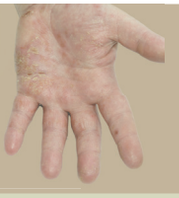
EXPERT perspectives

A Pathophysiologic Basis for Evidence-Based Treatment of Moderate-Severe Atopic Dermatitis



Overview

In this activity, Alan Fleischer, Jr, MD, and Lindsay Strowd, MD, discuss the evolution in targeted treatments for atopic dermatitis based on improved understanding of pathophysiologic mechanisms. Supported by patient vignettes, they provide strategies for assessing the patient disease burden and its importance in developing an individualized treatment plan. Suggestions for greater patient engagement and improved self-management are also provided. The role and use of evidence-based nonpharmacologic and pharmacologic therapies are reviewed, focusing on dupilumab, for moderate-severe atopic dermatitis.

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Learning Objectives

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

- Describe the current understanding of the pathophysiology of atopic dermatitis
- Conduct a thorough assessment, including differential diagnosis, to establish the diagnosis and severity of atopic dermatitis
- Develop treatment plans that address both symptoms and patient concerns
- Integrate evidence-based therapies for moderate-severe atopic dermatitis into treatment plans
- Identify and manage comorbidities of atopic dermatitis and treatment-related complications

Target Audience

This activity was developed for national audience (US) dermatologists, pediatric dermatologists, allergists, along with nurse practitioners and physician assistants within those specialties who manage patients with atopic dermatitis.

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Alan B. Fleischer, Jr, MD

Former Employee	AbbVie- clinical area: Atopic dermatitis, psoriasis
Consultant	Dermavant- clinical area: Atopic dermatitis
	Qurient- clinical area: Atopic dermatitis

Lindsay C. Strowd, MD, FAAD

Research Support	Galderma- clinical area: Atopic dermatitis
	Pfizer- clinical area: Atopic dermatitis
Consultant	Actelion- clinical area: Mycosis fungoides
	Sanofi- clinical area: Atopic dermatitis
	Regeneron- clinical area: Atopic dermatitis

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The following have no significant relationship to disclose:

Greg Scott, RPH, PharmD (medical writer)

Eugene Cullen, MD (peer reviewer)

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This activity was released on May 31, 2019 and is eligible for credit through May 30, 2020.

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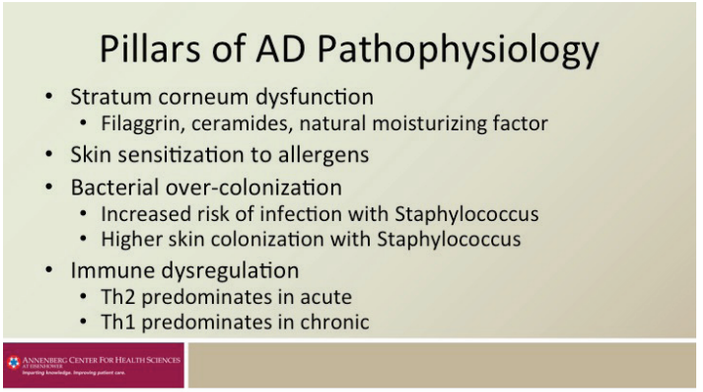
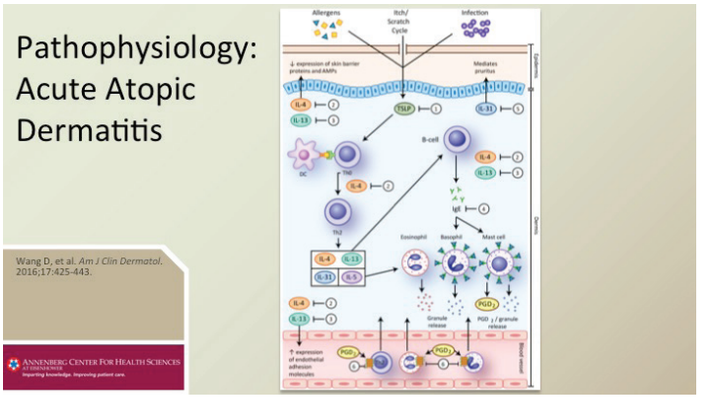
Pathophysiology

Alan Fleischer, MD: In this module we discuss key pathophysiologic mechanisms of atopic dermatitis such as barrier dysfunction, bacterial over-colonization and immune dysregulation. We'll also highlight some of the



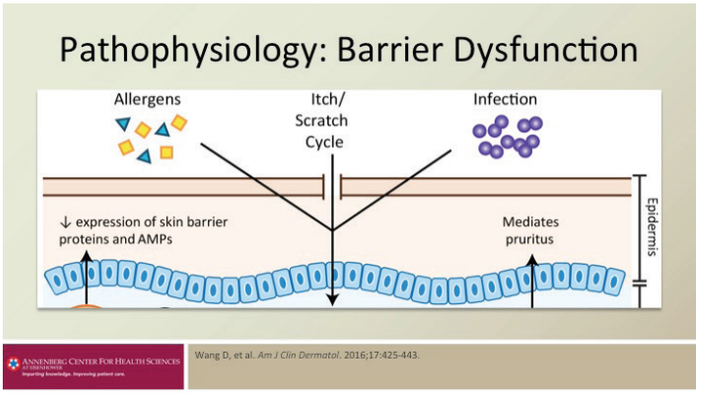
pathophysiologic mechanisms that serve as treatment targets. The pillars of atopic dermatitis pathophysiology include stratum corneum dysfunction, and this includes filaggrin, certain ceramides, and natural moisturizing factor among other active agents, skin sensitization to allergens, bacterial over-colonization, especially with staphylococcus, and there is high colonization with staphylococcus and the potential for super infection, as well as immune dysregulation. Th2 system seems to predominate in acute atopic dermatitis, whereas Th1 predominates in chronic atopic dermatitis.

Lindsay Strowd, MD: As we begin to talk about the pathophysiology of acute atopic dermatitis, this figure will illustrate the complexity of the pathophysiology of this disease. There is debate as to whether the inciting



initial event in atopic dermatitis comes from external allergens, also known as the outside-in hypothesis, or from initial primary immune dysregulation, also known as the inside-out hypothesis. Regardless of the initial event, we do know that both outside irritants and dermal inflammation create a cyclical and perpetuating pathway that ultimately results in the classic cutaneous findings and intense itch that we see in atopic dermatitis. In the next few slides, we will discuss this pathophysiologic diagram in more detail.

Let's start with barrier dysfunction. Normal skin has an intact lipophilic stratum corneum containing a mixture of dead keratinocytes, lipid molecules, and proteins. These function to provide a sound barrier between the epidermis and the outside world. In atopic dermatitis skin, this barrier



becomes damaged or dysfunctional, which allows external molecules to come in contact with the epidermis. These include cutaneous allergens found in the environment, as well as colonizing bacteria such as *Staphylococcus aureus*. Upon penetrance through the stratum corneum, these allergens and bacteria stimulate a Th2-mediated inflammatory process.

