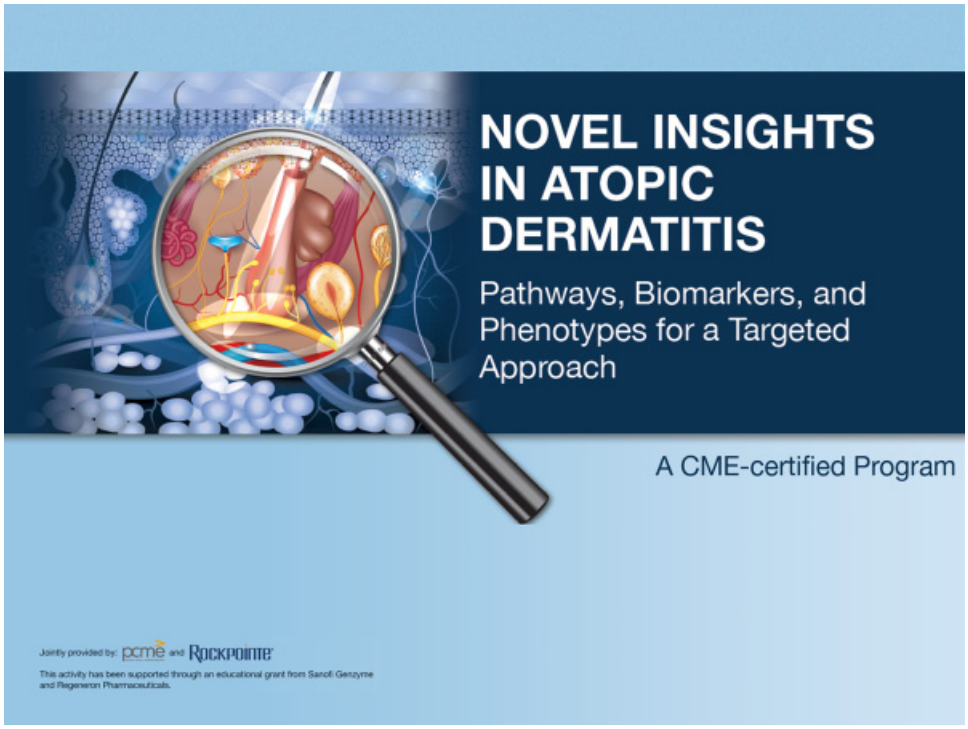
Novel Insights in Atopic Dermatitis:
Pathways, Biomarkers, and Phenotypes for a Targeted Approach

Transcript



Title Slide

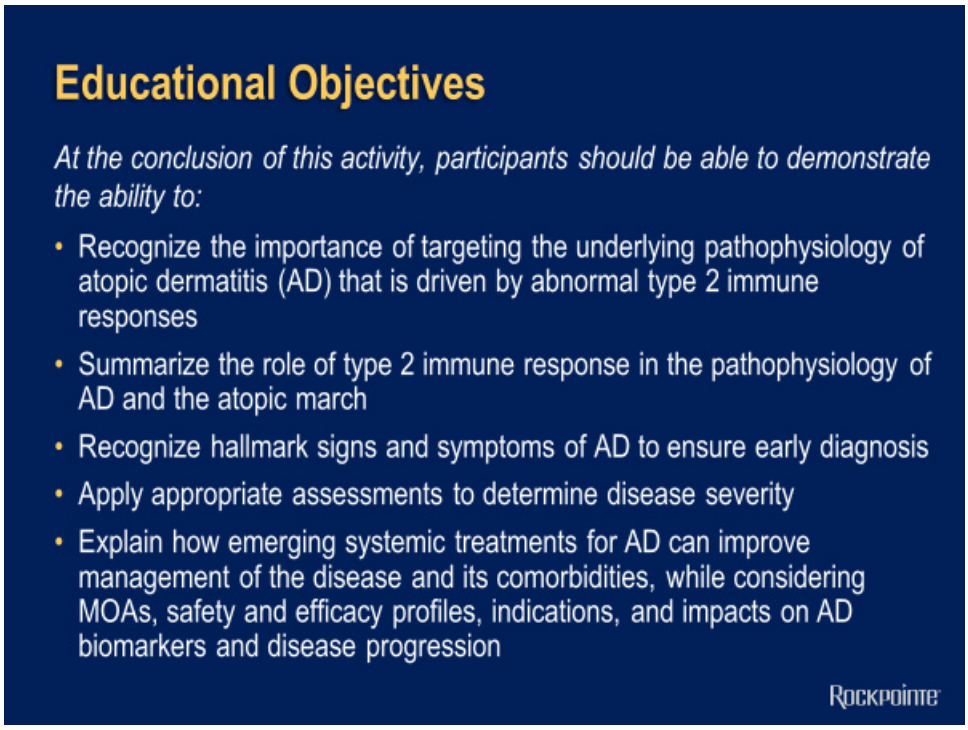
Welcome to the CME-certified program: “Novel Insights in Atopic Dermatitis; Pathways, Biomarkers, and Phenotype for a Targeted Approach.” This program is supported by an educational grant from Sanofi Genzyme and Regeneron. And is jointly provided by the Potomac Center for Medical Education and Rockpointe. And now we turn the program over to Dr. Gelfand.

Faculty Slide

Joel M. Gelfand, MD, MSCE: Welcome, I'm Dr. Joel Gelfand. I'm a professor of Dermatology and Epidemiology at University of Pennsylvania. I'm here with Dr. Jonathan Spergel, who is a professor of Pediatrics at the University of Pennsylvania, as well.

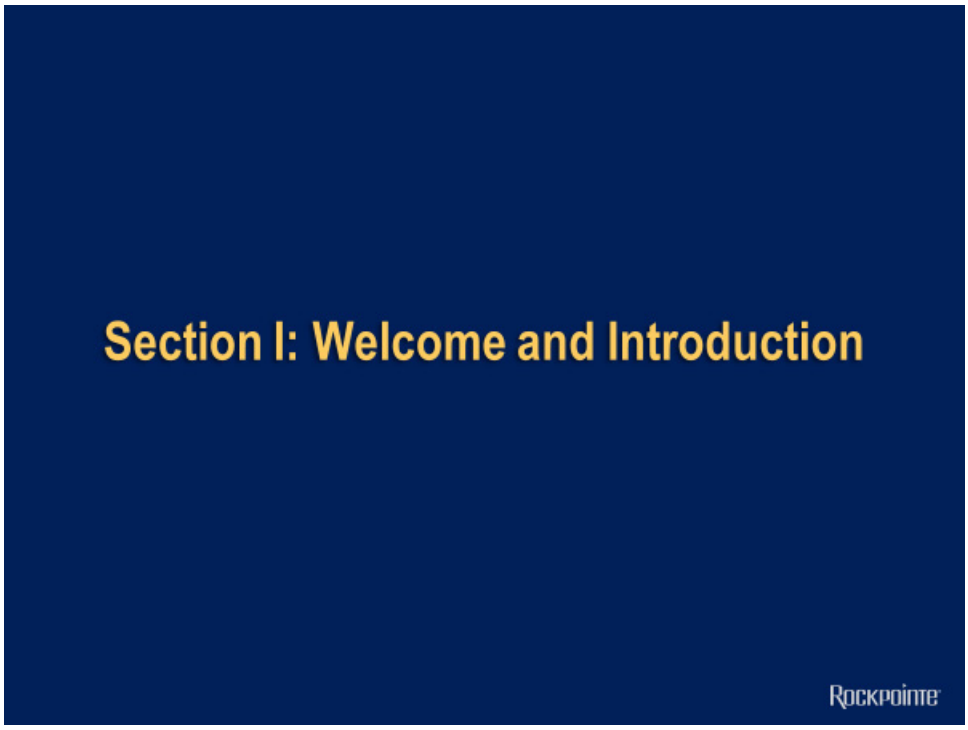
Disclosures Slide

Our disclosures are as shown on this slide.



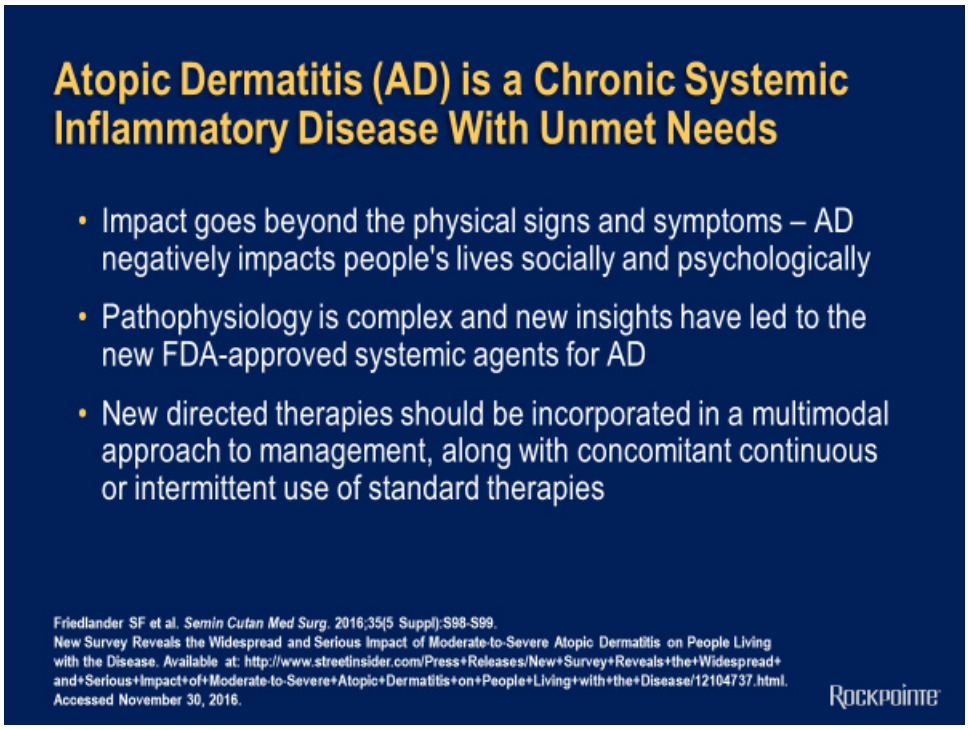
Educational Objectives

We have a number of educational objectives for this Program. At the conclusion of this activity, participants should be able to: demonstrate the ability to recognize the importance of targeting the underlying pathophysiology of AD that is driven by abnormal type 2 immune responses; summarize the role of type 2 immune responses in the pathophysiology of atopic dermatitis and the atopic march; recognize hallmark signs and symptoms of atopic dermatitis to ensure early diagnosis; apply appropriate assessments to determine disease severity; and explain how emerging systemic treatments for atopic dermatitis can improve management of the disease and its comorbidities while considering mechanisms of actions, safety, and efficacy profiles, indications and impacts on AD biomarkers and disease progression.



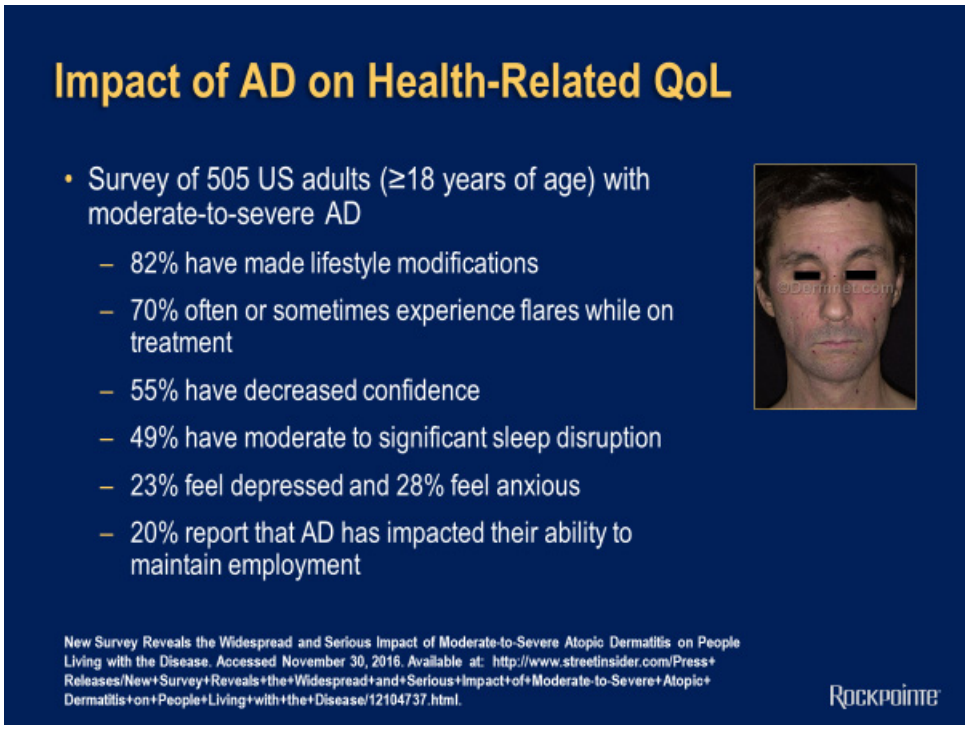
Welcome and Intro

Atopic dermatitis is a common condition that affects children and adults.



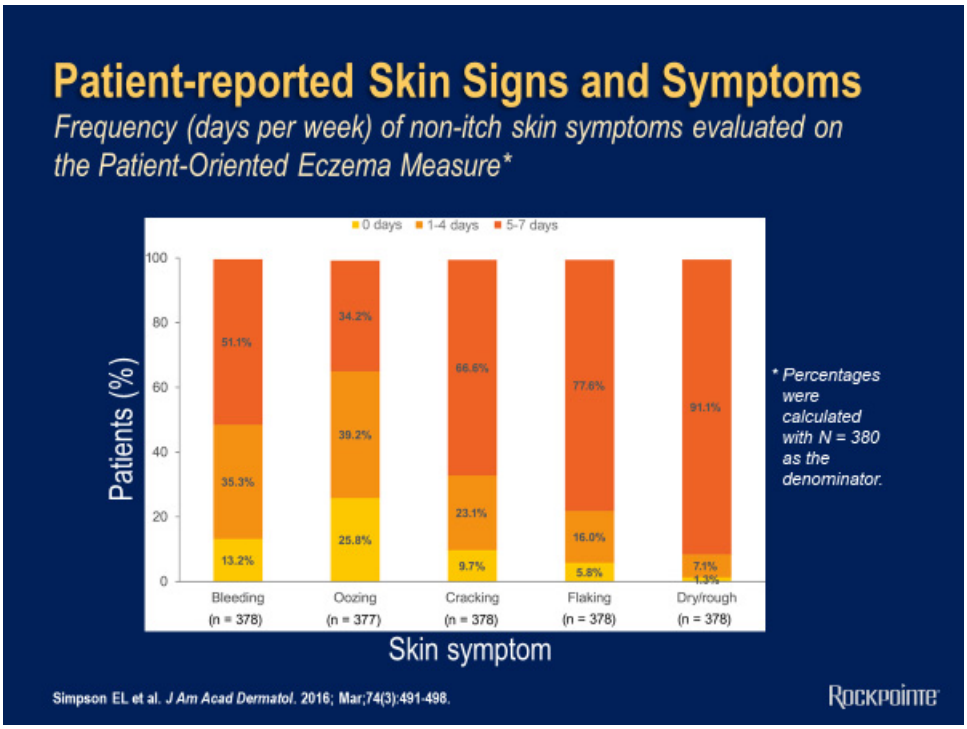
Atopic Dermatitis (AD) is a Chronic Systemic Inflammatory Disease With Unmet Needs

Atopic dermatitis is a chronic condition that's quite common in the general population and has many unmet medical needs with their being essentially very few FDA-approved systemic agents to help people have more severe atopic eczema. The impact of this disease goes beyond the physical signs and symptoms in the skin but has a more holistic approach on people's well-being and their health-related quality of life.



