratory, thoracic, and mediastinal disorders	4.6	3.0	–
Application site pain	4.4	1.2	0.001
Skin and subcutaneous tissue disorders	3.7	4.2	–
Nervous system disorders	1.4	0.4	–

*Treatment-emergent adverse evens (≥1% of patients)

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Paller AS, et al. *J Am Acad Dermatol.* 2016;75(3):494-503.

The other adverse events that showed up above that 1% threshold were no differences, other than application site pain and stinging and burning, there were no differences between crisaborole and vehicle that came up, or any statistically significant differences. The one you want to counsel your patients on is that this may sting and burn, and that could limit their tolerability, their ability to use it.

There are many other treatments that have been tried over the ages for atopic dermatitis.

Wet wrap therapy is a very effective treatment and one that can be used with topical corticosteroids. There are many different versions of wet wrap therapy that have been applied, ranging from the soak and smear done in the outpatient setting, to using sauna suits, to the classical wet wrap therapy where patients are just wrapped from head to toe in Kerlix in the inpatient setting.

Concerns about this is that you're using it on a more extensive body surface area. There certainly is a concern about potentially getting more systemic absorption. And then, of course, the cutaneous side effects may be more pronounced in terms of potentially getting folliculitis or secondary infections and things like that.

Bleach bath has been used quite widely in the pediatric dermatology realm, although a recent systematic review and meta-analysis found that bleach baths are actually no more effective than just taking a straight water bathe without the bleach. We still need a lot more studies to truly demonstrate the evidence around this and maybe the subsets of patients that would do well.

Some will commonly use either topical or oral antihistamines for patients with atopic dermatitis. These are actually not recommended in our guidelines because the potential for adverse events and there are no demonstrable efficacy for itch and for the inflammation in the disease.

Coal tar has been used, but there are concerns about possible carcinogenic effects. Investigation is ongoing to identify the ingredients in coal tar that contribute to its effectiveness.

How to optimize topical care? And some anecdotal experiences. Well, topical treatment can be extraordinarily effective. And I completely agree with Steve that adherence is absolutely crucial. It's something that is very hard for patients to build into their lifestyle. We are getting busier and busier by the minute.

It's hard for people to build in, especially when they are traveling. There is a premium on keeping things simple. One thing that I often will do is actually use a higher potency agent, recognizing that patients may do well with lower frequency of use. That may be a little bit more feasible for them.

But just trying to instill good practices at each encounter. Reinforcing those best practices. But we always have those challenging patients, those difficult ones where we do think they are adherent, and they may be the exception. And they don't do as well as we would hope. Or it's just not possible for them.

I have elderly patients that they are never going to clear their back, because they just can't put it on their back, no matter how they try. And we've tried creative strategies. That is a scenario where sometimes they do need to be admitted to the hospital for a quick admission for wet wrap therapy. Or where we start thinking about stepping up therapy to systemic agents because as much as they are coming with potential for adverse events, they are more feasible for the patient to be able to stick with on a daily basis.

Another scenario that comes up is, for many patients where they truly are adherent, and they do remarkably well, when they tend to have more persistent, chronic disease. As long as they are on the steroids they do well, but at some point, when they stop because there is concern about adverse events, they may go right back to square one. That is where we certainly have to start thinking about the appropriate use of nonsteroidal agents or steroid-sparing agents as well.

Steve, in terms of your cases that you see, and you're working very carefully on adherence, do you still use hospitalization for wet wrap therapy a lot? Or do you typically step up more towards some of the either older-fashion systemic therapies or the newer ones that are available now?

Steven R. Feldman: I cannot remember the last time I admitted somebody to the hospital for atopic dermatitis, now that we have the array of systemic options that we have. That may be a good next topic for us to discuss. The patient that we started with was a 6-year-old child who'd had nearly lifelong atopic dermatitis, was reported doing the bathing and was having insufferable itching. What would be the basic things to do for her?

Jonathan I. Silverberg, MD: If she truly is adherent with these approaches, the next step would be to step up to prescription topical therapy. Then, we have to decide, based on the areas of involvement, past response, if she's used any of these prescription treatments in the past.