Some of the stratum corneum players include natural moisturizing factor, which acts in the stratum corneum to maintain normal skin pH and prevent transepidermal water loss. Natural moisturizing factors result from degradation of filaggrin protein, found in keratinocytes in the stratum granulosum.

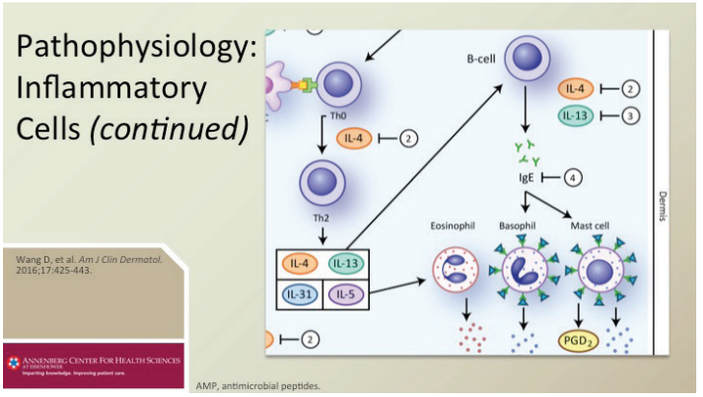
Some patients with atopic dermatitis have a mutation in the filaggrin gene, which results in decreased production of filaggrin and natural moisturizing factors. Other stratum corneum proteins that are decreased in atopic dermatitis include loricrin and involucrin.

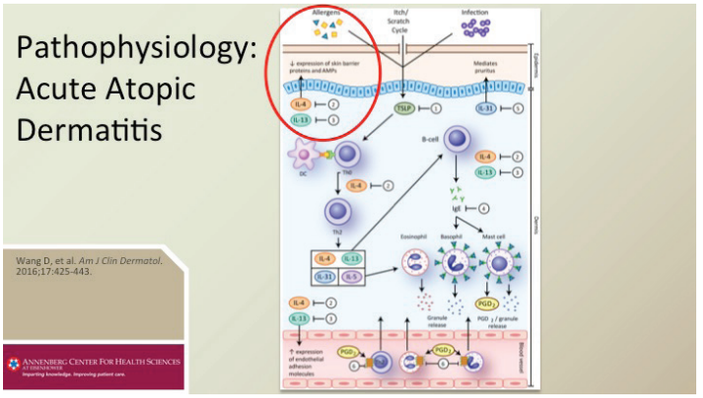
Studies have shown that atopic dermatitis patients with filaggrin mutation have increased *Staphylococcus aureus* colonization of their skin. The degree of this colonization can correlate with atopic dermatitis disease severity. Atopic dermatitis skin demonstrates decreased density of microbial pattern recognition receptors such as toll receptors. It also shows decreased expression of antimicrobial peptides, including cathelicidins and human beta-defensins.

External allergens, irritants and bacteria activate what is known as thymic stromal lymphoprotein, a type of cytokine, upon entrance into the epidermis. This is also called TSLP. TSLP stimulates dendritic cells to bind to naïve Th0 cells and mature them into Th2 cells. These mature and activated Th2 cells release a variety of pro-inflammatory cytokines, including interleukin-4, -13, -31, and -5.

Production and release of IL-4, IL-13, IL-31, and IL-5 results in further immune activation. IL-5 directly activates eosinophils, causing degranulation and release of eosinophilic granules. IL-4 and IL-13 activate B cells to produce IgE immunoglobulin. This IgE binds to receptors located on the surface of basophils and mast cells. IL-4 and IL-13 also travel to the cutaneous blood vessels and increase endothelial adhesion molecule activity, allowing for more immune cells to hone to the active atopic dermatitis skin. IL-4 also provides a positive feedback loop to naive Th0 cells causing more Th0 cells to differentiate into Th2 cells. IL-31 is thought to mediate pruritus in the epidermis.

Cytokines released by Th2 cells, including IL-4 and IL-13, further perpetuate the skin barrier dysfunction by directly decreasing expression of skin barrier proteins and antimicrobial peptides. This helps to perpetuate this





inflammatory cycle by allowing greater penetration of cutaneous allergens and bacteria to enter the epidermis.

We have discussed what happens in acute atopic dermatitis. Chronic atopic dermatitis lesions display a mix of Th1 and Th2 cells. Interleukin-22 is a cytokine that is released from Th17 and Th22 cells. It has a unique role in atopic dermatitis by mediating keratinocyte proliferation and epidermal hyperplasia. This suggests that a transition from Th17 to Th22 is associated with chronic disease. This may help differentiate atopic dermatitis from psoriasis and is an emerging target for treatment.

Alan Fleischer, MD: The pathophysiologic mechanisms on a molecular and cellular level are very complex. As well, there are a series of diseases associated with atopic dermatitis. Similar to other inflammatory skin diseases, atopic dermatitis can be associated with a series of comorbid diseases. Some of these share similar IgE- and Th2-mediated pathogenesis including asthma, allergic rhinitis, hay fever, allergic conjunctivitis, and food allergies.

Other comorbidities may be a result of the impact of atopic dermatitis on overall health, including depression, anxiety, sleep disturbance, and a whole host of other conditions.

We have talked quite a bit about the mechanisms of atopic dermatitis and it's dazzling what's been discovered since I began in dermatology over 30 years ago.

Lindsay Strowd, MD: I agree, it's very impressive that we now know so much about the pathophysiology of this complex disease.

Epidemiology and Risk Factors

In this module, we discuss the basic epidemiology of atopic dermatitis, noting its close association with other atopic diseases. We will focus on the impact of atopic dermatitis on patients and their caregivers and hear from a patient about their own experience.

We will discuss the epidemiology of atopic dermatitis. Although it occurs most frequently in children, it does affect adults. Up to 25% of children are affected and up to 7% of adults. There's some evidence that the prevalence is higher in women than in men. The onset is typically between the ages of 3 and 6 months, but late-onset disease certainly occurs.

Further, as a component of epidemiology are the symptom severity. The majority–over 65%–have mild disease, but a quarter have moderate severity disease, and severe is approximately 10%. The percentage of patients with severe disease increases with age, and it's also interesting that later onset of disease tends to predict worse severity. So, if you have it early on in childhood, there's a greater likelihood of it disappearing.

More about the epidemiology of AD. Atopic dermatitis in infancy often leads to asthma, allergic rhinitis, conjunctivitis. This is called the atopic march. Infants with recent onset atopic dermatitis often develop an allergic condition over the next 3 years, up to 11% develop asthma, 22% allergic rhinitis, 16% food allergies, and we get allergic conjunctivitis. And not infrequently, more than one atopic comorbidity such as asthma and allergic rhinitis.

Deon [Patient]: Before I was diagnosed with atopic dermatitis, the symptoms that I saw at that time were basically scaly, dry skin. Sometimes it would go into blisters. The itching became so severe that it felt like I wanted to scratch my skin with a bristle metal brush.