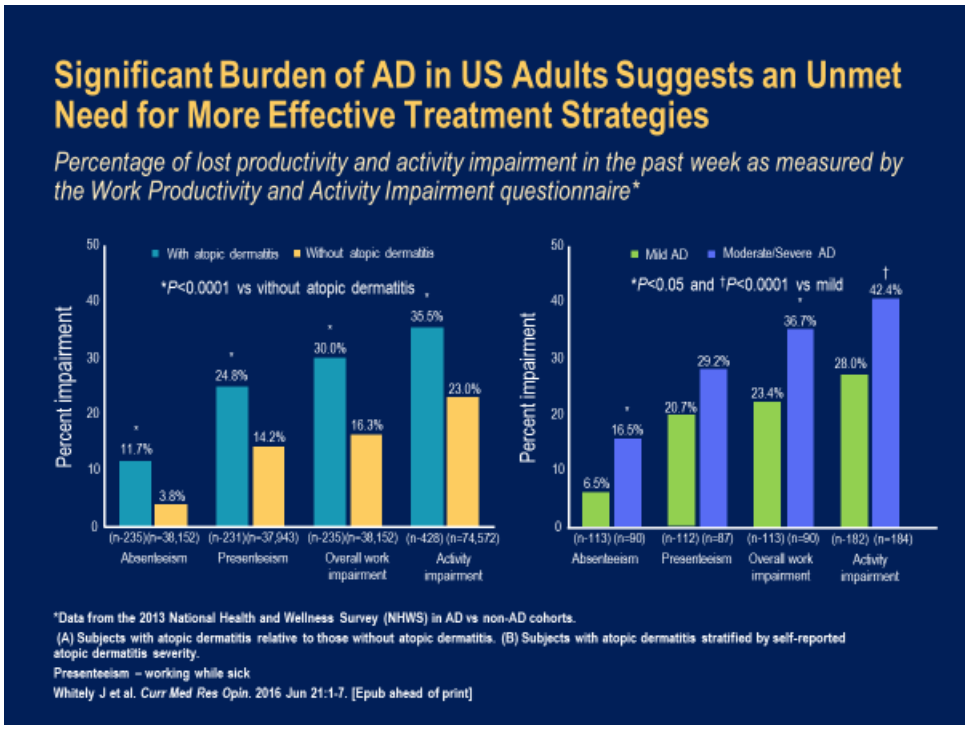
Impact of AD on HRQoL

Atopic dermatitis has a number of effects on health-related quality of life. Most typically people felt that atopic dermatitis is affecting primarily children, but, clearly epidemiological data supports this is quite a common condition in adults, as well. In a recent survey of more than 500 adults with atopic dermatitis, more than 80% had to make lifestyle modifications to deal with this disease. 70% often or sometimes experienced flares while on treatment. More than half of patients reported decreased confidence. 49% had moderate-to-significant sleep disruption. 23% felt depressed, and 28% felt anxious, and 20% reported that atopic dermatitis has impacted their ability to maintain employment.



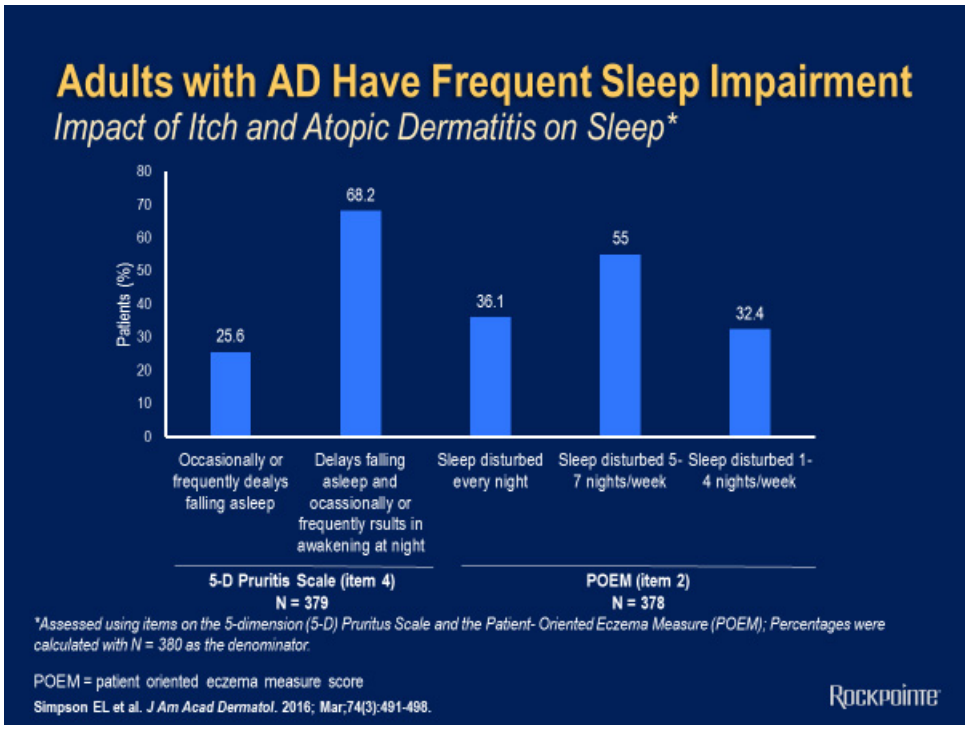
Patient-reported Skin Signs and Symptoms

There are a number of signs and symptoms that people with atopic dermatitis experience beyond the hallmark of chronic itching. Bleeding of the skin, oozing lesions, cracking, flaking, and a dry or rough texture sensation are all very common in patients



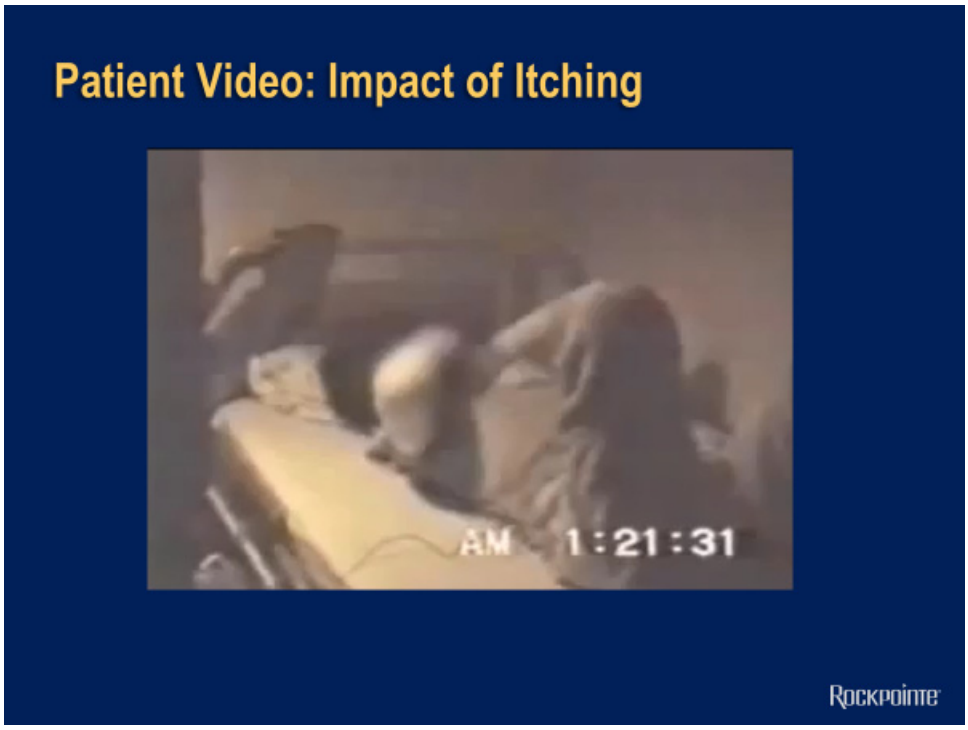
Significant Burden of AD in US Adults Suggests an Unmet Need for More Effective Treatment Strategies

As mentioned earlier, the number of symptoms also impacts functioning especially when we think about people's role in the workplace. And so there's two ways of thinking about this both, the ability to work as well as having trouble, when you're at work, what we call "presenteeism," to be as efficient and productive. And we see from this study of the National Health and Wellness Survey, that patients with atopic dermatitis report impairments in both absenteeism – missing work – and presenteeism –their overall work impairment is elevated as is their activity impairment. And this is correlated in a dose-response manner – I mean, that people who report more severe atopic dermatitis have worse impairment in all these work-related metrics compared to people who have mild atopic dermatitis.



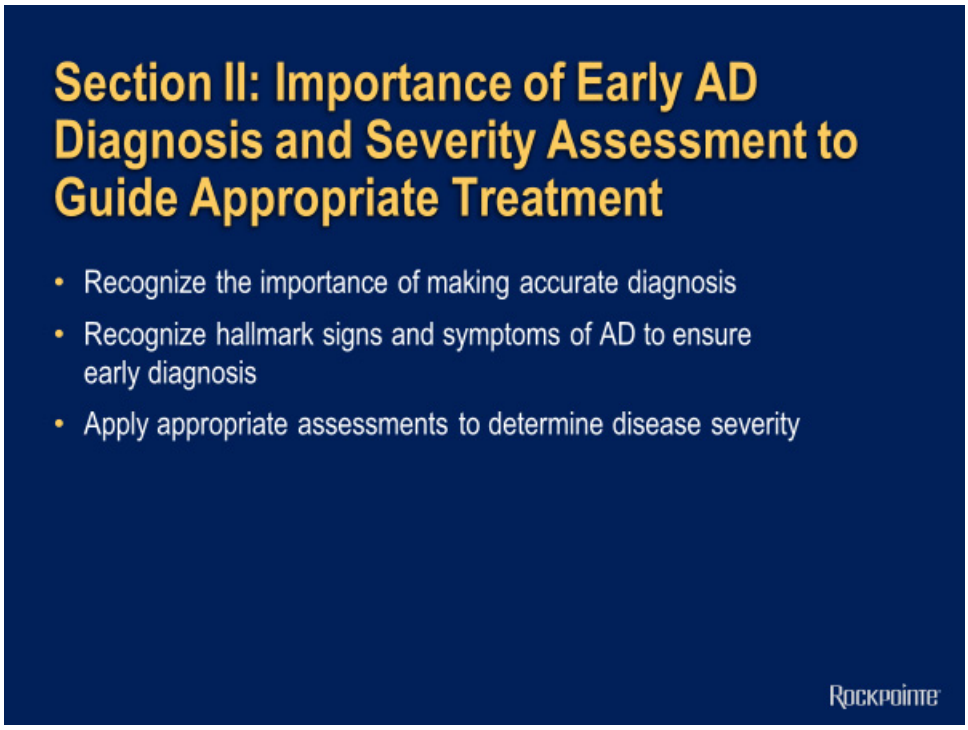
Adults with AD Have Frequent Sleep Impairment

Now, not surprisingly, some of this may come from sleep disturbance. Adults with atopic dermatitis have frequent impairments in their sleep. This is another study by Dr. Simpson. We see that, for many patients, there are significant impairments on their ability to sleep.



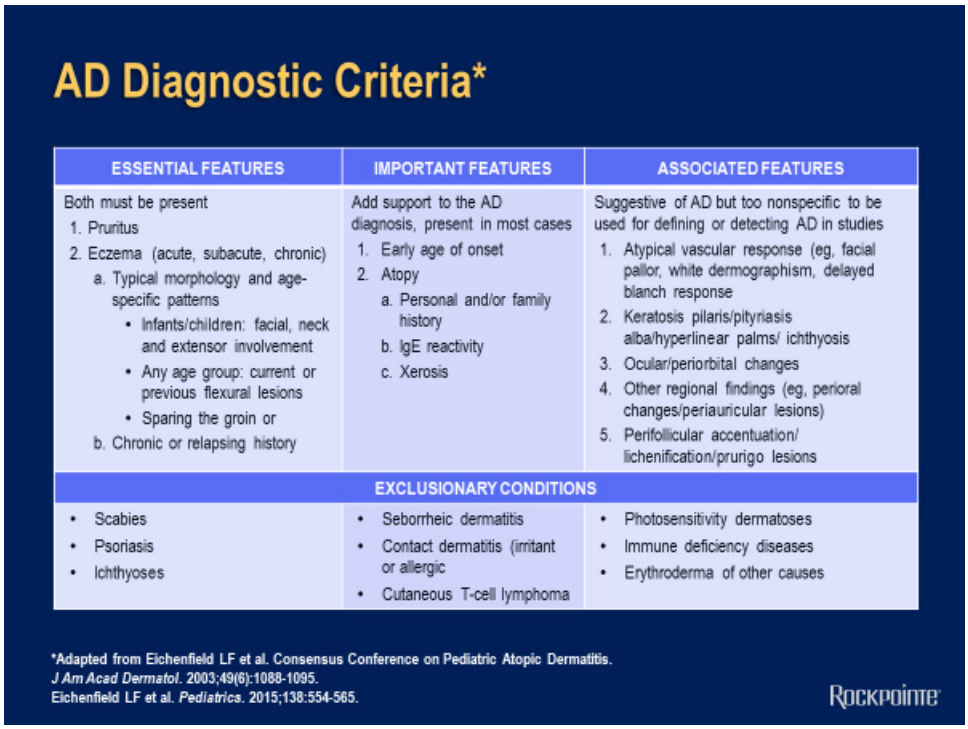
Patient Video: Impact of Itching

In fact, this video of a patient sleeping at nighttime shows the impact that atopic dermatitis and its symptoms have on the quality of a patient's sleep. And we can see the clear disruption that this patient is undergoing related to their atopic dermatitis.