Here's a scenario where a low- to mid-potency topical corticosteroid might work quite well and be relatively cheap and effective, and accessible for the patient and their family to do. But, of course, emphasizing the importance of proper frequency of use, proper adherence, and making sure that mom and patient understand those concepts so that they get optimal outcomes.

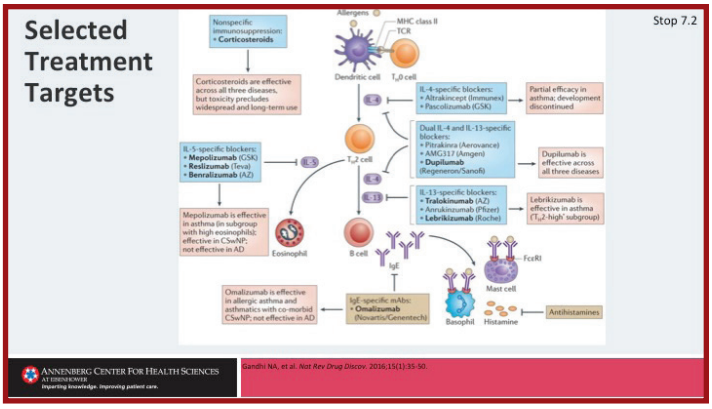
Module 7: Optimal Use of Systemic Treatments

Jonathan I. Silverberg, MD: In this module we will review the efficacy and safety of medications with extensive evidence to support their use in atopic dermatitis, such as systemic immunosuppressants, dupilumab, and phototherapy. We will also briefly discuss those with little or conflicting evidence relating to their use in atopic dermatitis.

Phil is a 20-year-old male with a 4-year history of atopic dermatitis. He's being referred by his primary care physician for worsening symptoms. Although he has done his best to identify and minimize his triggers, his atopic dermatitis has worsened since he began attending college and living in a dormitory.

He is diagnosed with moderate atopic dermatitis, and an IGA score of moderate lesions with a body surface area affected of 12%. And his current treatment approach is he's using daily bathing with twice daily moisturizer. He's also using twice daily crisaborole. Steve, why don't you take us through the different treatment targets and options that are available for us.

Steven R. Feldman, MD: Topical therapies are highly effective for atopic dermatitis. But when you have extensive disease, they are just not practical. And treating all of the skin at once with a systemic agent or phototherapy makes sense. With our understanding of the immune system, we have clearly a lot of options. The topical corticosteroids affect all kinds of pathways.



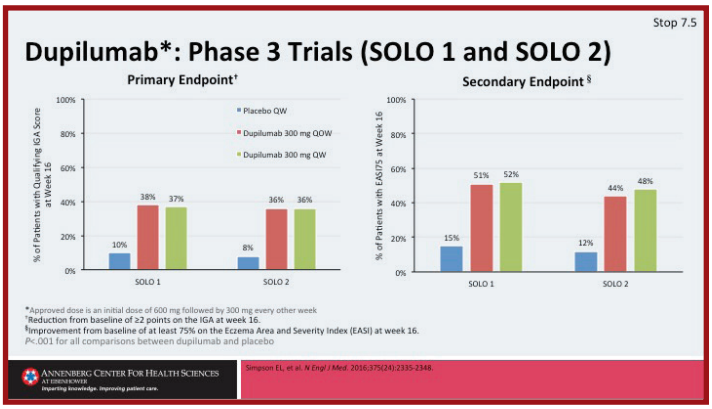
The cytokines, now we know several of them that are involved with atopic dermatitis, and we can either seek to block them directly or block their receptor. We can move on and look at what effect might we get with blocking the IgE at the end of this T-helper 2 pathway.

For patients who've had extensive atopic dermatitis, we can use systemic immunosuppressants, small molecule ones like cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine. These were things that we used more extensively before newer, more effective, safer options have been discussed. And there are no specific recommendations regarding optimal dosing.

I use so much methotrexate in psoriasis that I just sort of use my expertise with psoriasis use to give patients methotrexate for their atopic dermatitis in a very similar way. These drugs can have a lot of adverse events, and there is close monitoring, particularly with methotrexate, that we are monitoring the blood counts and the liver enzymes, to make sure we are not causing a serious problem, would be critical.