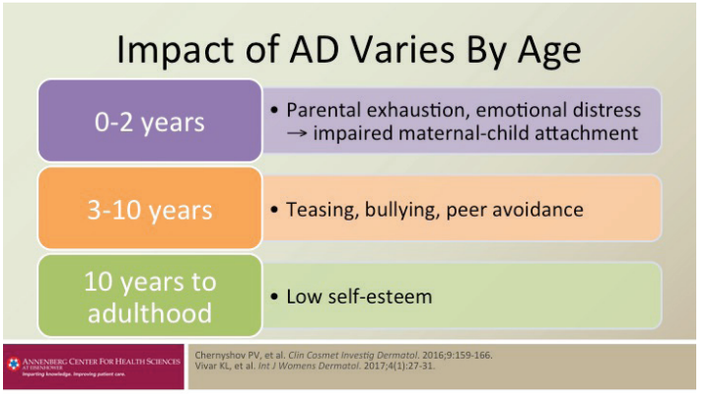
Linette [Patient]: I would flare up and then not only get itchy but very hot, and then I would crack. My skin would be cracked. A lot of lesions. When water would touch, I would be in a lot of pain. But mainly, a lot of itchiness. Also, there's just so much as far as the mental and emotional aspect of eczema. I think that is just as much as the physical part.

Alan Fleischer, MD: You just heard from patients who have been affected greatly by atopic dermatitis. It occurs in adults just as well as children.

Lindsay Strowd, MD: When we think about the impact of atopic dermatitis in a patient's life, there are many aspects of their life that can be negatively impacted by this disease. This can include their overall quality of life, their participation in social activities, the quality of their sleep, their productivity, how often they are absent from work or school, as well as the psychologic impact on their mental health.

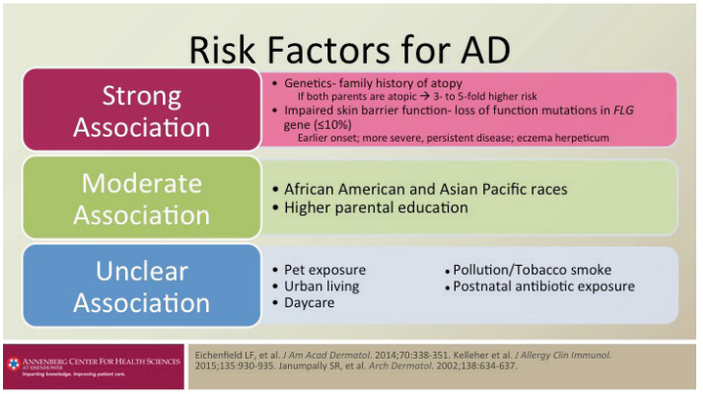
The impact of atopic dermatitis can vary depending on the age of the patient. In very young patients, oftentimes their caregivers are experiencing severe distress, parental exhaustion, emotional distress, and it can negatively affect the relationship between the child and their caregivers.

As children get older and enter school, it can negatively impact their social relationships with their peers. They may be subject to teasing or bullying based on the appearance of their skin. As children age into teenage years



and adulthood, they oftentimes can be impacted by chronic low self-esteem. And this may further negatively impact their social relationships.

Alan Fleischer, MD: There are a series of risk factors for atopic dermatitis. There's a strong association with genetics, that is, a family history of any of the atopic diseases. If both parents are atopic, there's a 3- to 5-fold higher risk of children being affected with one or more atopic diseases. As well, impaired skin barrier function, including the loss of functional mutations in filaggrin, can play a role, although, interestingly, this is found only in about 10% of people in the United States. If, however, they do have filaggrin mutation it predicts earlier onset of disease, more severe and persistent disease, as well as a higher risk of complications.



There is a weaker but still present association with race. African Americans and Asian Pacific Islanders have a bit higher risk of presenting with atopic dermatitis than white Americans or those of European ancestry. Higher parental education is a risk factor in and of itself.

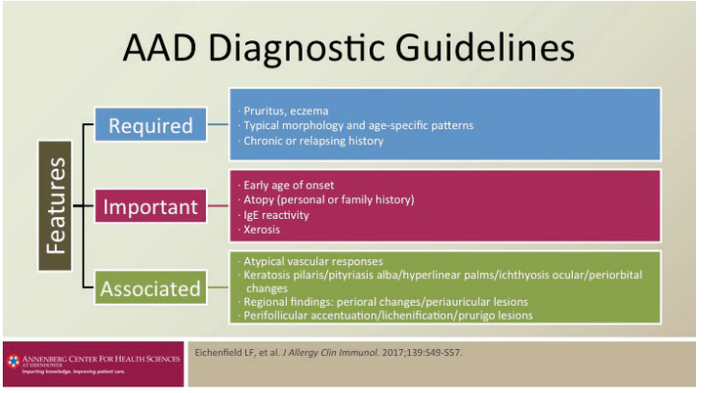
There is a bit of an unclear or uncertain association with things like pet exposure, urban living, day care, air pollution, tobacco smoke, and postnatal antibiotic exposure.

Lindsay Strowd, MD: In this module, we learned about who is affected by atopic dermatitis, we learned that it can affect both children and adults. It can be a temporary disease as well as a more chronic disease and there's a range of severity. We also learned some of the risk factors that are associated with atopic dermatitis. We learned about some of the comorbid diseases associated with this disease and we were also able to hear from a patient about the impact of the disease on their life.

Clinical Features

Alan Fleischer, MD: As an overview of this next module, we will discuss atopic dermatitis as a clinical diagnosis and review diagnostic guidelines developed by the American Academy of Dermatology. We review the 4 major morphologic features of atopic dermatitis as we consider several other skin diseases included in a differential diagnosis. As we learned in an earlier module, understanding the disease burden is critical. Therefore, we highlight several strategies for assessing disease severity. Finally, we include discussion of common comorbidities.

Atopic dermatitis is primarily a clinical diagnosis and the distribution of the lesions can vary greatly by age. Lesions can also have a variable appearance that differs with different skin types, anatomic location, severity and degree of excoriation.



Here, we look at the diagnostic guidelines of atopic dermatitis from the American Academy of Dermatology. There are required, important, and associated features in the required elements. These include pruritus, eczema. In addition, typical morphology and age-specific patterns which we will discuss later, a chronic or relapsing history is important.

Then, we go down to important features which include early age of onset. Atopy, and that includes personal or family history. It's very important to ask about this. IgE reactivity and xerosis. Next, associated features can help since its sometimes quite difficult to make a diagnosis. As a result, looking for atypical vascular responses, looking for keratosis pilaris, pityriasis alba, hyperlinear palms, ichthyosis, as well as ocular or periorbital changes. There can be changes, as well, in other parts of the body, including follicular accentuation, lichenification, and prurigo lesions with chronic scratching behavior.

Lindsay Strowd, MD: Atopic dermatitis diagnosis is largely clinical in nature. To ensure that you're making the correct clinical diagnosis, you should consider other diseases that can mimic atopic dermatitis. Many of the diseases listed here can be eliminated based on the patient's history and the physical exam. Anytime you're considering the diagnosis of atopic dermatitis, you should also think about diseases such as psoriasis, scabies, contact dermatitis, cutaneous T-cell lymphoma, seborrheic dermatitis, congenital ichthyosis, a nutritional deficiency, photosensitive disorders, or immunodeficiencies.