Section II: Importance of Early AD Diagnosis and Severity Assessment to Guide Appropriate Treatment

Jonathan M. Spergel, MD, PhD.: Hello, I'm Dr. Jonathan Spergel, and I'm going to be talking on the importance of early atopic dermatitis diagnosis. The first thing we're going to talk about a general approach or management of atopic dermatitis. With any treatment of a disease, we always are going to make sure that we have the right disease, so we'll go over the next few slides what atopic dermatitis is and some general consensus definitions. But once we have the diagnosis, there's a few basic steps, which is true almost for anything.

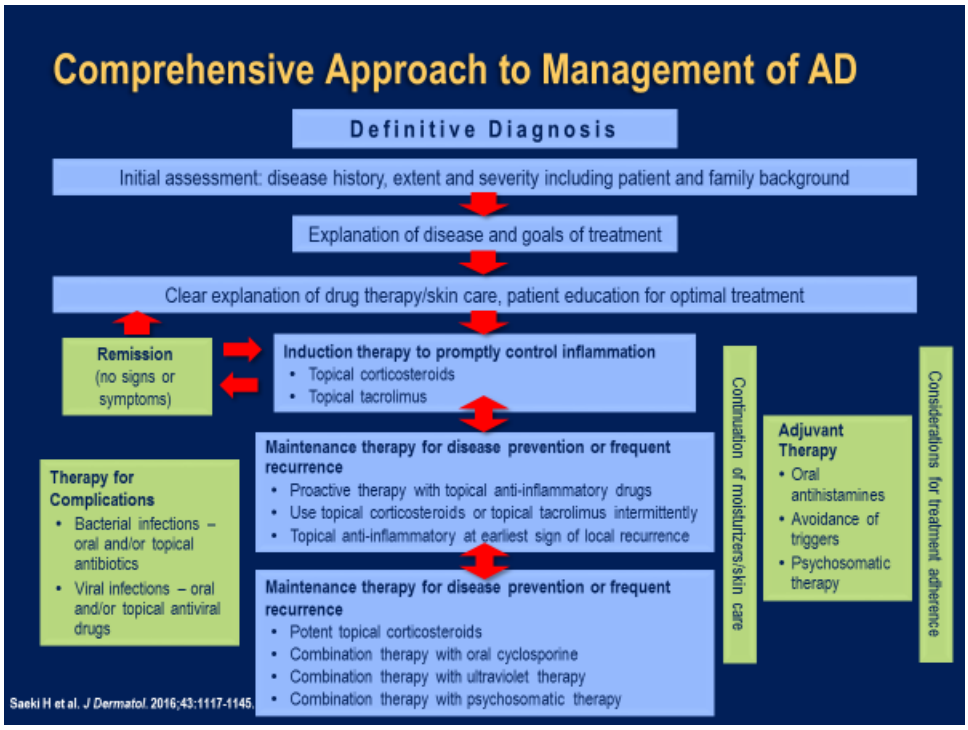


AD Diagnostic Criteria*

The first thing is you always want to make sure you have the right disease; otherwise, the therapy is not going to work. There are a couple basic diagnostic criteria for atopic dermatitis. There's no one blood test or a skin test, or a skin biopsy that proves the disease; it is a clinical diagnosis. One, is you have to be itching; you have to have pruritus. The other criteria is eczema, itchy rash. And the rash depends on the age. For, infants and children, it typically involves the face. As you get older, it moves to different areas, particularly the flexural areas, and it generally avoids the groin area.

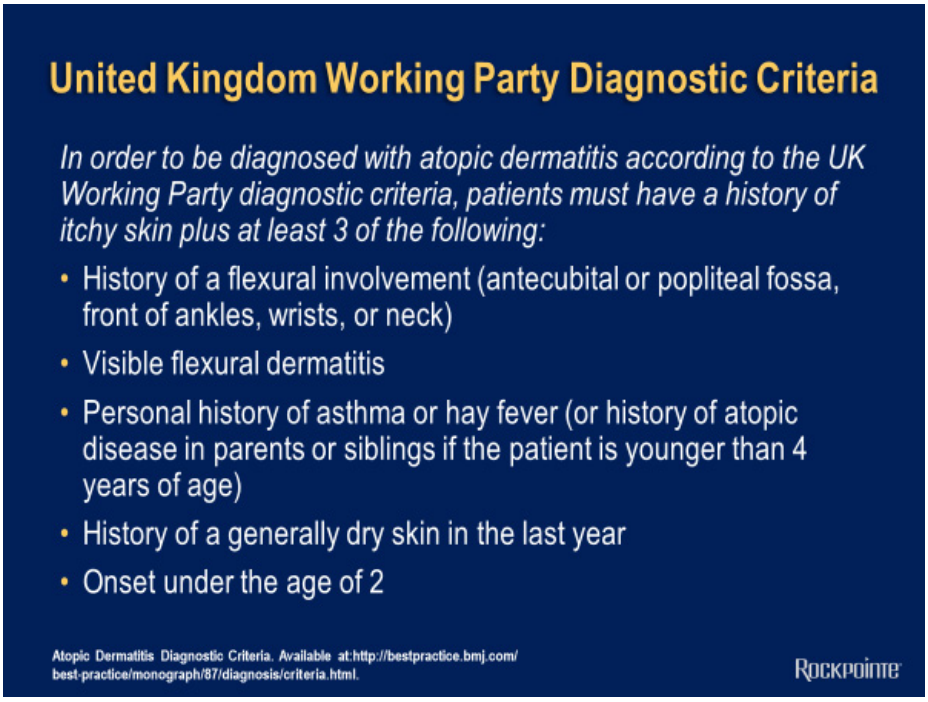
Typically, it's a chronic disease and it does relapse; it gets better and worse. There are other criterias. It usually occurs early on in life. These patients typically are atopic, so have other allergic features such as asthma, allergic rhinitis, or even food allergy.

But it is important, to exclude other things. Whether it's scabies, psoriasis. It could be also just generalized dry skin, seborrheic dermatitis, a generally irritant dermatitis, all those things we need to rule out.



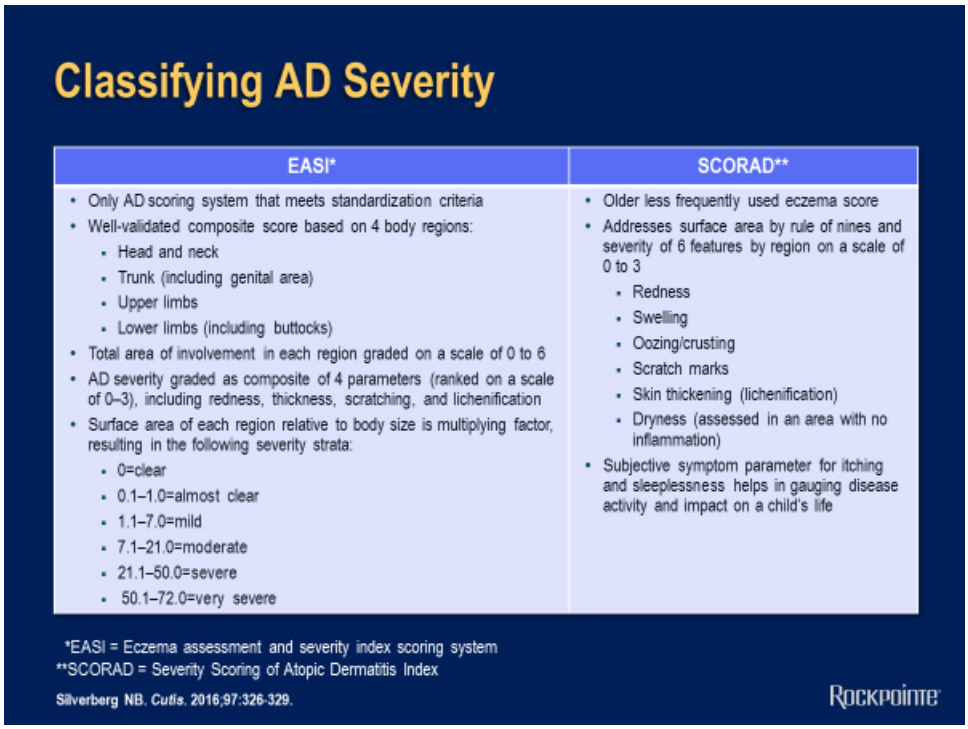
Comprehensive Approach to Management of AD

After atopic dermatitis has been diagnosed, there are multiple steps for the treatment of a patient and their family for atopic dermatitis. The first step, which is true for any disease, is basic education. Explaining what you expect from the disease, the goals of treatment, and understanding different parts of their therapy. When we think about therapy, there are really two basic therapies, which is similar to many diseases, one is getting the disease under control, which in this slide is called induction therapy and that's usually done with various topical steroids or topical calcineurin inhibitors. The second is, if you're having multiple flairs, or having lots of different disease, you do maintenance therapy. Like we do this in asthma, putting people on a daily inhaler corticosteroid. In atopic dermatitis, you can do almost the same thing. We are calling this now proactive therapy and you can do this with bi-weekly or tri-weekly which we will go over a little bit with topical calcineurin inhibitors or topical corticosteroids and even as you start flaring that, then we move on to some of the systemic agents. And we will go over those later on, including the new biologic which has been recently approved.



United Kingdom Working Party Diagnostic Criteria

Another definition is from the United Kingdom. And, again, it's very similar but, it's this flexural rash, you need itchy skin plus three things: you need to have the rash, the right location, a personal history, and early onset.



Classifying AD Severity

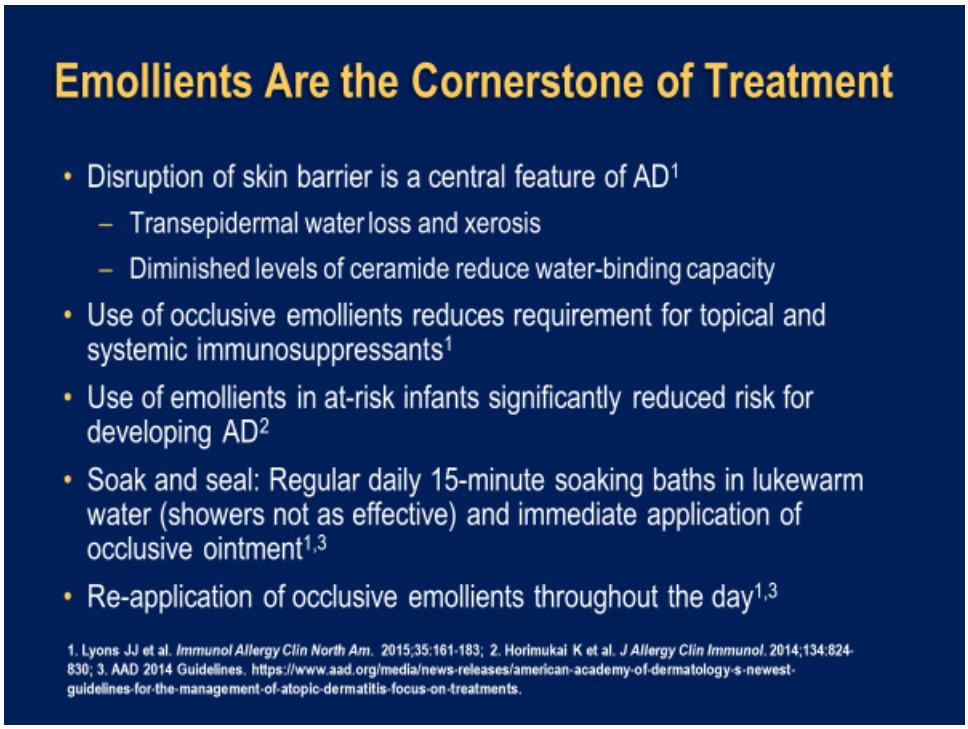
The other thing, which is not used as much, clinically, but it's important to sort of keep it in the back of your mind – because, as we go along we're going to talk about therapies for mild-to-moderate and more severe disease – is how to classify moderate-to-severe atopic dermatitis. There are two basic scoring systems – one is called EASI or Eczema Assessment of Severity Index Scoring System; the other is SCORAD – and both of these have general criteria. EASI is the one that people tend to use a little bit more often, and it involves a composite score, so you look at each different body parts, like, head and neck, and the trunk, and the upper limbs and the lower limbs, and each is scored on four different things: a redness, thickness, scoring a lot of lichenifications on a scale 0 to 3; each area is then added up, and you get a total score.

And, as you can see on the slide, the scores go from 0 all the way up to 72. Most patients that you'll see actually end up having relatively mild scores of 0, 1, 2, 3. But your moderate-to-severe are now in double digits, from 7 all the way up to 20, and sort of 21 and above is considered severe and very severe.

There are similar scoring systems for SCORAD, but EASI is what has been used in various clinical trials.

Patient Video: Impact of AD

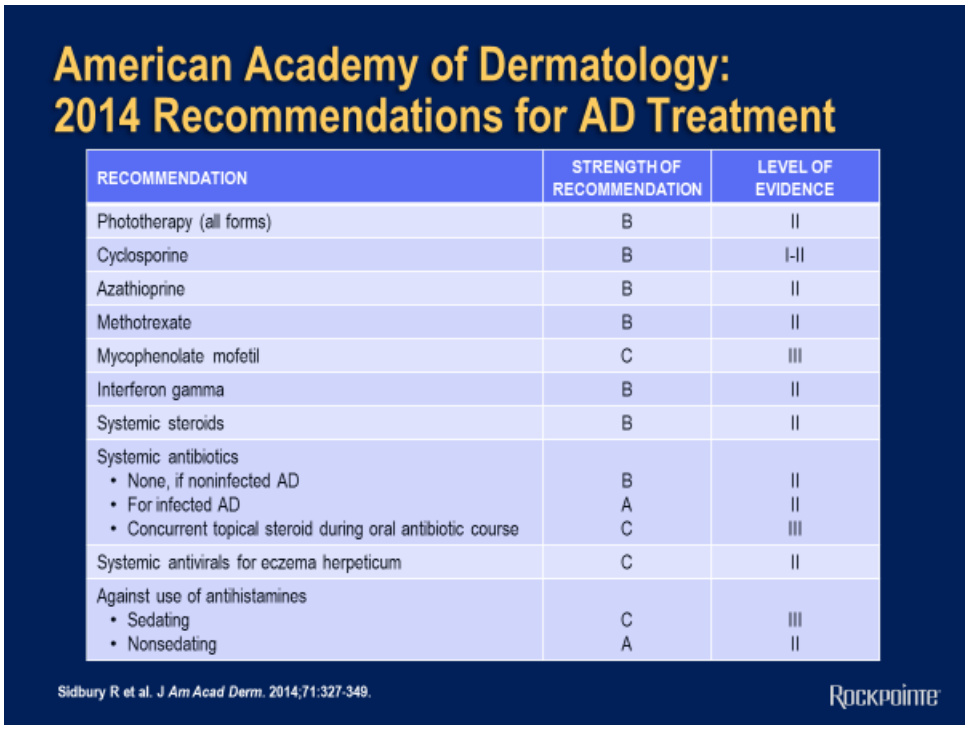
Next, we're going to hear a little brief video from Jane Smith, who talks about her diagnosis of atopic dermatitis and how long it took to come up with the disease.