Although systemic corticosteroids are widely used for atopic dermatitis, existing evidence does not support their use. Thus, they are to be avoided, particularly in children and for long-term use. A systemic corticosteroid might be appropriate as bridge therapy where rapid control of symptoms is needed.

The real advance that has happened in my lifetime in the management of atopic dermatitis has been dupilumab, which blocks the receptor for both interleukin-4 and interleukin-13. In phase 3 studies, they looked at the percentage of patients who achieved



at least a 2-grade improvement in their Investigator Global Assessment, and you see nearly 40% of patients are reaching that level of success.

That is a high level of success. It underestimates the true clinical benefit of the drug, as we'll discuss. Improvements of 75% on an EASI score, an Eczema Area and Severity Index score, was achieved by a higher number of patients. Another reason this underestimates what we see in clinical practice is because this is a monotherapy study. We are not giving people topical corticosteroids to say use on their worse, more lichenified lesions. And if we did, we would see even much greater improvement.

In the dupilumab phase 3 trials there was greater improvement with dupilumab compared to placebo regarding the itching, the sleep, and the anxiety and depression, quality of life as well. In the study, rescue medication was used by a certain fraction of patients. In the dupilumab group, it was only about 20% of patients.

What that means is that if you give somebody dupilumab, 80% of them are going to do well enough that they wouldn't need a rescue medicine. And in real life, there is no rule against giving people rescue medicines like topical corticosteroids and other options. In clinical practice it's been our experience that the efficacy rate is very, very high for the use of dupilumab in patients with atopic dermatitis.

Adverse events where recorded. And you can look at the serious adverse events and see that looks like it might be even a little less than placebo. We often find serious adverse event rates with really effective treatment that are less than the placebo group.

Dupilumab*: Phase 3 Trials (SOLO 1 and SOLO 2) (cont)

Adverse Event, %	SOLO1			SOLO 2		
	Placebo (n=222)	Dupilumab QOW (n=229)	Dupilumab QW (n=218)	Placebo (n=234)	Dupilumab QOW (n=236)	Dupilumab QW (n=237)
≥1 AE	65	73	69	72	65	66
≥1 Serious AE	5	3	1	6	2	3
Injection site reaction	6	8	19	6	14	13
AD exacerbation	30	13	10	35	14	16
Headache	6	9	5	5	8	9
Allergic conjunctivitis	1	5	3	1	1	1
Conjunctivitis	1	5	3	<1	4	4
Nasopharyngitis	8	10	11	9	8	8
Non-skin infection	22	30	31	24	25	26

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*Approved dose is an initial dose of 600 mg followed by 300 mg every other week
Simpson EL, et al. *N Engl J Med*. 2016;375(24):2335-2348.

What's happening in that situation is that when patients are doing well on a drug in a clinical trial they don't want to stop. And they may not be as quick to report adverse events as people in the placebo group who are still suffering.

Injection site reactions were more common than with placebo, but that is really about it. You do see a low rate of conjunctivitis, maybe something like 1 in every 10 or 20 patients having some kind of conjunctivitis.

Phototherapy is another option for patients with extensive atopic dermatitis that doesn't get better with topicals alone. You can use narrowband UVB, you can use various forms of UVA, with or without psoralen. The psoralen plus UVA you might use in a patient who had severe, widespread, refractory atopic dermatitis. But nowadays, I find myself doing little to no PUVA because I have other good options available, both in psoriasis and atopic dermatitis.

The potential adverse effects of phototherapy include, acutely, a sunburn reaction; long-term, perhaps there might be some increased risk of skin cancer. But people's faces get so much light over their lifetime that you can probably give a fair amount of light to their body without them ever reaching the levels of UV that their face has been exposed to.

The use of other systemic therapies is quite limited. You can give people a sedating oral antihistamine if you want to help them sleep, but other antihistamines are not particularly effective in atopic dermatitis. There is good evidence against the use of non-sedating antihistamines.

Antimicrobials should not be used unless there is infection. If there is infection, go ahead and give an appropriate antibiotic. Vitamin D, I guess, could be given if somebody has low vitamin D, but I don't know that it's of any particular strong effect for atopic dermatitis. And other treatments, I don't think there is much, if any, evidence.