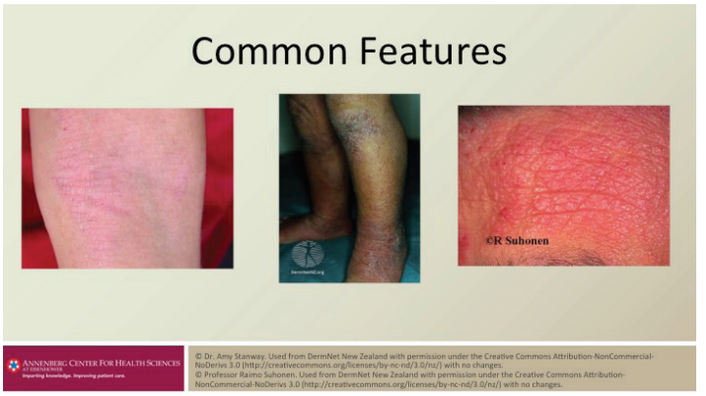
The distribution of lesions in atopic dermatitis can change based on the patient's age. In infants, we typically see disease activity located on the face,

scalp, trunk and extensor surfaces of the extremities. As children get older, the disease tends to manifest in the flexural folds, including the antecubital and popliteal fossae, as well as around the neck and ankles. In adults, we tend to see atopic dermatitis on the arms, the back, wrists, hands, fingers, feet and toes.

When you're looking at atopic dermatitis disease in the skin, you should consider these 4 main categories when you're assessing the skin lesions. These include erythema. Mild atopic dermatitis tends to have faint erythema or more of a pink appearance, while more severe lesions tend to develop a darker erythema. Very severe atopic dermatitis can present as erythroderma, which is diffuse redness of the skin covering at least 90% of a patient's body surface area.

You should also look for xerosis, as this is a hallmark of atopic dermatitis. Lichenification may or may not be present. Mild lesions may show no lichenification at all, whereas severe lesions may have significant thickening of the skin that results from repetitive scratching or itching by the patient. And finally, excoriation, mild lesions may have few to no excoriations, while severe lesions may have extensive bleeding and even ulcerations from excoriation.

[Here] we can see some classic atopic dermatitis skin lesions. It's important to understand how atopic dermatitis can appear based on a person's underlying skin type. You can see here the picture on the left shows a patient with Fitzpatrick 1 or 2 skin type. Here you can see a pale pink lichenified plaque on the antecubital fossae.



The picture in the middle shows a lichenified lesion of atopic dermatitis in a patient with a darker skin type. And finally, the picture on the right shows a more severe lesion of atopic dermatitis with the deeper erythema that we discussed earlier, as well as accentuated skin markings.

You can get atopic dermatitis on the face. The classic findings of facial skin involvement include perioral skin involvement, periorbital skin, and periauricular skin. Oftentimes, patients with atopic dermatitis that have involvement around the ears may get a fissure, which is shown here in the upper picture on the right.

Alan Fleischer, MD: Do not forget to look for other findings to patients that you suspect could have atopic dermatitis, such as keratosis pilaris, often found on the arms and legs, particularly the lateral aspects. Pityriasis alba, the slightly white, slightly scaly eruption that often occurs in association with atopic dermatitis, and ichthyosis vulgaris that lizard skin-like look of excessive scaling that you often find on the legs and, to a lesser extent, arms.

There are a variety of tools for assessing the severity of atopic dermatitis and it's essential to understand [from] the patient's perspective, how to prioritize treatment. There are many assessment tools that are available, used in clinical trials, but not necessarily in clinical practice. For instance, we have the Eczema Area and Severity Index, or EASI score. This is a score that encapsulates in 1 score the severity of atopic dermatitis. There's the SCORAD or Scoring Atopic Dermatitis scale and this includes not only a severity score, but as well, an assessment of the itching and sleep interruption.

The Dermatology Life Quality Index and the DLQI is used to assess the impact of the disease on the patient's whole life. In reality, very few of us use these in clinical practice. Rather, at best, we might use a global assessment such as clear, almost clear, mild, moderate, and severe. Also, just assessing the body surface area can give us a good idea of how severe the disease is. Some people ask about the itch severity in terms of a numeric ratings scale, such as 0 is no itch and 10 is itch as bad as you can imagine. A 0-10 scale can help [us] understand, at a later point, where patients started. The AAD practice guidelines suggest asking about the itch intensity and sleep disturbance. Both itch intensity and sleep disturbance are included in the SCORAD, as well as the impact on activities of daily living.

Lindsay Strowd, MD: There are other diseases that can be associated with atopic dermatitis. Some of these other diseases share a similar IgE- and Th2-mediated pathogenesis including asthma, allergic rhinitis, hay fever, allergic conjunctivitis, and food allergies. It's important to ask your patients specifically about the presence or absence of these other diseases. Additionally, other comorbidities may be a result of the impact of atopic dermatitis on a patient's overall health, including depression and anxiety.

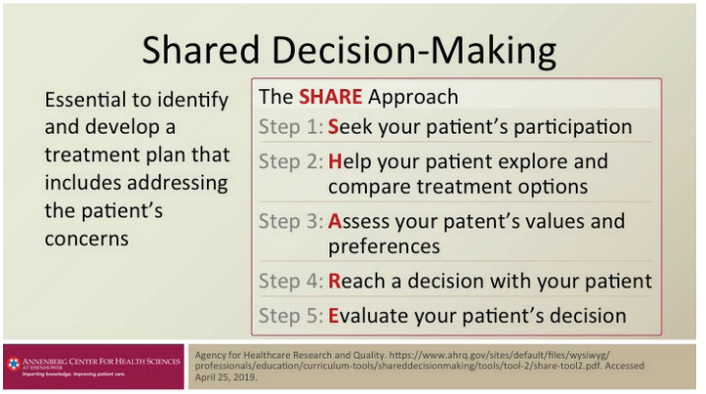
There are other diseases that are less well defined in their relationship to atopic dermatitis. There is currently conflicting literature about an association of cardiovascular disease in patients with atopic dermatitis, as well as an association of malignancy in patients with atopic dermatitis. Specifically, there is controversy over whether cutaneous T-cell lymphoma is more common in atopic dermatitis patients or perhaps the CTCL was initially misdiagnosed as atopic dermatitis.

Alan Fleischer, MD: It's also important to recognize that some patients with atopic dermatitis do develop allergies, for instance, to ingredients that are within topical products. You can have atopic dermatitis, as well as having contact dermatitis at the same time. Not all of these conditions are mutually exclusive.