Emollients are the Cornerstone of Treatment

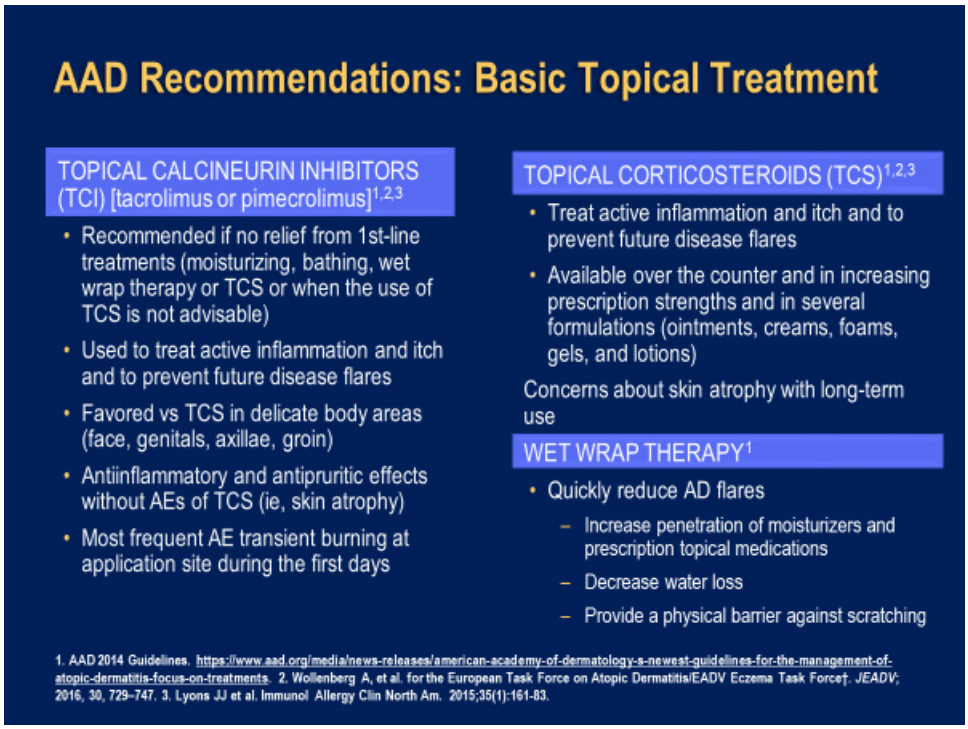
As you can hear, from Jane Smith, taking care of the disease can be typically challenging, and like many patients, it's been really a hard thing to do, and so we want to come up with a good therapy. One of the key features of atopic dermatitis is this broken-down skin barrier. The most important thing is having the appropriate emollients for the skin, really trying to just repair that skin barrier. They have water loss. There's xerosis, or dry skin. They're losing that basic fat or the ceramides to leave onto the skin. It's important to use these, occlusive emollients. There's lots of them out there. And the interesting thing – when you have used some of these occlusive emollients in infants, early on in life, there have been two studies now that have shown that, you've actually decreased the risk for developing atopic dermatitis.

One of the ways that we talk about doing it is sort of the soak-and-feel method. The idea is to get water into your skin and seal it in. But whether you bathe every day or don't bathe every day, that emollient twice a day makes a big difference.



AAD 2014 Recommendations for AD Treatment

Whether it's from the American Academy of Dermatology or whether through the various allergy societies, they've done various ratings looking at what works well for atopic dermatitis. As you can see, certain things like cyclosporine and methotrexate, and phototherapy work well as systemic agents, while other things such as sedating antihistamines never really work well.

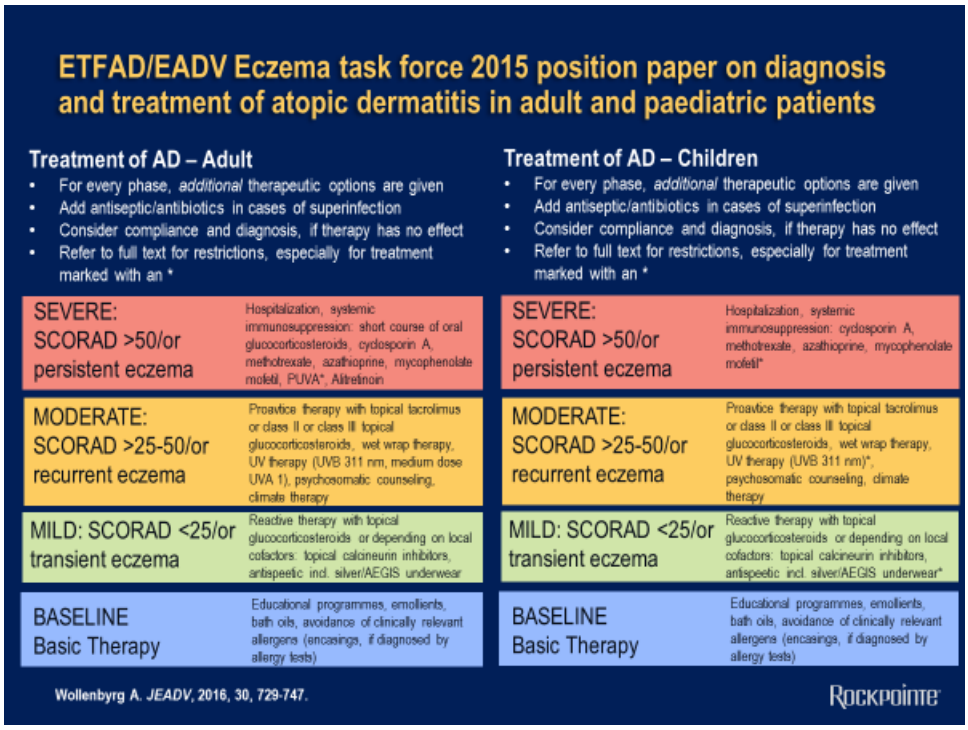


AAD Recommendations: Basic Topical Treatment

There are two basic therapies; one are topical steroids and the others are topical calcineurin inhibitors. The topical corticosteroids are the backbone, or the initial therapy for treating atopic dermatitis. They come in various strengths from anywhere from a class I to a class VII, with class I being the most potent. And you tend to use those for very severe cases, and you can't use those all the time because you do warn about skin atrophy. My personal preference is always to use ointments because I really want to use that occlusive dressing.

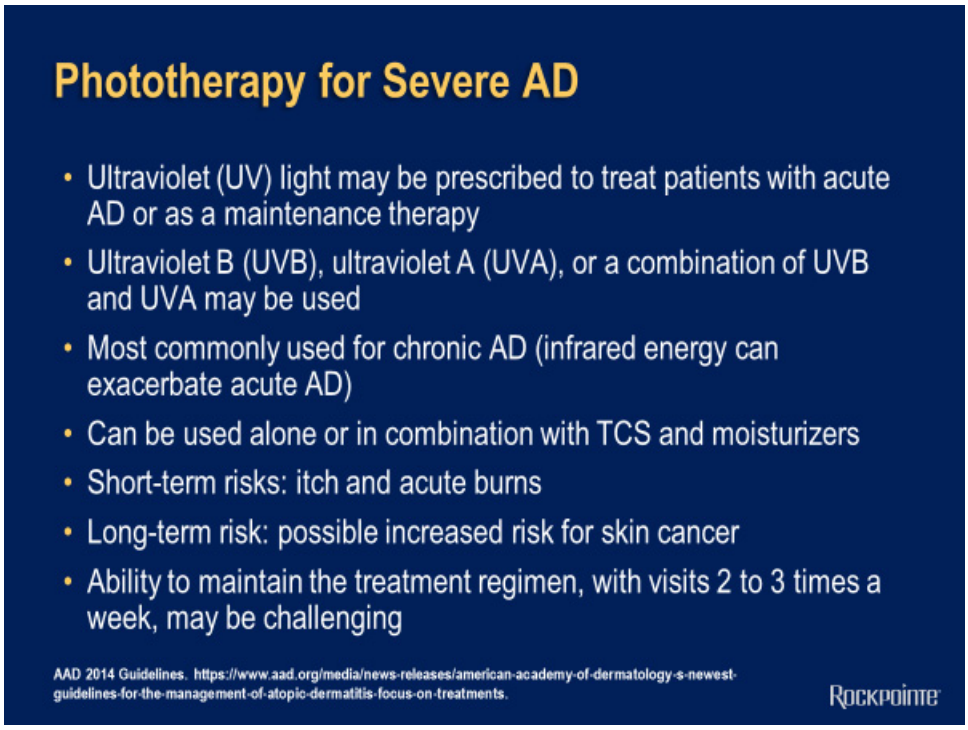
The other ones are the calcineurin inhibitors, and these are recommended when you failed at initial opical steroids. They have some advantages because they can be used in some areas where topical steroids can't be used, like the face and what we call delicate body areas, sort of axillae and groin areas. They're less likely to have the skin atrophy, but they do get some more transient burning in the first few days.

The other thing we do, for some of our severe patients is wet wraps. This is basically putting a topical steroid on or even no topical steroid, putting a wet dressing on and leaving it on for one to two hours.



ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients

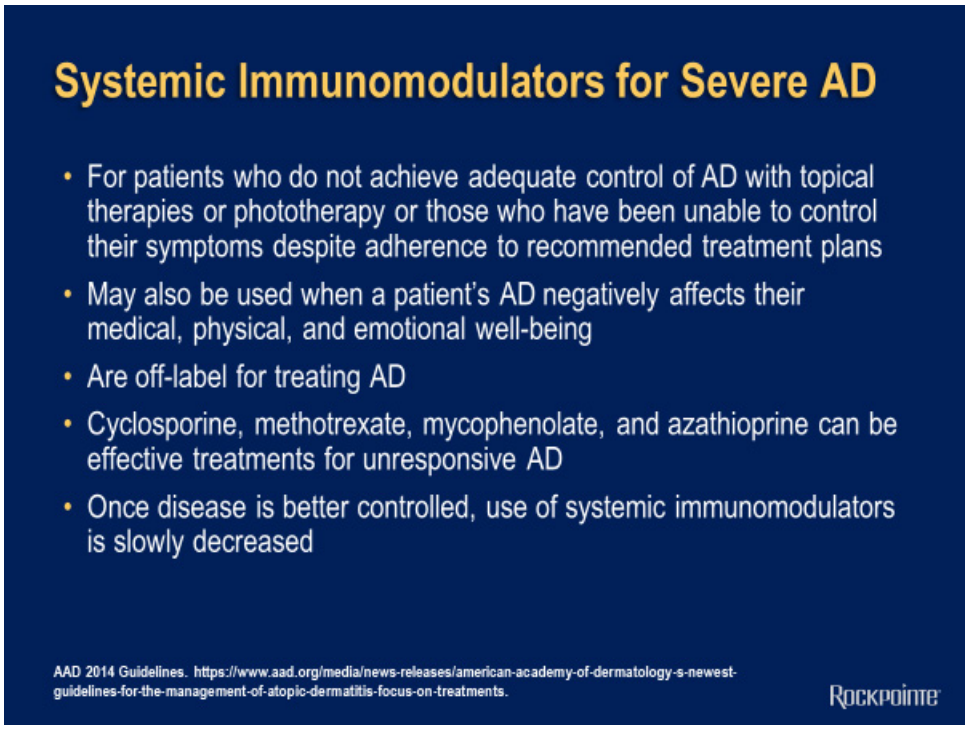
There are various different potential treatment algorithms that exist for the treatment of atopic dermatitis. This is one that is out of the European Academy published a couple of years ago now, that looks again at basic therapy: mild, moderate and severe. The basic therapy is just to use an emollients, when you have the mild eczema. With transient, we are using what they are calling reactive therapy or what we call induction therapy. Now for your moderate, this is now where you are getting on to your proactive therapy and your systemic agents. And your severe almost always use systemic agents, which at that point are the general immunosuppressives and at this point probably where you're going to put your new biologics, which will go into the moderate to severe categories.



Phototherapy for Severe AD

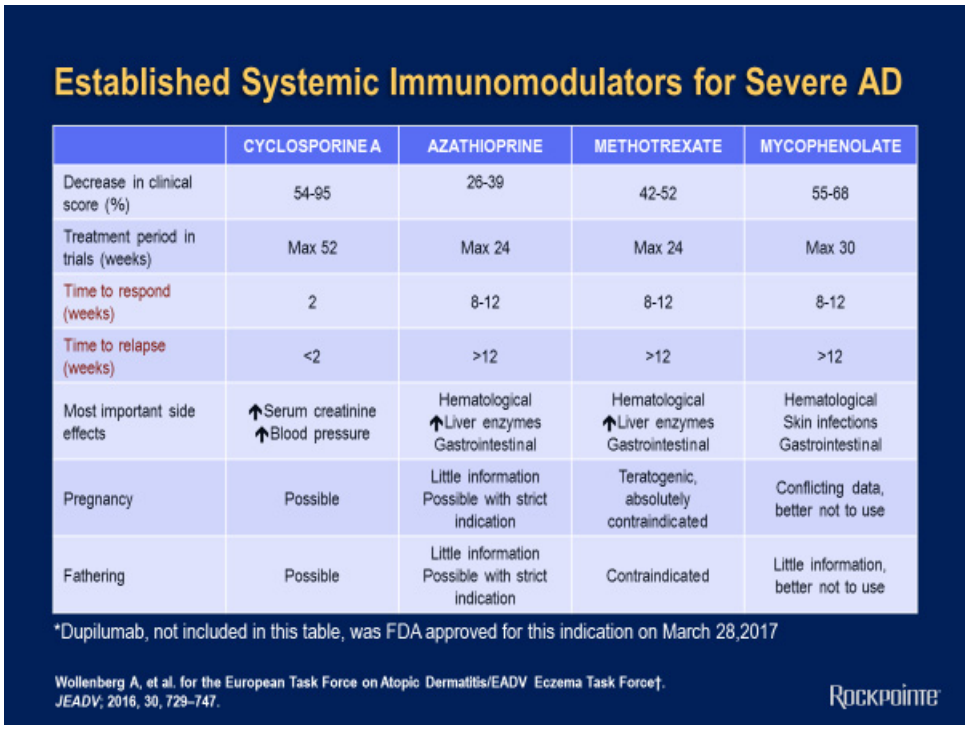
When patients begin to fail both topical steroids or topical calcineurin inhibitors, we need to begin to think about systemic therapies. One that's been around for a long time is phototherapy. Phototherapy has been used either to treat acute atopic dermatitis or more as a maintenance. It tends to work much better for a chronic atopic dermatitis. Using it in acute can exacerbate things. It can be used alone or in combination with the topical steroids and moisturizers. We almost always use moisturizers.