Jonathan, we started with a 20-year-old with extensive disease refractory to topical therapy. Giving this patient a systemic or phototherapy seems to me to be a completely appropriate approach., I would be very quick to give patients dupilumab in a situation like this. What are your thoughts?

Jonathan I. Silverberg, MD: I agree. There is, of course, access and insurance issues that have to be navigated in the real world. But when those are not issues, this would be a good candidate for dupilumab, and, for that matter, for pretty much any other systemic agent if we couldn't get access to it.

There are probably opportunities to optimize topical therapy a little bit more. But, as you described, at some point it just becomes not feasible. And the combination therapy approach, here, of optimizing topical therapy a little bit more, as well as a systemic agent, it makes a lot of sense.

Steven R. Feldman, MD: I imagine you've had a lot of experience with dupilumab. And you look at these efficacy rates of roughly 40%, maybe, give or take, in the clinical trial. Is your experience that only 40% of patients do well on the drug?

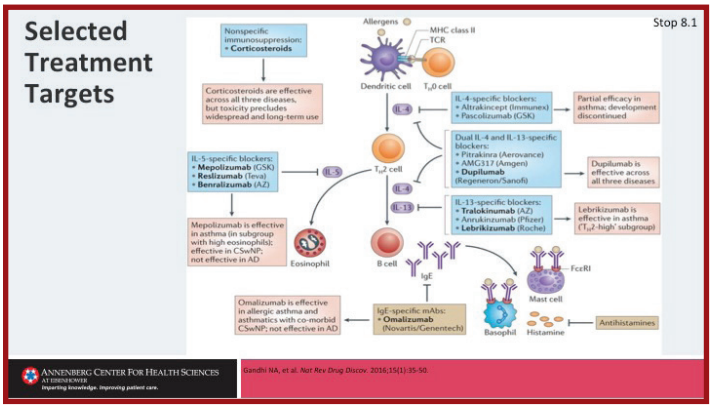
Jonathan I. Silverberg, MD: The numbers are pretty correct, but you have to know how to interpret them in the sense that, the other 60% are by no means non-

responders. I view the 40% as being super responders. Those patients who just do phenomenally well that they may use topicals never, or fairly rarely.

Whereas the other patients, the majority of them are doing quite well, but they may need to use topicals a little bit more. They may do very well, but they may not get 100% clear. It is important to have patients have realistic expectations in this respect, that some will get just complete clearance, and others will maybe not completely clear, but do just fantastic. But they still have some active spots. The numbers are valid, it's just you have to know how to interpret some of these trial outcomes.

Module 8: Emerging Therapies for Moderate/Severe Atopic Dermatitis

Jonathan I. Silverberg, MD: In this module, we will review the key treatment targets based on our improved understanding of the pathophysiology of atopic dermatitis. And we'll focus on the medications that are in later stage, phase 2 and phase 3 development that will target these mechanisms.



In terms of selected treatment targets, and we touched upon some of these already, what pathways we think are super important in atopic dermatitis, in the pathogenesis, would be those T-helper 2 cells. And we've already discussed the role of interleukin-4 and -13. We actually have new agents that are in development, that are selectively targeting simply the interleukin-13 part of the equation and don't go after the interleukin-4.

We have a number of other pathways that have been implicated as well. Some have suggested that interleukin-5 is an important pathway because we know that eosinophils are present in the skin and certainly that histologic pattern we see, spongiotic dermatitis with eosinophils, but (there are) some questions. Is it really pathogenic or sort of more of an epiphenomenon than anything else? Then there are a number of other pathways, as well, that have been implicated in terms of innate immunity and cell-mediated immunity pathways, that have been implicated.

Those agents which are currently investigational status in phase 2 or phase 3, we have the oral agents, the small-molecule JAK, Janus kinase inhibitors, or JAK inhibitors. And these are working at the intracellular level because those JAK pathways really lie inside the cell as the downstream signaling cascades for many of these different cytokine pathways that have been shown to be at least implicated or important in atopic dermatitis.

And we have a variety of different agents. The ones that are farthest along right now for the systemic development in atopic dermatitis, would be baricitinib, upadacitinib, and PF-04965842. These are oral agents right now being studied for atopic dermatitis.