Basic Management

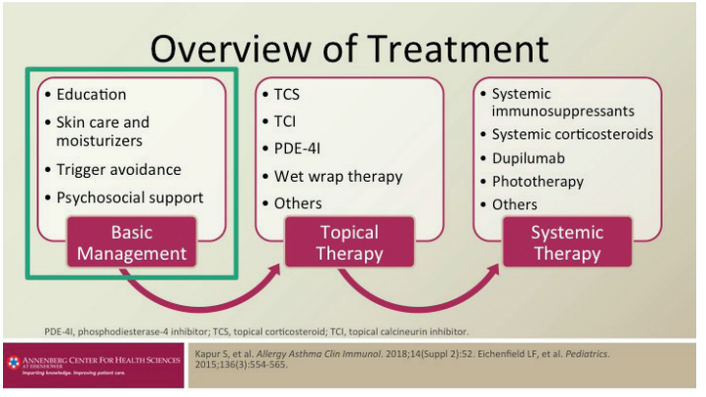
Lindsay Strowd, MD: In this next module, we're going to keep in mind the goals of therapy and provide an overview of the basic management for all patients with atopic dermatitis, paying particular attention to general skincare that includes the liberal use of moisturizers. We will discuss the challenges of poor treatment adherence and the importance of and key steps in shared decision-making with our patients. Finally, we provide suggestions for patient education.

It is imperative to utilize shared decision-making with your patient in order to develop a treatment plan that will address the patient's concerns and also optimize their treatment adherence. You should ask for your patient's participation in the development of this treatment plan and help your patient explore and compare different treatment options to find the right one for them.



You should take time to assess your patient's values and preferences for treatment and come together to mutually reach a decision with your patient. You should evaluate your patient's decision and give them feedback on their choices.

Alan Fleischer, MD: We address the goals of therapy for atopic dermatitis. These include to reduce the number and severity of flares, to maximize the disease-free periods, to improve the quality of the patient's life, to prevent infectious complications, to maintain normal activities of daily living, and to avoid or minimize the side effects of therapy.



The 3 main pillars of treatment includes basic management, topical therapy, and systemic therapy. In this next section, we'll talk about basic management first, including education, skin care and moisturizers, trigger avoidance, and psychosocial support.

In terms of general skin care, moisturizers are critical in helping to repair the skin barrier. The skin barrier I think of as the part of the body that keeps the good things in and the bad things out. Whether you believe in the pathophysiologic mechanism that atopic dermatitis is an outside-in disease, that is, bad things coming from the outside or an inside-out disease, the inflammatory responses are making the barrier disruptive. Either way, moisturizers play a key role in helping to protect the skin.

The best moisturizer choice is the one the patient is willing to use. Limit bathing to not hot water, but 5-10 minutes of warm water, and emphasizing the use of appropriate amounts of medication to all affected areas.

Additionally, patients may need control of their itch, behavioral disorders, and sleep disturbances. They may have comorbidities, asthma, allergic rhinitis, that may need its own management. And particularly in the family unit of younger children, psychosocial support for the patient and the family. Sometimes spouses of patients or families of patients don't get sleep through the night because some important family member of theirs is scratching all night long.

Lindsay Strowd, MD: It's important for providers taking care of patients with atopic dermatitis to understand that despite the impact of the disease on a patient's life, oftentimes their adherence to topical medications can be quite poor. This was a study that asked patients with atopic dermatitis to apply a topical medication to their skin. Every time they opened the topical medication, a computerized chip in the cap of the medication recorded the date and time that they opened it. You can see here the number of patients that were adherent dropped off very quickly within several days after their initial visit. Around 28 days, you can see there's an increase in the use of the medication. This correlates with their 4-week return office visit.

How can we help our patients do better with their medication? Part of it is increasing their education about the nature of the disease, things that can lead to flares or exacerbations of their atopic dermatitis, as well as the efficacy and safety of the treatments that you're prescribing.

We should demonstrate skincare techniques to our patients and provide them with written information that they can take home and refer back to.

We should refer to other health care providers as needed and advise patients about the presence of patient support organizations.

We should utilize shared decision-making at every visit. Each time we see the patient we should be asking them, "Are they satisfied with how their treatment is performing? Are they experiencing any difficulties or side effects from their medications?" You should support your patient and their self-management and adherence and try to keep their treatment regimen as simple as possible.

Optimal Use of Topical Therapies

In this next module, we're going to move on to talk about topical medications. Topical medications in atopic dermatitis remain a cornerstone of therapy for this disease. Yet, as we hear from patients, there are factors to consider in their use. We will highlight the topical medications that are supported with good evidence for their use, including topical corticosteroids, calcineurin inhibitors, and crisaborole. We will review the efficacy and safety of these medications. And in the case of crisaborole, we will discuss its mechanism of action.

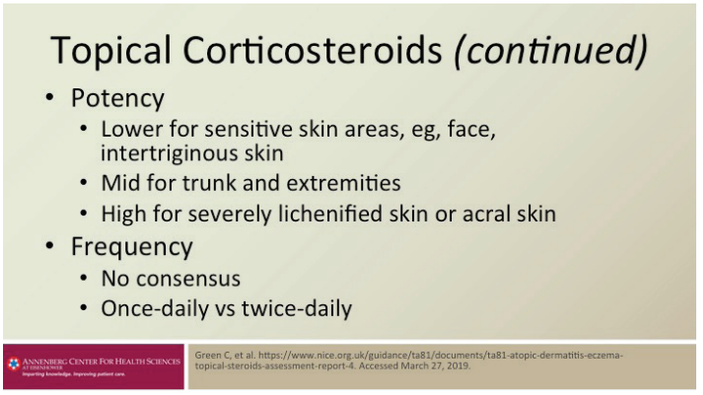
Deon [Patient]: Taking the oatmeal baths, daily, was very helpful with the eczema and especially with the blisters and the scaling of the skin.

Linette [Patient]: Depending what part of my body, I would use thicker lotions or balms or stuff and lip balm and stuff like that as well. But as far as cleansing goes, it was very simple. It was always a cleanser, a very simple cleanser with no scents or anything like that. I don't wear perfumes. I didn't moisturize too frequently because it feels uncomfortable.

Patients oftentimes have inadequate symptom relief with basic management and require additional therapy. Let's review the evidence-based topical therapies and how we might optimize their use.

Some of the topical therapies that we commonly utilize for atopic dermatitis are listed here. These include topical corticosteroids, topical calcineurin inhibitors, phosphodiesterase inhibitors, amongst others.

Alan Fleischer, MD: Topical corticosteroids are the cornerstone of management of many patients with atopic dermatitis. There's strong evidence supporting the effectiveness of treating both the inflammation and the pruritus of atopic dermatitis with these topical corticosteroids. As you may know, the potency of corticosteroids is from very high class 1, to very low class 7, and every class in between. The best approach in atopic dermatitis is a bit unclear. Some physicians prefer to recommend high-potency drugs for short periods of time during flares vs lower potency drugs as a maintenance therapy to prevent flares.