It can lead to some itching and acute burns if not used correctly. And anytime you use ultraviolet light for a long time, you do have to worry about skin cancer. But, when used by a dermatologist, with careful supervision, that risk tends to be very low. It is a major time commitment because, typically, the visits two to three times a week.



Systemic Immunomodulators for Severe AD

For patients who don't want to do that, we talk about systemic or oral systemic agents. These are all off-label use. To even get them in control, you will wean them down over time, but they tend to be used for more of the severe atopic dermatitis.



Established Systemic Immunomodulators for Severe AD

	CYCLOSPORINE A	AZATHIOPRINE	METHOTREXATE	MYCOPHENOLATE
Decrease in clinical score (%)	54-95	26-39	42-52	55-68
Treatment period in trials (weeks)	Max 52	Max 24	Max 24	Max 30
Time to respond (weeks)	2	8-12	8-12	8-12
Time to relapse (weeks)	<2	>12	>12	>12
Most important side effects	↑Serum creatinine ↑Blood pressure	Hematological ↑Liver enzymes Gastrointestinal	Hematological ↑Liver enzymes Gastrointestinal	Hematological Skin infections Gastrointestinal
Pregnancy	Possible	Little information Possible with strict indication	Teratogenic, absolutely contraindicated	Conflicting data, better not to use
Fathering	Possible	Little information Possible with strict indication	Contraindicated	Little information, better not to use

*Dupilumab, not included in this table, was FDA approved for this indication on March 28,2017

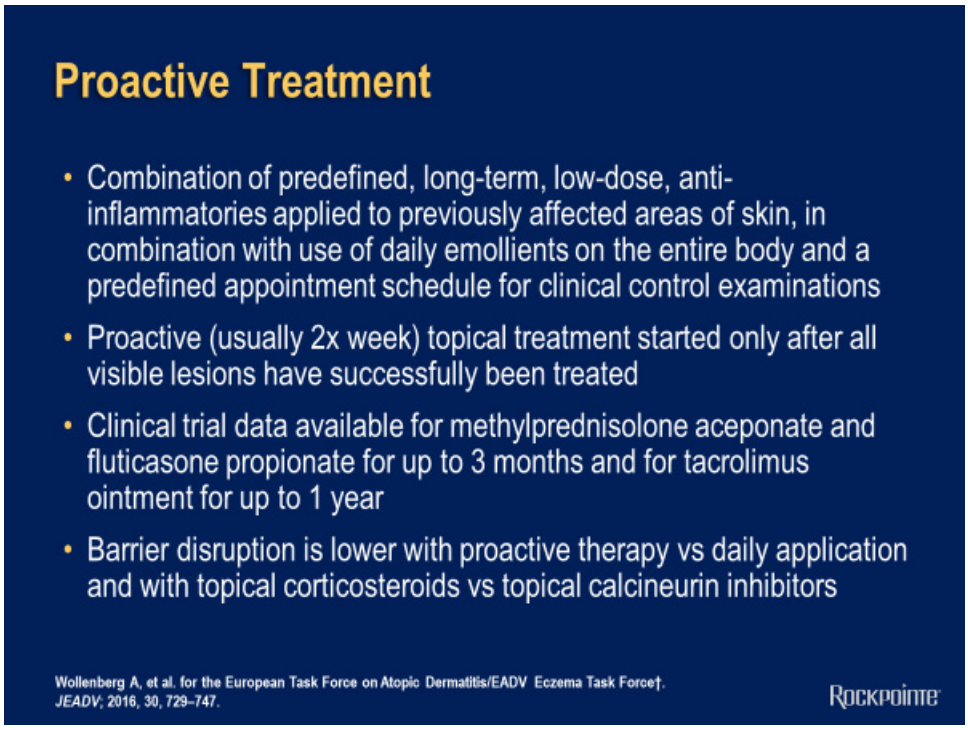
Wollenberg A, et al. for the European Task Force on Atopic Dermatitis/EADV Eczema Task Force†. *JEADV*; 2016, 30, 729–747.

Rockpointe

Established Systemic Immunomodulators for Severe AD

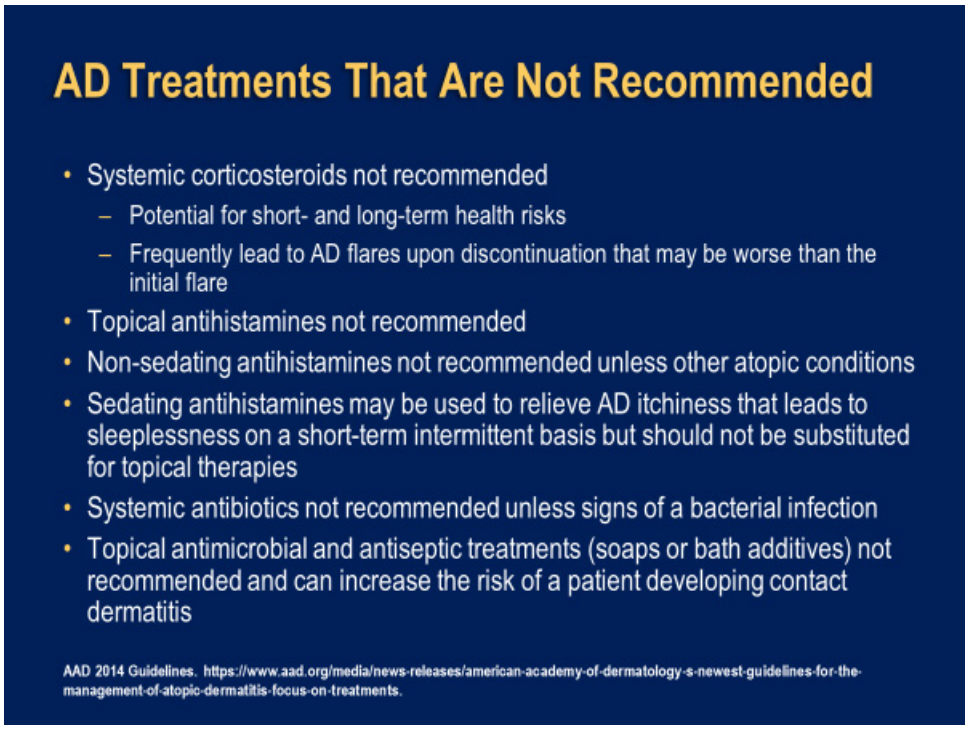
The four that are typically used are listed on this slide here, such as: cyclosporine, azathioprine, methotrexate, mycophenolate. All of these agents do have significant risks. For cyclosporine, you do need to worry about creatinine levels and blood pressure. When you use methotrexate, you worry a little about more of your LFTs being elevated. As you can see, the clinical scores do improve anywhere from about 25% to about 75% to 90% depending on which agent.

It's important to note that on March 28, 2017 dipilumab was approved by the FDA for this indication. We will be talking later on about the various side effects and efficacy of dipilumab.



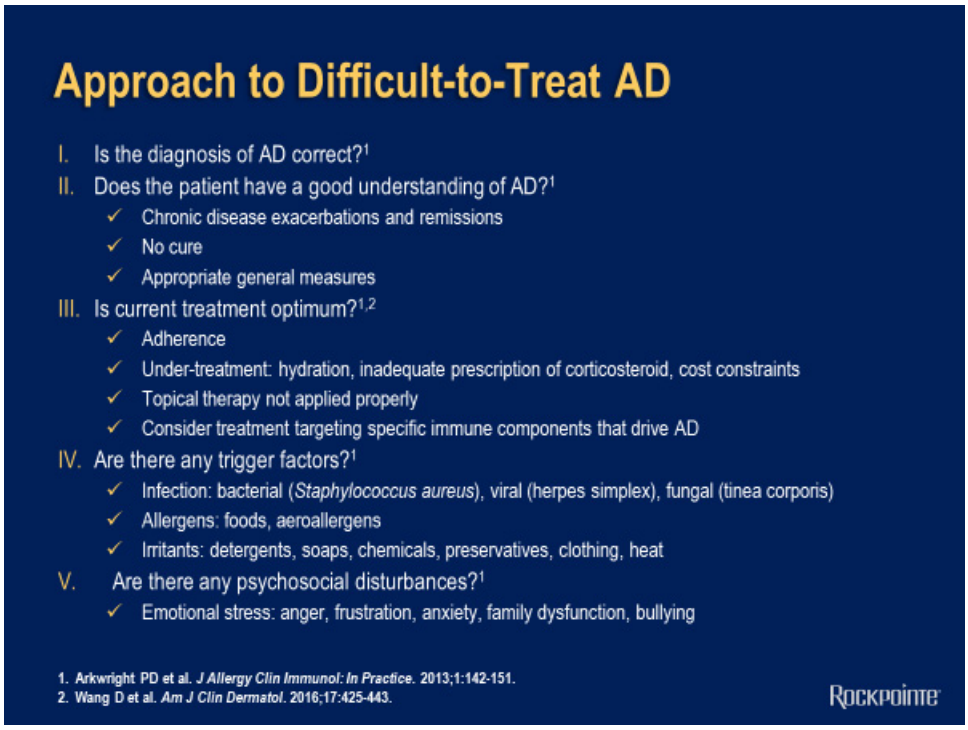
Proactive Treatment

The other way, also, is what we call proactive therapy, and this comes from what has been done in other atopic diseases. We put patients on controller therapy. And this idea was to use controller therapy either with topical steroids or topical calcineurin inhibitors as a maintenance, using them once or twice, or three times a week to help control things. For example, a patient always gets flaring of their atopic dermatitis in their antecubital fossa. As soon as they stop the steroids, it comes back. What they found when you use either the topical calcineurin inhibitors such as tacrolimus, or the topical corticosteroids such as fluticasone on those areas, they had decreased number of flares, and you end up using less in medication because you can control it by just using this intermittent use. This seems to also help with better barrier disruption; this can advance to heal better.



AD Treatments That Are Not Recommended

Some things are not recommended for atopic dermatitis. We talk briefly about non-sedating antihistamines that really have not been shown to be effective at all. Topical antihistamines are not recommended; if anything, they actually can cause some sensitization. Systemic corticosteroids – the major issue, aside from all the side effects of systemic corticosteroids of adrenal suppression, once you stop a patient, they actually rebound and tend to get worse. If you have a patient using topical steroids for their asthma, and they have severe atopic dermatitis, you actually need to be careful as you wean their topical steroids for their asthma so they don't flare and get more difficult, or disease gets worse.



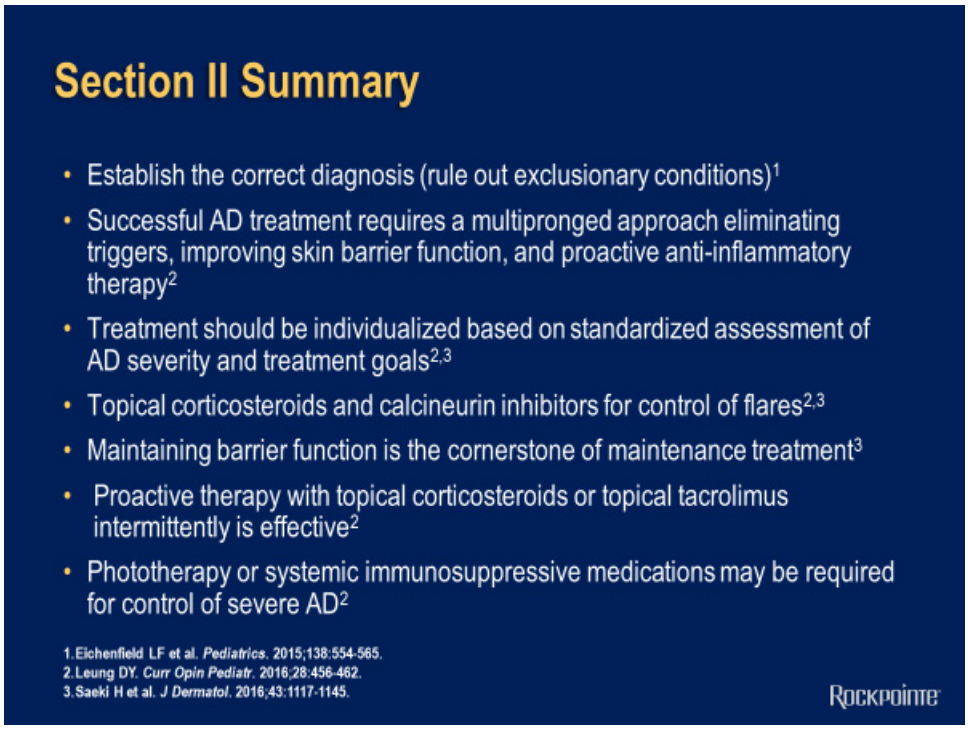
Approach to Difficult-to-Treat AD

A general approach when we talk about atopic dermatitis we have to make sure we have the right disease. The second thing is you have to make sure the patients know what they need to do, that they are understanding how to treat the disease; they're adherent with the therapy; they're doing hydrations and topical therapies. Because it's really not uncommon. They take too little emollient, and they say, "Oh, this should last me a day." You need to go through almost a whole, big tub of emollient on a weekly basis to control a normal-size older child or an adult. You need to make sure they use the right amount of medications. A lot of patients offer various trigger factors. The most common trigger factors are infections, whether they're bacterial or viral, or fungal can definitely trigger their atopic dermatitis. A lot of these things – typically Staph will have super infection in one area, will trigger atopic dermatitis.

Various irritants can cause problems, whether you're using various detergents or soaps.