Tofacitinib had some data for mild-to-moderate atopic dermatitis in some case series, but I don't believe it's being developed commercially for atopic dermatitis. We have topical delgocitinib, which is being studied now for atopic dermatitis, as well.

When we look at the specific cytokine targets, we have 2 agents, that are being studied right now for targeting interleukin-13 by itself. And those are lebrikizumab and tralokinumab. Each binds slightly differently in terms of how it blocks the interleukin-13. We also have interleukin-17 blockers that have been studied. These should sound familiar to those of you who are familiar with the psoriasis story, and some have questioned whether or not these may or may not be effective also in atopic dermatitis.

We have also interleukin-31 receptor-alpha blocker, known as nemolizumab, which blocks the receptor for interleukin-31, which is thought to be the itch cytokine, but also has certain pro-inflammatory affects. And then, there is fezakinumab, which is being studied, or was studied, as a blocker for interleukin-22 for atopic dermatitis. Although it's not clear if that will go forward beyond those past studies.

And then we have a variety of other pathways as well. The neurokinin-1 receptor antagonists have

Selected Phase 2/3 Investigational Agents (cont)

Class/Target(s)	Agent(s)				
Janus kinase inhibitors	Baricitinib	Tofacitinib	Upadacitinib	PF-04965842	Delgocitinib
Anti-IL-13 mAb	Lebrikizumab	Tralokinumab			
Anti-IL-17 mAb	Secukinumab				
Anti-IL-22 mAb	Fezakinumab				
Anti-IL-31RA mAb	Nemolizumab				
NK-1 receptor antagonist	Tradipitant				
Anti-IgE	Ligelizumab	Omalizumab	MED14212		

Agents shown in red have published results of a phase 2/3 clinical trial for atopic dermatitis

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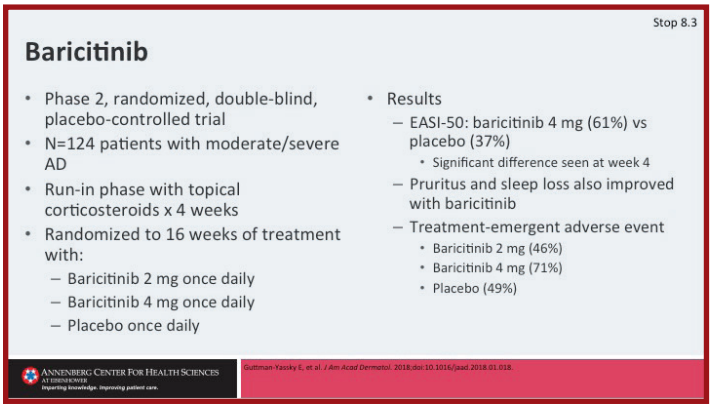
been studied as treatments, adjunctively, for itch in atopic dermatitis, and are an attractive pathway. You mentioned earlier the anti-IgE blockers that have been studied. Omalizumab, which has been examined, both in phase 3 studies and real world. Not shown to be very effective. And then also ligelizumab, which has been studied, as well, in phase 2.



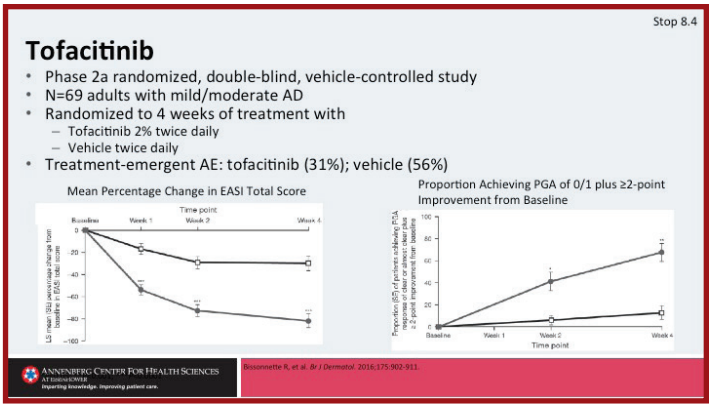
Let's talk about some of these in a little more depth. All right. Baricitinib is an oral agent. It is a more selective Janus kinase inhibitor. And it was studied in a phase 2, randomized, double-blind, placebo-controlled trial of 124 patients. And these are moderate-to-severe patients. It is not mild. These are moderate-to severe-patients.