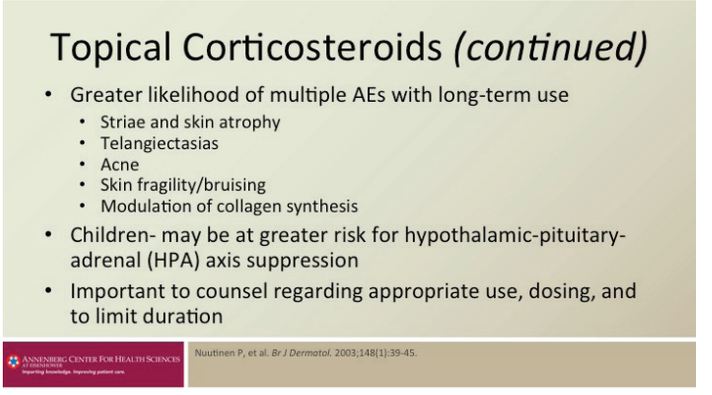
What is important to realize is that almost all vehicle-controlled trials of topical corticosteroids in atopic dermatitis are 4 weeks in duration or shorter. As a result, people may talk about the years of experience using topical corticosteroids. However, that's not years of experience in an individual patient. We don't know a lot about the long-term adverse events.

We'll talk about the potency for sensitive skin areas such as the face and intertriginous areas, lower potency corticosteroids are likely far safer. For the trunk and extremities, you may need mid-potency topical corticosteroids, and for very lichenified skin, that exceptionally thick skin that you see with chronic lichenification, short-term, high-potency corticosteroids can really be advantageous.

The frequency as to the treatment is a bit unclear, there's no evidence that twice-daily treatment is more effective than once-daily treatment.

We have talked about trying to keep the treatment regimen as simple as possible, and trying to streamline your therapies to, say, once-daily, can help in that regard.

As for side effects, there's a greater likelihood of multiple adverse events or side effects occurring with longer term use. Striae and skin thinning is a huge issue with corticosteroids, as well as telangiectasias, acne, increased bruising and skin fragility. These drugs decrease collagen synthesis. In a nice study of 3 weeks' utilization of just hydrocortisone, our weakest drug, 80%-90% reductions in collagen synthesis is seen.



Children may be at much greater risk of hypothalamic-pituitary axis suppression, and that's because they have a greater surface-to-volume ratio. It's important to counsel patients regarding the appropriate use of dosing and to limit the duration. I like to encourage patients to use a large amount of treatment for a short time, not keep using their topical corticosteroids indefinitely.

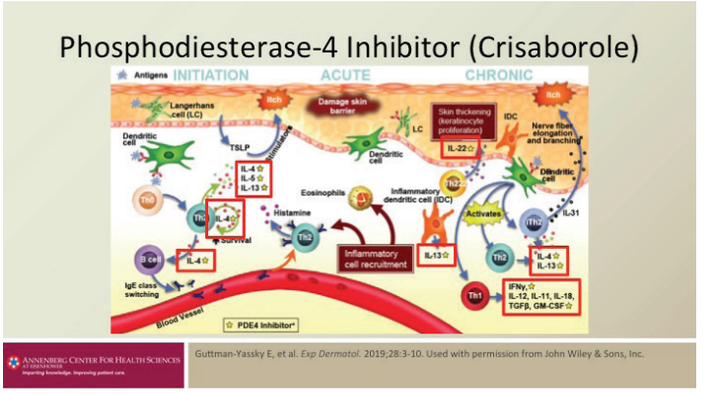
The next class of drugs are the topical calcineurin inhibitors. These drugs are non-corticosteroid agents that decrease inflammation by blocking calcineurin-dependent T-cell activation. They are a second-line therapy if inadequate responses to topical corticosteroids are seen.

We have 2 different topical calcineurin inhibitors. These include pimecrolimus, which is indicated for mild-to-moderate atopic dermatitis patients in those 2 years and older, and tacrolimus, which is used for moderate-to-severe atopic dermatitis, and it is available in 2 concentrations. The 0.1% concentration

in adults and the 0.03% concentration in those greater than 2 years of age. There's no question, however, that tacrolimus 0.1% is more effective than the 0.03% concentration.

It is worth noting for topical calcineurin inhibitors that there is no risk of cutaneous atrophy occurring even as these are used over the long term. However, they do have some irritating properties in as much as they can cause transient burning of the skin where applied, stinging, and they can even cause transient itching. This is most likely due to a direct neuronal effect of the drug on the skin. There's also a black box warning for the risk of malignancy in as much as some cancers have been seen in the millions of people who have used these drugs.

Lindsay Strowd, MD: We will discuss the newest topical agent that has been approved for atopic dermatitis, and this is crisaborole. Crisaborole is a boron molecule that binds to the bimetal center of a phosphodiesterase-4 enzyme. As you can see in this figure here, phosphodiesterase-4 is a molecule that is critical to the pathophysiology of atopic dermatitis, both in the acute phase, as well as in the chronic phase. Blockage or inhibition of phosphodiesterase-4 can decrease many pro-inflammatory cytokines involved in atopic dermatitis.



Guttman-Yassky E, et al. *Exp Dermatol.* 2019;28:3-10. Used with permission from John Wiley & Sons, Inc.

Cytokines that are affected by phosphodiesterase-4 inhibition have been outlined in a red box on this diagram. They include cytokines such as IL-4, IL-5, IL-13, IL-22, and interferon-gamma, amongst others.

Crisaborole is a topical boron molecule that binds to [the] bimetal center of the phosphodiesterase enzyme and results in a blockage of inflammation. This is currently FDA-approved for mild-to-moderate atopic dermatitis in patients ages 2 years and older. In the studies comparing crisaborole to an emollient vehicle, they found that significantly more patients achieved clear or almost clear skin at day 29 of use with crisaborole.

Similar to topical calcineurin inhibitors, the most common adverse effect of crisaborole is application-site burning and pain. Similar to topical calcineurin inhibitors, it is safe to use in all parts of the skin, including sensitive skin areas such as intertriginous skin sites and the face. In contrast to topical calcineurin inhibitors, crisaborole does not have a black box warning.

Alan Fleischer, MD: We have learned about topical treatments including topical corticosteroids, and a series of non-corticosteroidal topical drugs including crisaborole, and the topical calcineurin inhibitors. No drug is perfect and certainly these are, however, great adjuncts to our armamentarium in the management of long-term, atopic dermatitis and improving the quality of life of those affected.

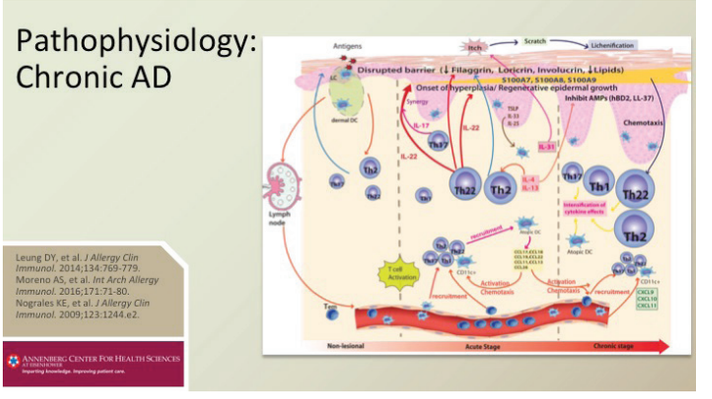
Optimal Use of Systemic Therapies

As an overview, in this module we hear of 1 patient's experiences with systemic therapies for atopic dermatitis as a prelude to our thoughts on how to individualize systemic therapies. We discuss the efficacy and safety of evidence-based systemic therapies.