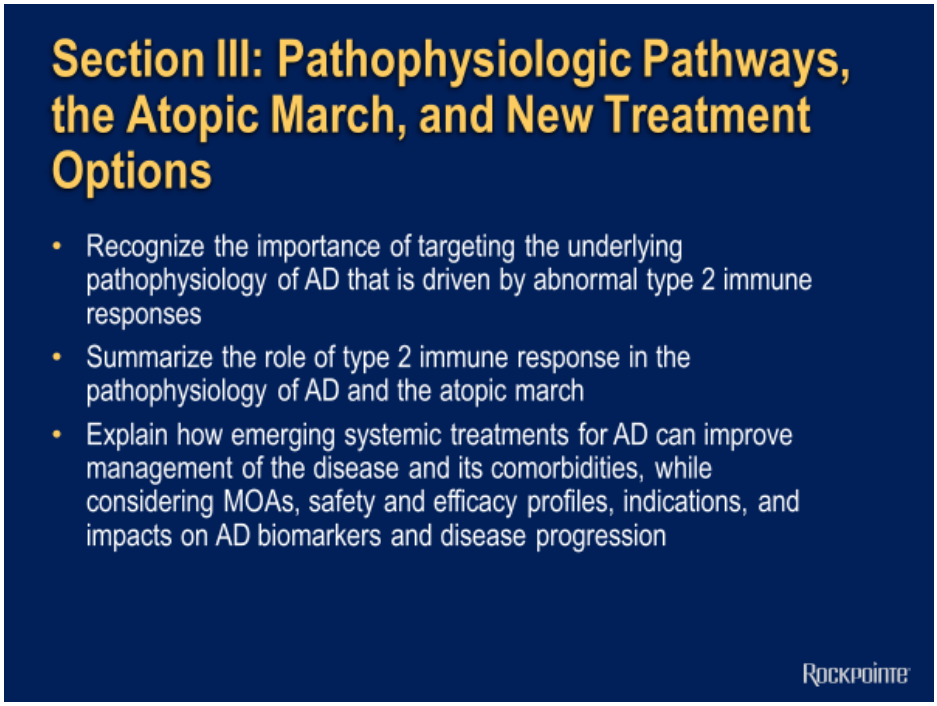
Food allergies are only majorly an issue in young children. Food allergies typically do not cause atopic dermatitis in adults.

And a lot of these patients have significant psychosocial disturbances.



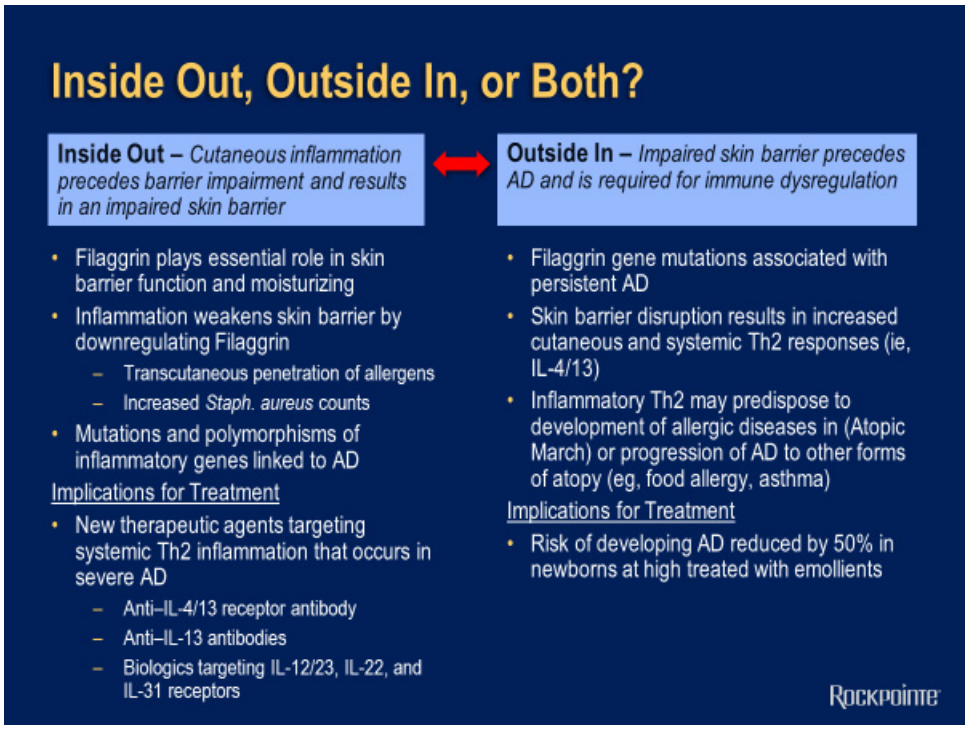
Section II Summary

Just to summarize, the treatment of atopic dermatitis, the most important thing always is make sure we have the correct diagnosis. Then, in terms of therapy, it's a multi-pronged approach needing lots of different things. We can eliminate those triggers, those infections, the irritants, making sure the person who's allergic to a food is not taking it. Improving that skin barrier function. Then we need to work on therapy, whether we use just intermittent therapies such as topical steroids or topical and calcineurin inhibitors, or if their eczema gets worse, whether we use a proactive therapy or systemic therapies with some of the oral agents, or phototherapy.



Section III: Pathophysiologic Pathways, the Atopic March, and New Treatment Options

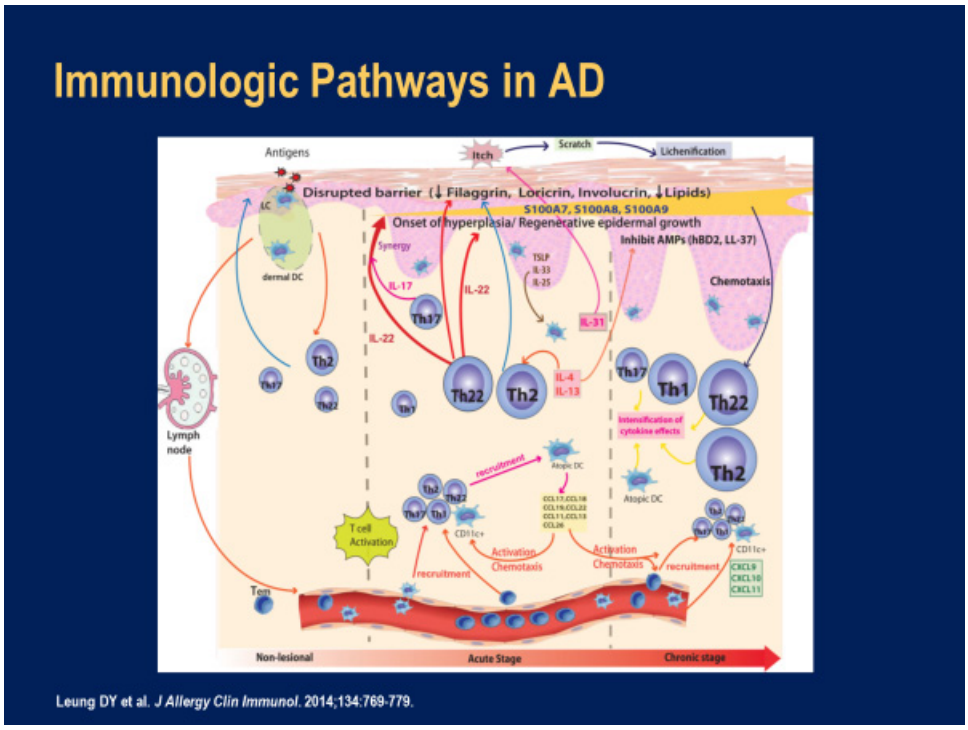
Our next section we'll go over some basic science and some of the pathophysiology of atopic dermatitis; the role of the classic type II immune system in this disease; and then, some new, exciting things that are coming along for the treatment of atopic dermatitis.



Inside Out, Outside In, or Both?

One of the biggest things that's always been a debate between the allergist and the dermatologist is, is this a disease from the skin, going to the body, which is what dermatologists always thought – or the allergist always thought it was a disease of ADP going out to the skin. And, of course, both of them are right. It's a combination of the two, so this is outside-in and an inside-out. Most patients with atopic dermatitis have abnormal skin barrier to begin with, so whether it's filaggrin defects or other defects in the epidermal barrier lead to increased penetration of allergens, leading to more disease.

Interestingly, most of these patients also have a disrupted immune system. They have more of these cytokines IL-4 or IL-13 even before they have a disrupted barrier, a lot of patients who have normal skin have increased levels. These IL-4 and IL-13 will actually decrease filaggrin, so you get this sort of cycle. We need to repair the barrier, and as we talked about earlier, just improving that barrier early on, in infants, you get decreased risk of atopic dermatitis. And there's new therapies affecting these new pathways – the classic Th2 pathways IL-4 and IL-13, potentially, in this treatment of disease.

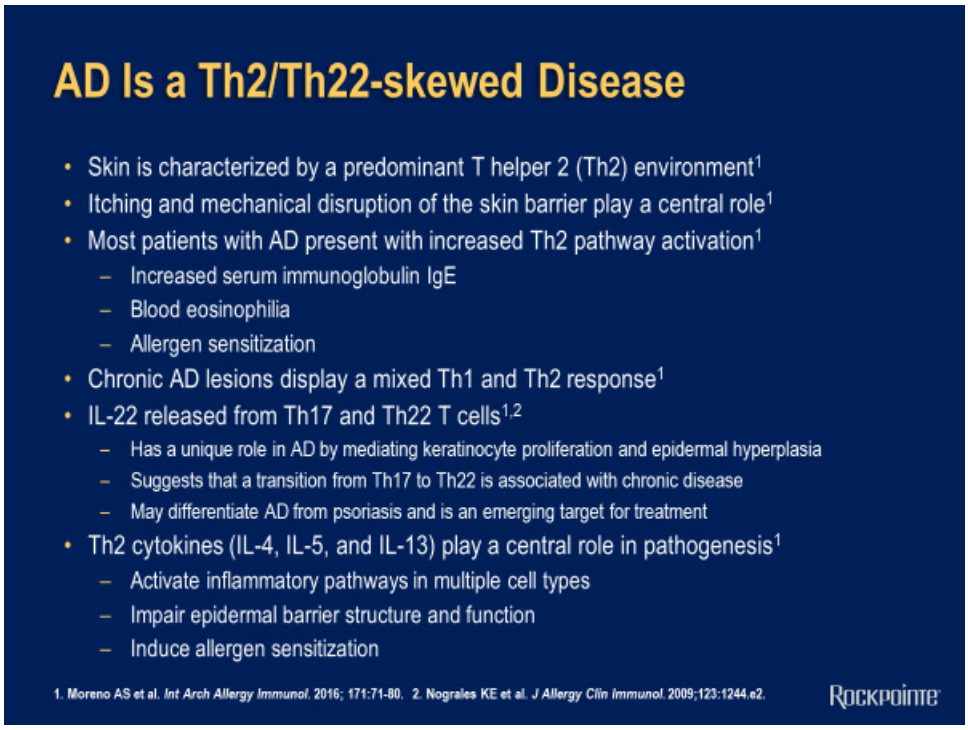


Immunologic Pathways in AD

This slide shows various pathways involved in atopic dermatitis. Using a figure from Donald Leung, you can see there are multiple different pathways involved in each different stage. Even in the non-lesional skin, there are cytokines and leukotrienes that can lead to disruption of epidermal barrier.

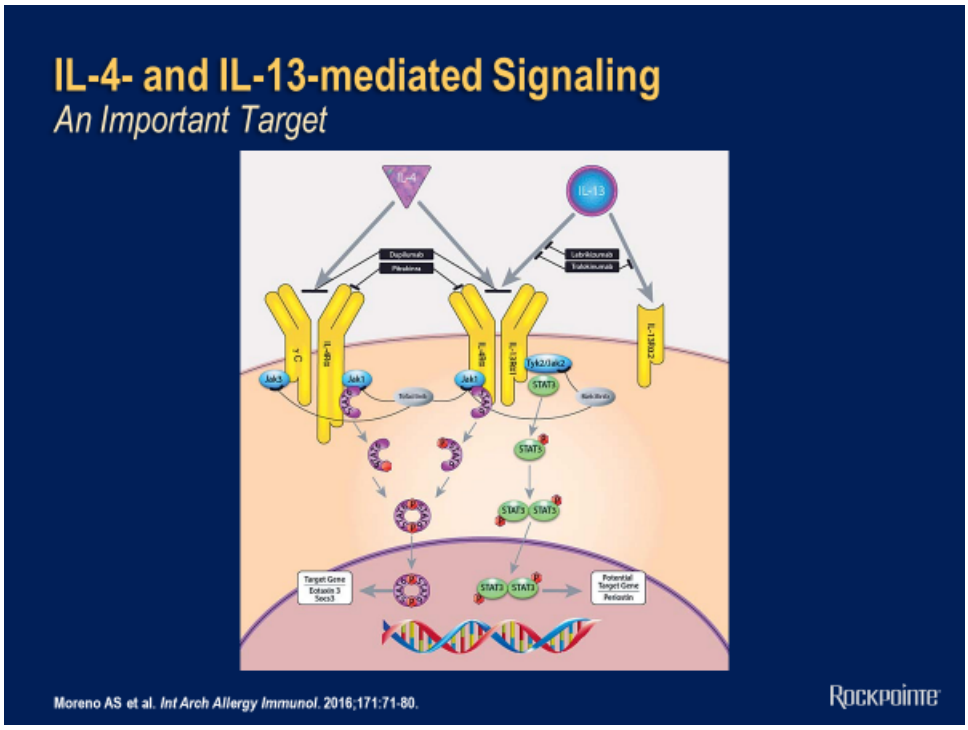
Just the act of scratching further induces these cytokines. These cytokines then cause the barrier to break. With the defect in the barrier, now you allow penetration of both allergens to the Langerhans cells and the dendritic cells to activate various T cells. These T cells are now involving both the acute and chronic atopic dermatitis lesions.

This further cycle leads on, whereas T cells release additional cytokines that lead to further disruption and a barrier dysfunction, including decrease in filaggrin production as well as an increase in the specific terminal differentiating genes that express barrier proteins such as the S100 family. All these factors, together, contribute to the epidermal hyperplasia and irritation.



AD is a Th2/Th22-skewed Disease

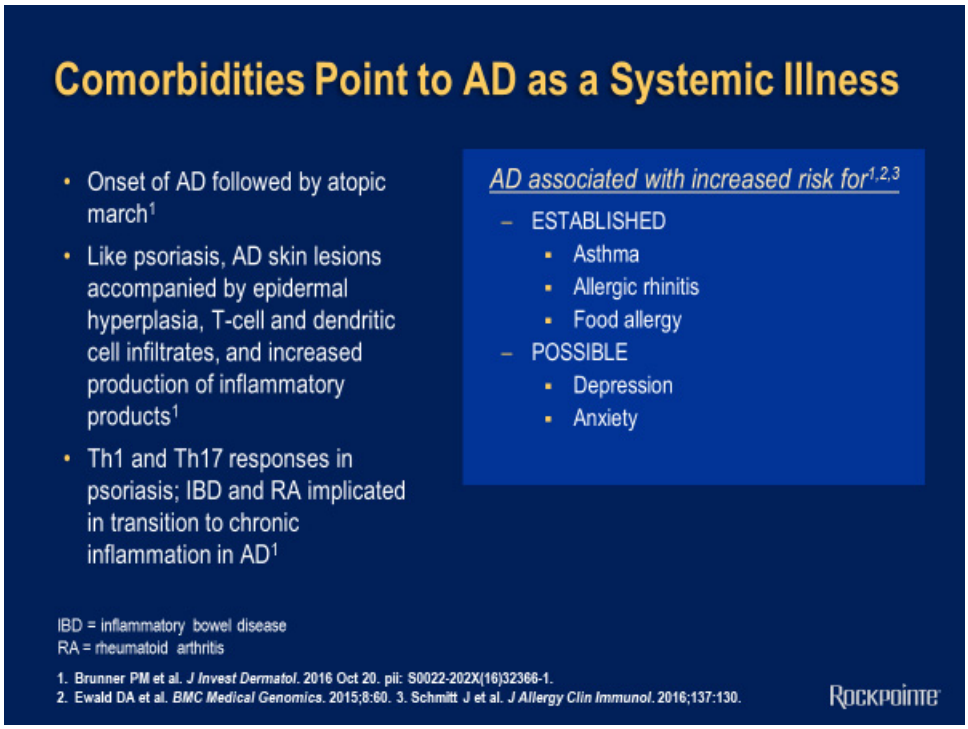
Overall, we think about atopic dermatitis being a classic Th2 disease. It's the sea of this abnormal skin barrier. You get an activation of the classic Th2 pathway of IL-4 and IL-13. These things lead to increase eosinophilia. You get allergen sensitization from the allergens going in. Then you also get some role of IL-22, which is coming from the Th17 into Th22, which may help but leads to some of the chronicity of the disease. And it probably helps differentiate a little between the atopic dermatitis and psoriasis.