In this particular study there was an active run-in with topical corticosteroids for 4 weeks. And that is very important for interpretation of the results because these patients, as far as we know, truly were adherent, or hopefully were adherent at least in the studies, and truly had refractoriness to topical therapy. And as we discussed, that doesn't always happen.

These patients, as far as we know, were using it in larger quantities and still didn't get a complete response. And then they were randomized into treatment with baricitinib in 2 different doses, of either 2 mg or 4 mg, or placebo, as a once-daily treatment. And what the study found was that there were significant improvements of a variety of endpoints. But 1 endpoint, the EASI 50, or a 50% improvement of the Eczema Area and Severity Index, was shown for baricitinib 4 mg compared to placebo.

Some significant differences were seen pretty early. And improvement also of itch and sleep loss, as well, with baricitinib. There were some treatment-emergent adverse events, but it is something we'll know more about with larger-scale studies. So, this is something that is being studied now in phase 3. And hopefully, we'll have some results soon.

Tofacitinib was studied in a phase 2A study. This was topically studied for patients with mild-to-moderate atopic dermatitis, where they were randomized to 4 weeks of treatment of topical tofacitinib as 2% twice daily, compared to vehicle. And found significant



improvements, actually some pretty substantial efficacy for a topical agent.

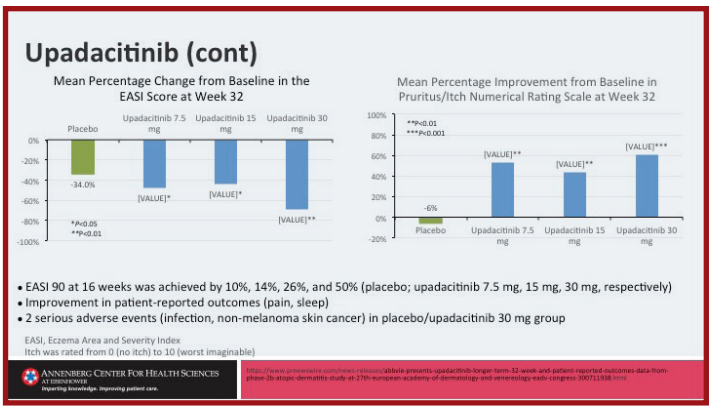
Keeping in mind this was a very different target population than what we were talking about with baricitinib, or what we discussed earlier about, with dupilumab. This is a milder patient population. But already by week 1 there were significant improvements, and those continued to improve and separate from vehicle by week 4.

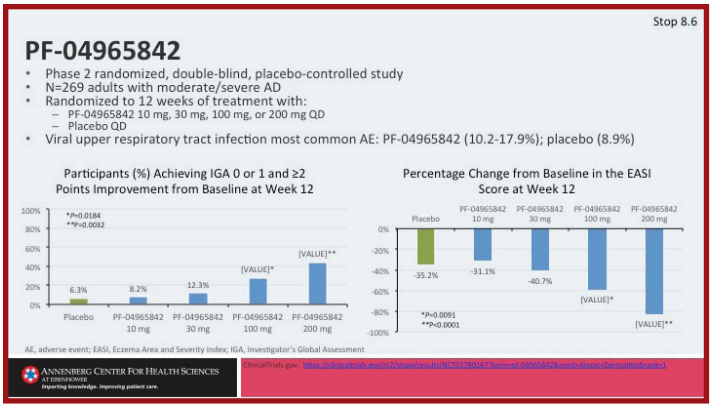
Significant improvements of the Eczema Area and Severity Index, IGA scores, pruritus scores, etc. This is one that has shown quite a bit of promise. Although, to my knowledge, I'm not aware of any future commercial development for this. So, this, if it will be used, it would be used as sort of an off-label compounded treatment for patients.

Upadacitinib is another oral selective JAK inhibitor also studied in a phase 2, randomized, double-blind, placebo-controlled trial looking at 67 adults with, again, moderate-to-severe atopic dermatitis. This was a little bit different, and that is why it is very difficult, almost impossible, to fully compare the results of this study with the baricitinib results because there were no topical steroids used in this study. There was no active run-in period with topical corticosteroids.