Deon [Patient]: I have not had any side effects from taking the dexamethasone. Before the dexamethasone it was prednisone 20 mg that I was taking for a little over a year. I gained maybe 30 lbs in approximately a year.

Linette [Patient]: Dupixent was effective in helping some of the symptoms, to relieve some of the symptoms to a certain degree. For itchiness, it decreased it about 30% to 40%, but I also noticed that I would still definitely have my intense hot itches in the night. It wasn't a night and day kind of difference, but it was enough that I did notice that itchiness was less and I was grateful. Then I started getting side effects, injection site reactions. I didn't realize at the time, but they're injection site reactions. Wherever I would inject on my body, I would get this numbing sensation.

In this cartoon, we see on the left side, the elicitation or initiation, we see the acute phase in the center, and then the chronic stage of atopic dermatitis on the right. As we get into the chronic disease, we have a whole series of events occurring immunologically that can be abnormal and can be blocked as well. The Th2 pathway is very active, but Th1 is active as well.



Leung DY, et al. *J Allergy Clin Immunol.* 2014;134:769-779.
Moreno AS, et al. *Int Arch Allergy Immunol.* 2016;171:71-80.
Nograles KE, et al. *J Allergy Clin Immunol.* 2009;123:1244.e2.

As an overview of treatment, we've talked about the basic management of the skin, topical therapy, and now we'll spend some time talking about systemic therapy. This includes systemic immunosuppressants, systemic corticosteroids, dupilumab, phototherapy, and a whole series of other treatments.

Lindsay Strowd, MD: When we think about systemic therapy, we can think about systemic agents that are targeting the pathogenesis of atopic dermatitis, as well as systemic therapies that may be used for symptom or complication management. We think about systemic therapy targeting the pathophysiology of atopic dermatitis, we consider systemic immunomodulatory agents.

These are indicated for a subset of adult and pediatric patients in whom optimized topical regimens and phototherapy do not adequately control the

signs and symptoms of their disease. These are indicated when their skin disease has significant negative physical, emotional, and social implications in their life. All immunomodulatory agents should be adjusted to the minimal effective dose once a response is attained and sustained.

Adjunctive therapy should be continued at the lowest dose and duration of the systemic agent, possible. There is insufficient data to firmly recommend optimal dosing, duration of therapy, and precise monitoring protocols for many of these systemic medications. Treatment decisions should be based on each individual patient's disease status, their comorbidities, and their treatment preferences.

Historically, medications such as cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil have been used for patients with severe atopic dermatitis. Systemic corticosteroids are generally avoided as they can lead to a flare after they are discontinued.

Phototherapy is an alternative treatment option for patients that can be used in moderate-to-severe atopic dermatitis. Most patients will receive narrowband UVB and this can be used in conjunction with systemic medications.

Some of our systemic therapies are more designed to target the symptoms or the complications of atopic dermatitis. These can include systemic antimicrobial agents and antihistamines. Antimicrobials are typically recommended if there is clinical evidence of *Staphylococcus aureus* super infection. If a patient presents with eczema herpeticum or secondary infection with herpes simplex virus, antivirals should be used. In terms of antihistamines, short-term use of these for sleep disturbance, secondary to intense itch, can be considered. There is not much evidence to advocate for the use of non-sedating antihistamines in the absence of urticaria or rhinoconjunctivitis.

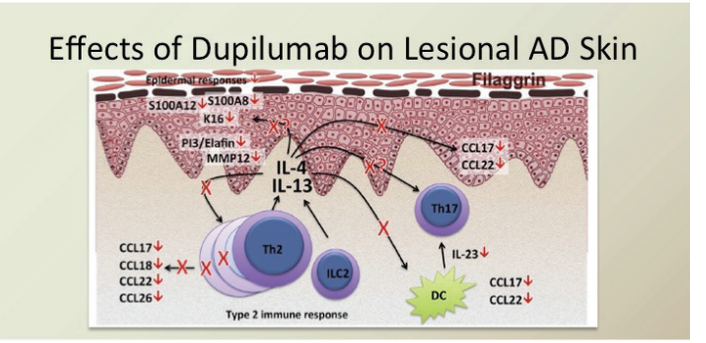
Alan Fleischer, MD: We've learned about a series of systemic treatments and it should be noted that none of them are FDA-approved for treating atopic dermatitis, and they lack a great deal of evidence-based [data] surrounding their use. We actually don't know much about the safety and efficacy of cyclosporine in treating atopic dermatitis, for instance.

Dupilumab

As an overview, we discuss the efficacy and safety of evidence-based systemic therapies. Our focus is on dupilumab as the most recent systemic therapy to become available, and we also discuss its mechanism of action.

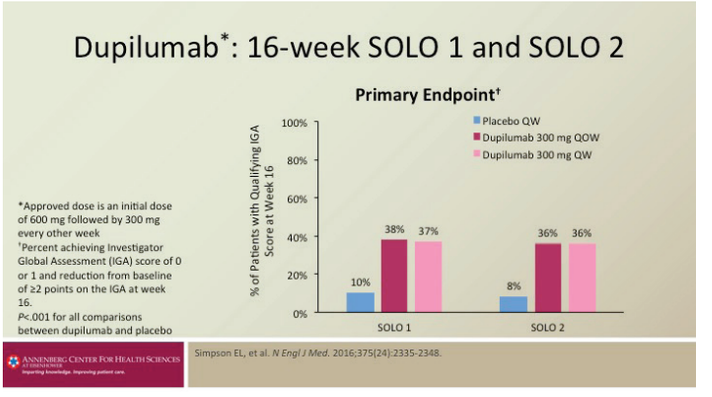
Dupilumab is indicated for patients age 12 and up with moderate-to-severe atopic dermatitis not controlled with topical prescription therapies or when those therapies are not advisable. It should be noted–and we'll talk about the adverse event profile in a moment–that one should monitor for new and worsening eye symptoms, especially conjunctivitis, as well as monitoring for a rare vasculitis rash, worsening of pulmonary symptoms in those with asthma and/or neuropathy. Especially if a patient has been managed with long-term corticosteroids, systemically stopping them can have problems.

We see the effects of dupilumab on lesional atopic dermatitis skin. Dupilumab blocks the effect of IL-4 and IL-13. And in doing so, a whole series of events cascade from this. The Xs indicate the steps that are blocked in the inflammatory cascade, including on the lower right, the dendritic cells, which have an effect then on Th17 cells. More in the center, the decrease in the activity of the Th2 pathway, and this then affects the generation of a series



of chemokines which are pro-inflammatory. And then a series of events which have happened with the epidermis, including the effect on the barrier function, as well as its ability to decrease the amount of bacteria that grow on the surface. In a whole series of ways, this affects both the barrier function, the risk of infection, as well as the inflammatory effects in the dermis.