IL-4- and IL-13-mediated Signaling

This slide looks at the signaling of both IL-4 and IL-13. They have some distinct and overlapping receptors. IL-4 signals through a type-I receptor, which contains the common gamma chains seen in multiple cytokine receptors as well as IL-4 alpha receptor. And also signals through a type-II receptor contains the IL-4 alpha and the IL-13 alpha 1 receptor. While IL-13 signals through the same type-II receptor, as well as a decoy receptor – called IL-13 or alpha 2 – which binds to a higher affinity. Various molecules and drugs that are in development and recently have been improved block these various receptors, such as pitakinra which is a protein that specifically binds the IL-4 receptor. While the recently approved dupilumab prevents both IL-4 and IL-13 signaling through the IL-4 receptor alpha.

Other agents block it, particularly at IL-13, such as lebrikizumab and tralokilumab. And there's further ones that signal, acting at the Jak/STAT pathway, which are some other proteins and molecules which are in clinical trials.



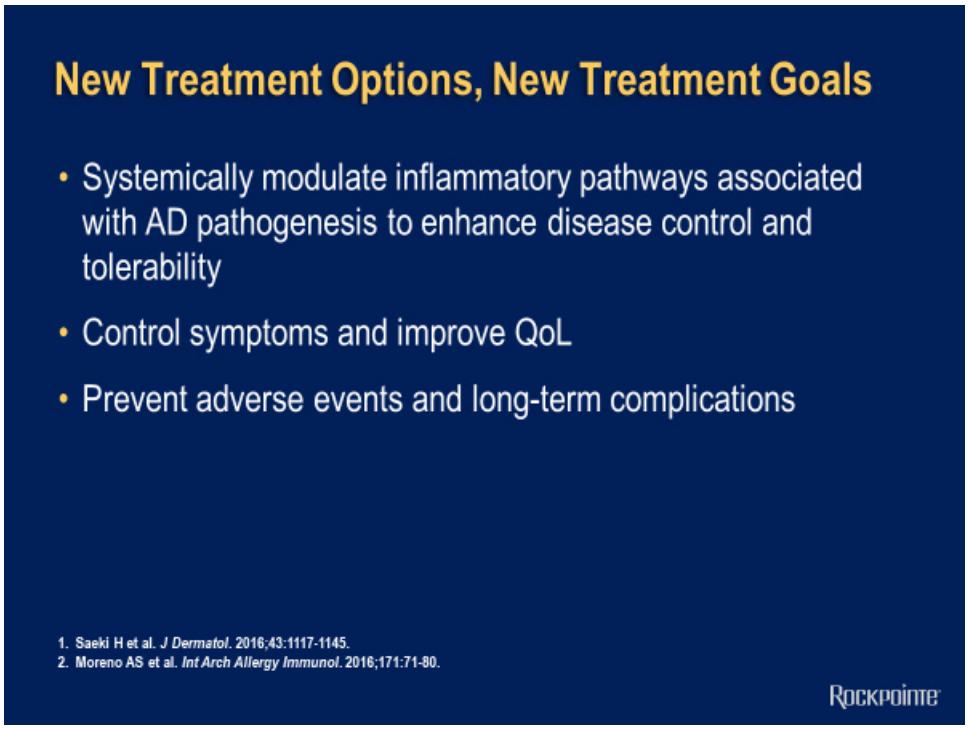
Comorbidities Point to AD as a Systemic Illness

It's clear that atopic dermatitis is not just a disease of the skin; it's the window to the whole immune system. These patients have an increased risk factor for other atopic diseases. About 20% to 30% of the patients with atopic dermatitis will go on later to develop asthma. It's clearly a risk factor for food allergists, which is the recent work shown by Gideon Lack for peanut allergy. These patients with atopic dermatitis also have a huge risk factor for allergic rhinitis.

But, recently, there is a report that's suggesting that you get not only inflammation of classic Th2 cytokines, but you may be getting to increase of some other Th1 cytokines like Th1 and Th17, which have been shown to play a role in psoriasis and inflammatory bowel disease, as well as rheumatoid arthritis, suggesting maybe this also has some association with depression and anxiety. It's unclear whether this is sort of a direct effect or just having direct effect due to having poorly controlled skin and having poor quality of life, feeling miserable, and not getting enough sleep, leading to this chronic depression and anxiety.

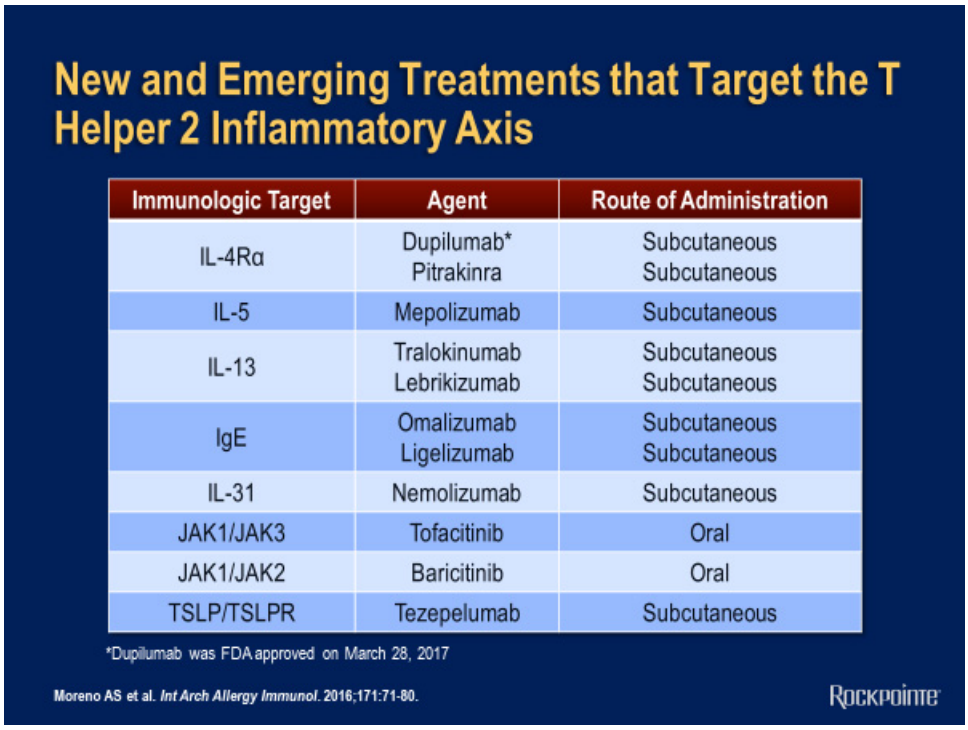
Patient Video: Unmet Treatment Needs

Next, we'll hear another video from Jane Smith again talking about how long it took to diagnose the disease and how it's a disease not just of her skin, it took a long time.



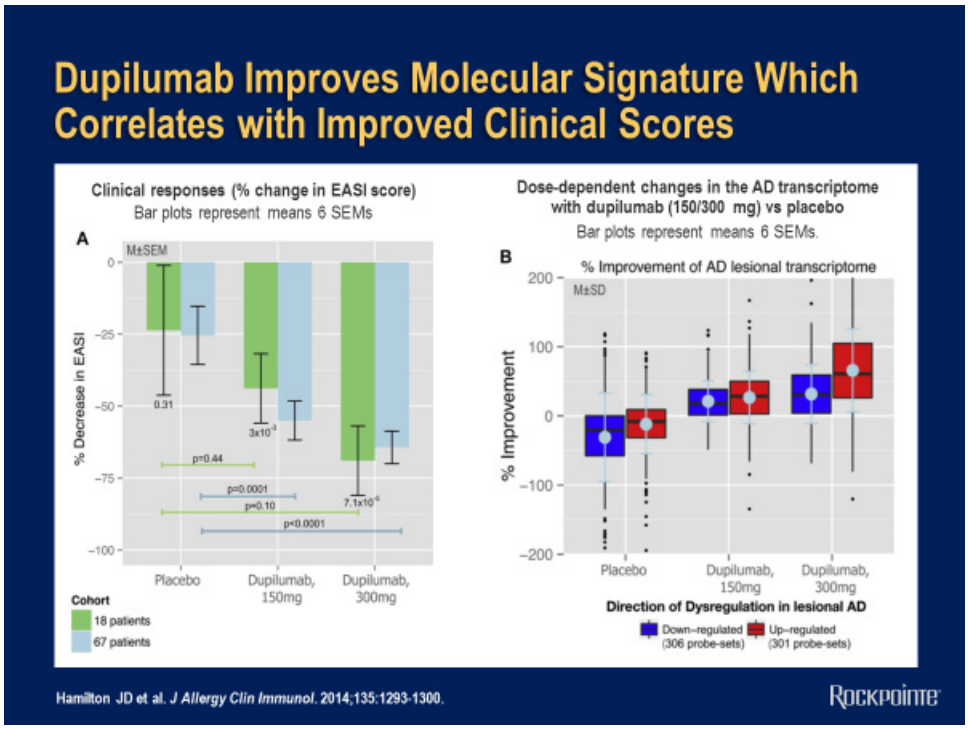
New Treatment Options, New Treatment Goals

This idea of it being systemic tells us we need to get total control of the disease, especially for patients like Jane of moderate-to-severe disease. We need to improve their quality of life, and really begin to prevent those long-term complications.



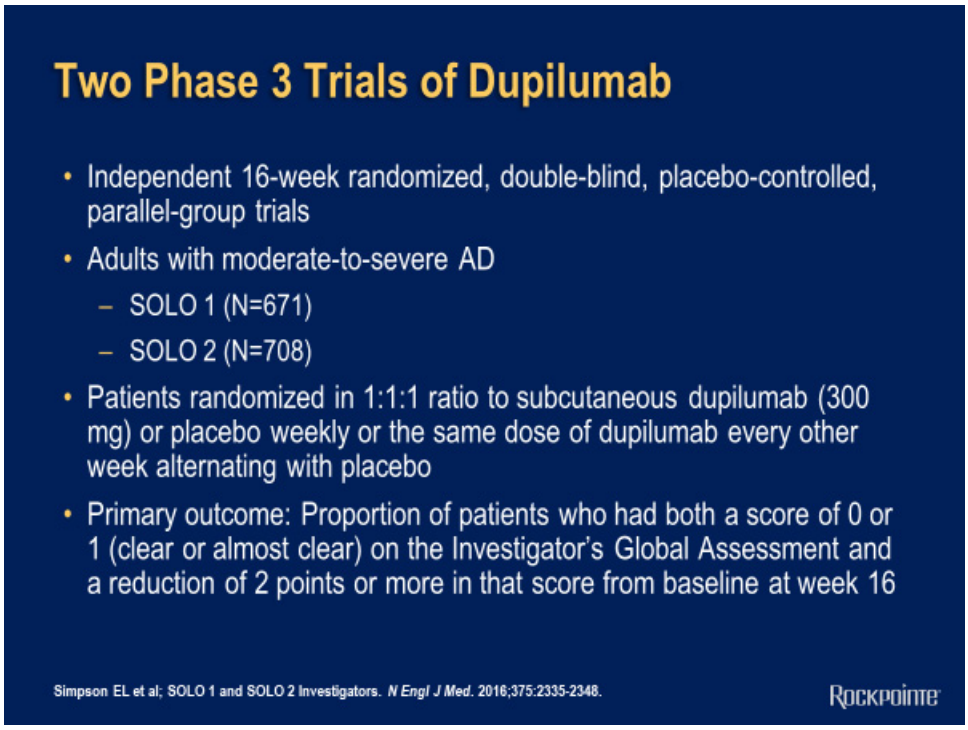
New Emerging Treatments that Target the T Helper 2 Inflammatory Axis

There are various agents that are on the clinical trials for the treatment of atopic dermatitis. Mepolizumab which is approved for asthma, as well as reslizumab, are two IL-5 agents being used. Dipilumab, which is the anti-IL-4 antagonist, which has had 2 phase III trials that were just published in the New England Journal of Medicine, has just been approved for the treatment of the disease, which we will go over in the next few slides, other agents are potential blocking anti-IGE like omalizumab, which is approved for asthma as well as chronic urticaria.