But at week 16, patients were also re-randomized. They were able to get access to the upadacitinib even if they had gotten placebo early on.

Really quite early, as well, in terms of the efficacy, it was demonstrated that there were significant improvements





of the Eczema Area and Severity Index, seen actually quite early, but continued out to week 32 as well.

A dose-dependent effect where the highest dose of upadacitinib of 30 mg was more robust in its efficacy compared to the lower doses. But all doses were more effective than placebo. And this pattern held up for a variety of different endpoints that were examined in terms of EASI 50, EASI 75, EASI 90—improvements of itch, patient-reported outcomes, etc.

There were some serious adverse events in terms of infection. But this is something that in order to understand that more, we are going to need larger-scale phase 3 studies to sort of elucidate that. Those studies are underway, and hopefully, we'll have readouts soon.

PF-04965842, similar to upadacitinib in terms of its selectivity, its mechanism, also studied as a phase 2, double-blind, placebo-controlled study in adults with moderate-to-severe disease. Also showing dose-dependent effects of efficacy in a variety of endpoints, the primary being the Investigators Global Assessment score of clear or almost clear, but significant improvements of the EASI score as well, again with that dose dependence. And similar efficacy seen for this particular molecule as was seen for the upadacitinib. We will need more studies to figure out how to distinguish between these 2, both efficacy and safety-wise.

Nemolizumab is the one that I mentioned blocks interleukin-31-receptor-alpha. This is blocking the signaling of interleukin-31, which is thought to be very important in the pathogenesis of itch in atopic dermatitis but may have some other inflammatory effects. This was studied in a phase 2, double-blind, placebo-controlled trial of 264 adults with moderate-to-severe atopic dermatitis and had inadequate control with topical therapy.

The dosing regimen here was a dose escalation but using a weight-based dosing strategy of different doses at every 4-week intervals. What they found was that there was a dose-dependent effect in terms of improvements of itch where the most efficacy appeared to occur with the intermediate dose, the 0.5 mg per kg dosing strategy for some endpoints.

Clearly, the 0.5 or the 2 mg per kg being more effective than the 0.1 mg per kg. And all doses being more effective than placebo. There were some adverse events that were observed, and we'll have to see more in future studies, and more studies are underway now.

Omalizumab is one that is FDA approved for chronic urticaria and has been studied for atopic dermatitis as well, but with very mixed results. There are several different meta-analyses that were performed, but with no compelling evidence to demonstrate the effectiveness of omalizumab for atopic dermatitis. Sometimes you talk to clinicians who will say anecdotally they have 1 patient here or there who does well. But certainly nothing for us to be able to say that this is going to be a reliably effective treatment across all patient subsets with atopic dermatitis.

There are adverse events that we are concerned about, particularly anaphylaxis, with omalizumab, and possibly cardiovascular events that we need to be thinking about for this drug. But it remains to be determined whether or not this might work in a subset of patients. But certainly not showing the same kind of consistent efficacy that we've seen with some of these other investigational agents in atopic dermatitis.

To summarize, there is a lot in terms of oral agents and small molecules. The JAK inhibitors seem to be the most promising, at least at this stage. And we are going to learn more and more about both their safety and efficacy. Some more selective Th2 blockers with interleukin-13-targeted agents. And we were excited to see what the results are there, how they compare with dupilumab—will they be better, or worse, the same?

There is a lot for us to still learn. And then nemolizumab is a whole new paradigm, targeting the itch and some inflammation in atopic dermatitis, and how well that will work, and how will that compare to other agents? And for now, it doesn't look like targeting IgE is the most effective approach. And we also have some data from ligelizumab that has shown, a very well-done study, but no efficacy at all for atopic dermatitis. Steve, any additional thoughts related to some of the things that are in the pipeline right now?

Steven R. Feldman, MD: I think of this kind of globally. That you have these patients who are suffering with atopic dermatitis. Even the mild disease is impacting people's lives. But the moderate-to-severe is horrible. Topical steroids can get a lot of patients under control, especially if we can figure out how to get the patients to use the drugs in a reliable way, because they'll work. But when you have this extensive involvement, they are just not practical. And while we have some advances we've seen so far, these new things coming down the pike are very attractive to me.

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