We see the endpoints of the 2 SOLO trials, and I was an investigator in 1 of these trials. These were 16-week studies, randomized controlled trials, which compared placebo injections weekly with either dupilumab 300 mg every other week or dupilumab 300 mg weekly. The primary endpoint was achieving clear or almost clear. And this is a meaningful endpoint for both patients and for physicians, achieving clear or almost clear, we can define as success.

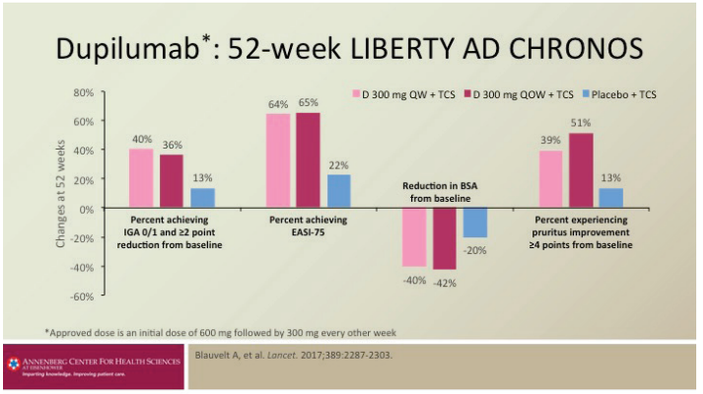


You can see both in SOLO 1 and SOLO 2 trials that only 8% or 10% of the placebo patients achieved control that is meaningful, that is clear or almost clear. By contrast, both weekly and every-other-weekly dupilumab in 35% to nearly 40% of patients achieved clear or almost clear, the primary endpoint.

In terms of the secondary endpoint achieving EASI 75, that is a 75% reduction in the Eczema Area Severity Index. In the SOLO 2 on the right, we see a 12% reduction in EASI 75 in placebo, and in the SOLO 1 trial, 15% in placebo and the other, whereas essentially half of all of the participants receiving dupilumab weekly or every other weekly, achieved EASI 75.

We see long-term results from the LIBERTY AD CHRONOS series of studies. These are 52-week results and on the left, we see again the percent achieving clear or almost clear with a greater than 2-point reduction from baseline. In the placebo group, we see only 13% achieve clear or almost clear, whereas 36% to 40% of the patients receiving weekly or every-other-weekly dupilumab, achieved it.

The next series of columns are those that achieved EASI 75, 75% reduction in the EASI score, roughly 65% vs 22%. Then on the other outcomes, reduction



in body surface area from baseline, roughly 40% in the 2 dupilumab groups vs 20% placebo. And those experiencing, on the far right, a meaningful reduction in itch severity, that is a 4-point improvement on a 0-10 scale. 39% with the weekly dosing of dupilumab achieved meaningful reduction, 51% achieved it in the every-other-week dupilumab study, whereas only 13% in the placebo group achieved this. Please note that in the United States, the approved dose of dupilumab is initially a loading dose of 600 mg followed by 300 mg every other week.

When we speak about drugs, it's most important to talk about the adverse event or side effect profile. These were the side effects that we're seeing most commonly in the 2 pivotal 16-weeks times, the SOLO 1 and SOLO 2. I want to draw your intention to serious adverse events, that first row and roughly the same number of series of events occurred in placebo vs the 2 dupilumab arms of weekly or every other week. Injection site reactions are much more common as expected with dupilumab treatment, but still only occur in the minority of people. Both allergic conjunctivitis, as well as conjunctivitis, we're seeing more commonly with dupilumab treatment than placebo.

Lindsay Strowd, MD: We know that patients with severe atopic dermatitis have historically had limited to no FDA-approved options for systemic treatment of their severe disease. With the development and FDA approval of dupilumab, we now have an option that is relatively safe and very effective for our patients with moderate-to-severe atopic dermatitis. To me, this is a sign that there's hope on the horizon and in future years we hope to have even more options available for this patient population.

Alan, can you tell me a little bit about how you use dupilumab now in your clinical practice of patients with severe atopic dermatitis [and] where that falls in your treatment algorithm for patients?

Alan Fleischer, MD: In the past, with atopic dermatitis, when patients weren't responsive to topical treatment and cleared relatively quickly, we oftentimes went to phototherapy and/or other systemic treatments for which there is not a lot of evidence. I've used, in many patients, cyclosporine, mycophenolate, azathioprine, and a whole host of other agents. I do think that it's much easier to use drugs like dupilumab from the perspective that the amount of systemic monitoring that's required for drugs like cyclosporine is large. We know from a long-term study done in psoriasis patients that essentially all patients treated with cyclosporine over the long term developed renal function impairment.

These other drugs are really problematic when it comes to long-term management. And now we have the safety profile of a drug that is very well-characterized and appears, at least to me, to be far safer than drugs such as azathioprine, as well as cyclosporine. I think that when patients are willing to overcome the barrier of doing self-injections, which they can overcome in almost all cases, we have a treatment that we really understand the safety profile for, and I believe is likely much safer than our old-fashioned small-molecule treatments.

Lindsay Strowd, MD: I think the systemic medications that we have historically used in this patient population is relatively high and dupilumab is such a safe medication that I feel much more comfortable using it in my patients with more severe atopic dermatitis. One of the things that I have been so pleased about with dupilumab is how quickly it works. So, my patients with atopic dermatitis tend to have significant reduction in their itch almost immediately after their loading dose. And typically, when I see them back after 6-8 weeks, they've had several injections, they are substantially improved from where they were prior to initiating dupilumab.

And the reaction of my patients to this medication has been overwhelmingly positive. It has been life-changing for many of my patients that have really struggled with this disease for many years. That's quite rewarding as a provider to be able to give these patients some significant relief, patients that have more severe disease.

Alan Fleischer, MD: As a result of working with these clinical trials, as well as a whole series of clinical trials for other atopic dermatitis interventions, I started asking my patients about their itch severity. Certainly, we can do our own global assessment as to their severity, but we don't have a very good way of assessing how severe their itch gives. But in the trials that were used to approve dupilumab for atopic dermatitis, they asked the question about the worst itch severity over the past 24 hours on a 0-10 scale. And now I routinely ask this of my patients to help get an insight into how their itch is affecting them.

And it's great to see that meaningful itch reduction that is greater than 4 points on this 0-10 scale is achieved in a reasonable proportion of the people who take the drug.

Lindsay Strowd, MD: I think that really reminds us that we should be asking our patients about the symptoms and the impact of this disease on their daily life, and our appointments with these patients are an opportunity for us to connect with them and to hear what's really been going on with their disease when they've been at home, managing it on their own. And I think this also helps with understanding what disease treatments that they are going to want to do and is an important part of that shared decision-making with the patient. I think getting the patient perspective is critical.