Dupilumab Improves Molecular Signature Which Correlates with Improved Clinical Scores

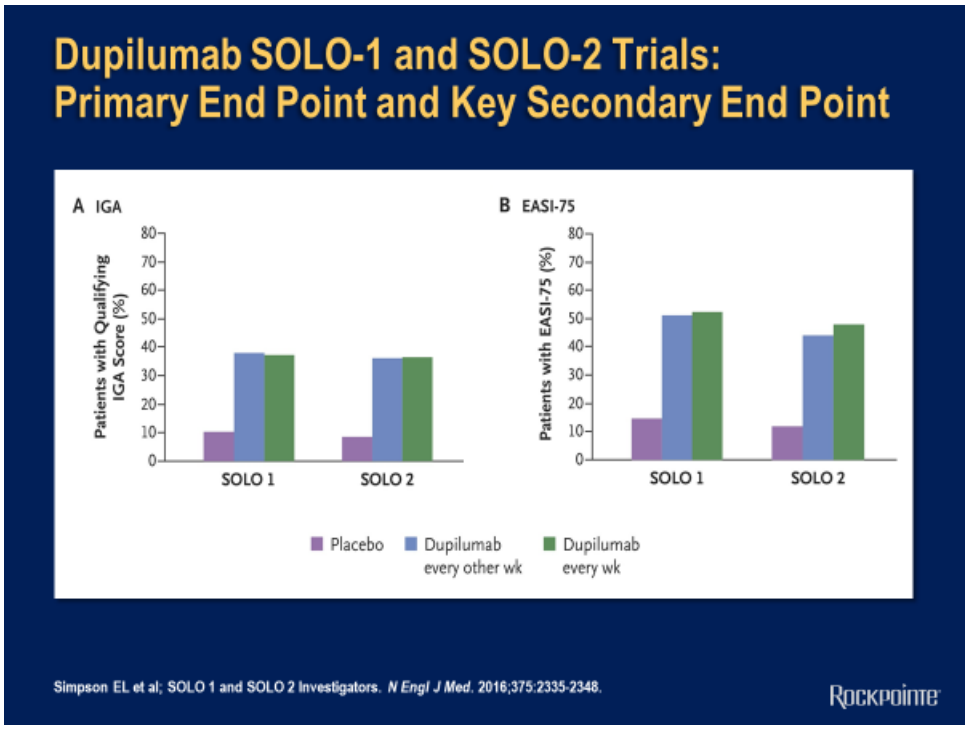
We'll go over dupilumab because that's the most recent one that's been published in *The New England Journal of Medicine*. The initial study looked at two different doses. In looking at the correlation of what they call molecular signature, which is this improvement in the transcriptomes, They looked at, basically, 181 different genes. And you can see, as they increase the dose compared to a placebo, to the 150 to 300, you saw an increasing improvement in Eczema Severity Score. As you got improvement in symptoms the transcriptome beginning to improve, getting back to sort of a baseline whether it's expression in genes of Th2 cytokines or improvement in down-regulation of some of the dendritic cell markers that show activation.



Two Phase 3 Trials of Dupilumab

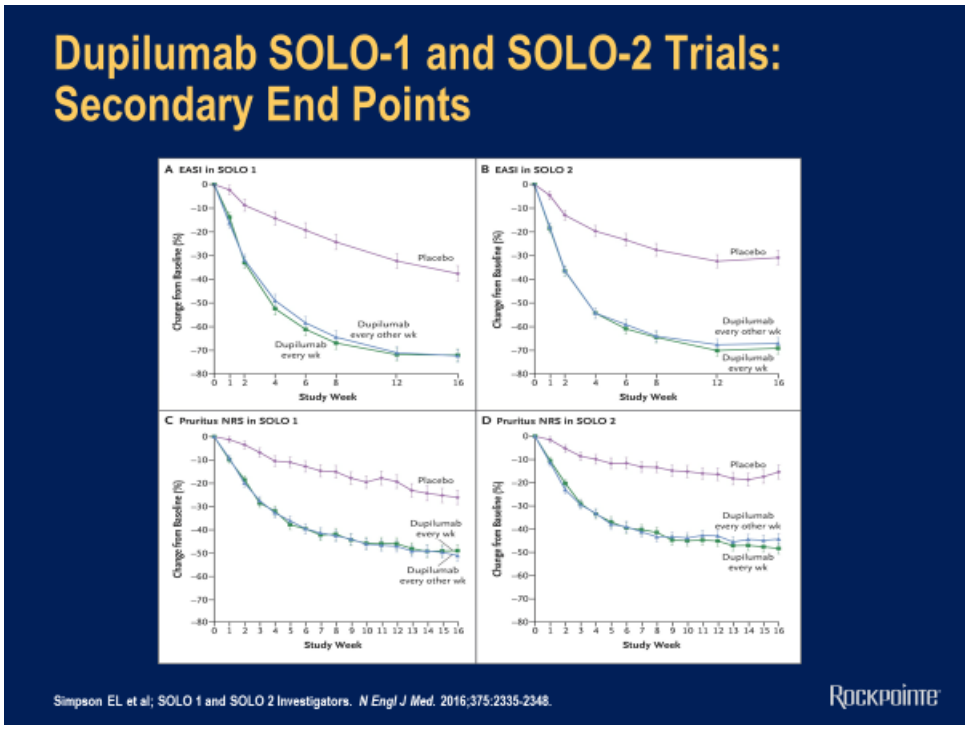
They did two Phase III clinical trials which were published in *The New England Journal of Medicine*; these were two independent trials. They're called SOLO Trial 1 and 2, and the patients were randomized in three groups: one to dupilumab weekly, or the one with every other week, and the third group just got placebo alone.

In this study, they looked at two, primarily, outcomes; one is reduction of the Investigator Global Assessment list, so this is the physician doing the study looking at the patients, how much is their eczema getting better. And they also looked at EASI scores having reduction greater than 75%.



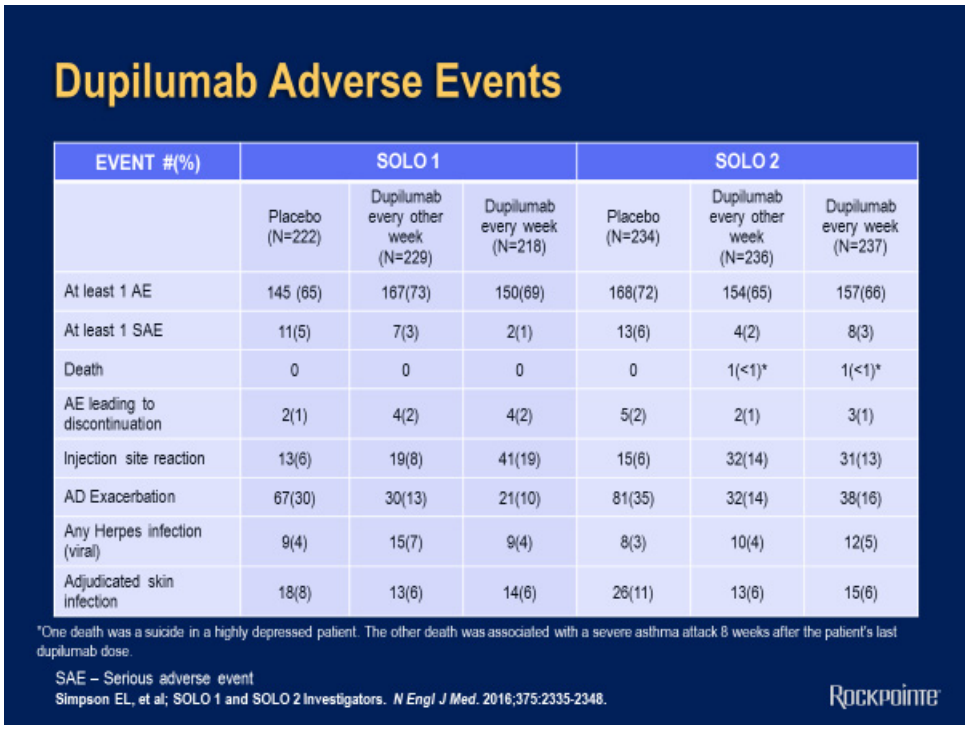
Primary End Point and Key Secondary End Point

You can see both the patients on dupilumab every other week or weekly had basically the same improvement. About 35% of the patients had significant improvement after 16 weeks of therapy compared to about 10% in the placebo group. And there was about a 15% improvement in both groups and about a 75% reduction on their Eczema Area Severity Index after 16 weeks. This was highly significant in both groups.



Secondary End Points

When you begin to look at more detailed data, looking at EASI scores for pruritus – you saw patients really had improvement within the first week, similar for both every other week or weekly compared to placebo. And improvements really continue to about week 12. In week 12, we seem to plateau for eczema severity while pruritus, again, you saw some improvement within the first week. And it continues to improve, maybe slowing down a little around week 10 but really improvement throughout the whole study for both treatment regimens.



Dupilumab Adverse Events

EVENT #(%)	SOLO 1			SOLO 2		
	Placebo (N=222)	Dupilumab every other week (N=229)	Dupilumab every week (N=218)	Placebo (N=234)	Dupilumab every other week (N=236)	Dupilumab every week (N=237)
At least 1 AE	145 (65)	167(73)	150(69)	168(72)	154(65)	157(66)
At least 1 SAE	11(5)	7(3)	2(1)	13(6)	4(2)	8(3)
Death	0	0	0	0	1(<1)*	1(<1)*
AE leading to discontinuation	2(1)	4(2)	4(2)	5(2)	2(1)	3(1)
Injection site reaction	13(6)	19(8)	41(19)	15(6)	32(14)	31(13)
AD Exacerbation	67(30)	30(13)	21(10)	81(35)	32(14)	38(16)
Any Herpes infection (viral)	9(4)	15(7)	9(4)	8(3)	10(4)	12(5)
Adjudicated skin infection	18(8)	13(6)	14(6)	26(11)	13(6)	15(6)

*One death was a suicide in a highly depressed patient. The other death was associated with a severe asthma attack 8 weeks after the patient's last dupilumab dose.

SAE – Serious adverse event

Simpson EL, et al; SOLO 1 and SOLO 2 Investigators. *N Engl J Med*. 2016;375:2335-2348.

Rockpointe

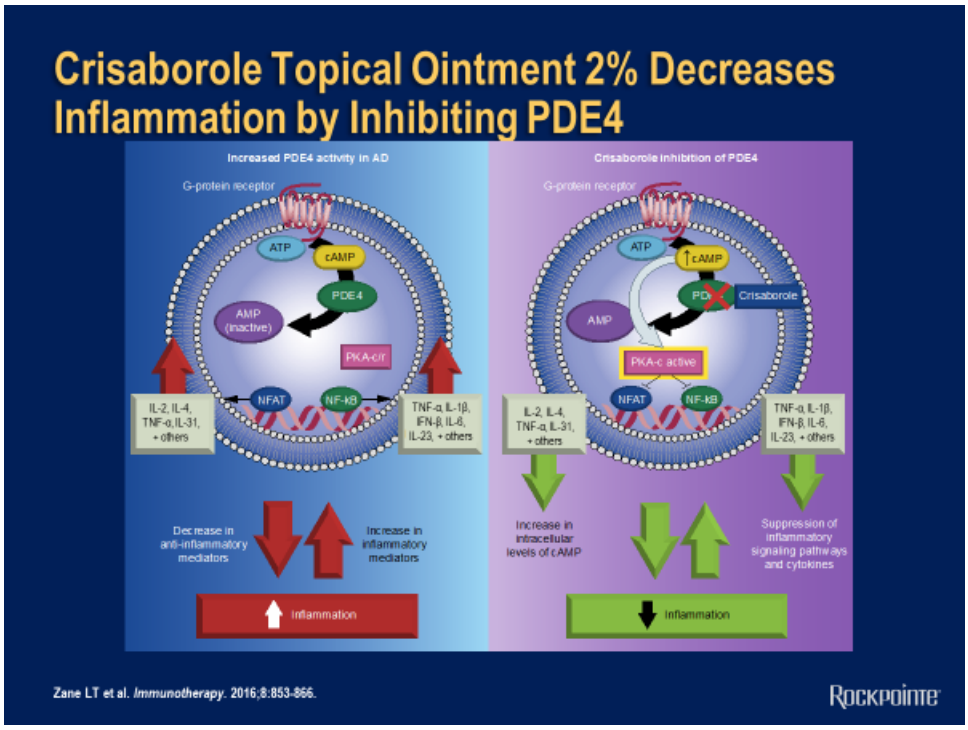
Dupilumab Adverse Events

One important thing when we think about therapies, we need to think about adverse events.

If you look at adverse events, they were basically the same in both studies compared to placebo. If anything, the serious adverse events were slightly lower in the active therapies compared to placebo, but not significantly different.

There were two deaths in the SOLO 2 Trial; one was an asthma death eight weeks after trial, and the other was a suicide by a depressed patient. Both of these were not thought to be related to the drug whatsoever.

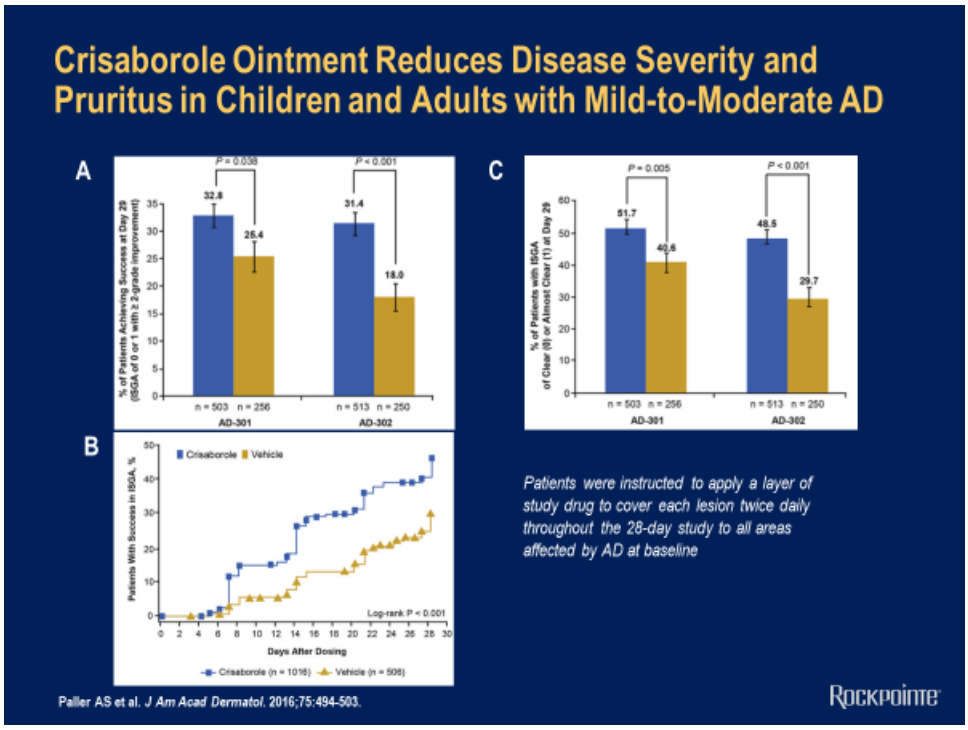
There were some injection-site reactions, slightly higher in the patients taking dupilumab weekly compared to every other week. Eczema exacerbations, not surprisingly, were less. And along those therapies, the rate of skin infections were similar in both placebo and active two therapy groups.



Crisaborole Topical Ointment 2% Decreases Inflammation by Inhibiting PDE4

Crisaborole, a recently approved topical ointment, looks at the PDE4 pathway. Looking at the pathway, as you can see on the left-hand panel, PDE4 is involved in the basic inflammatory pathway. Inflammation work done by Jon Hanifin a long time ago, looking at seeing elevated phosphodiesterase inhibitor in patients with atopic dermatitis. When this PDE4 is activated, you lead to an inactivation of the of AMP and result in increase of production of inflammatory cytokines like the interleukins and the TNF-alphas. These interleukins, IL-4, et cetera, lead to disruption of the barrier dysfunction.

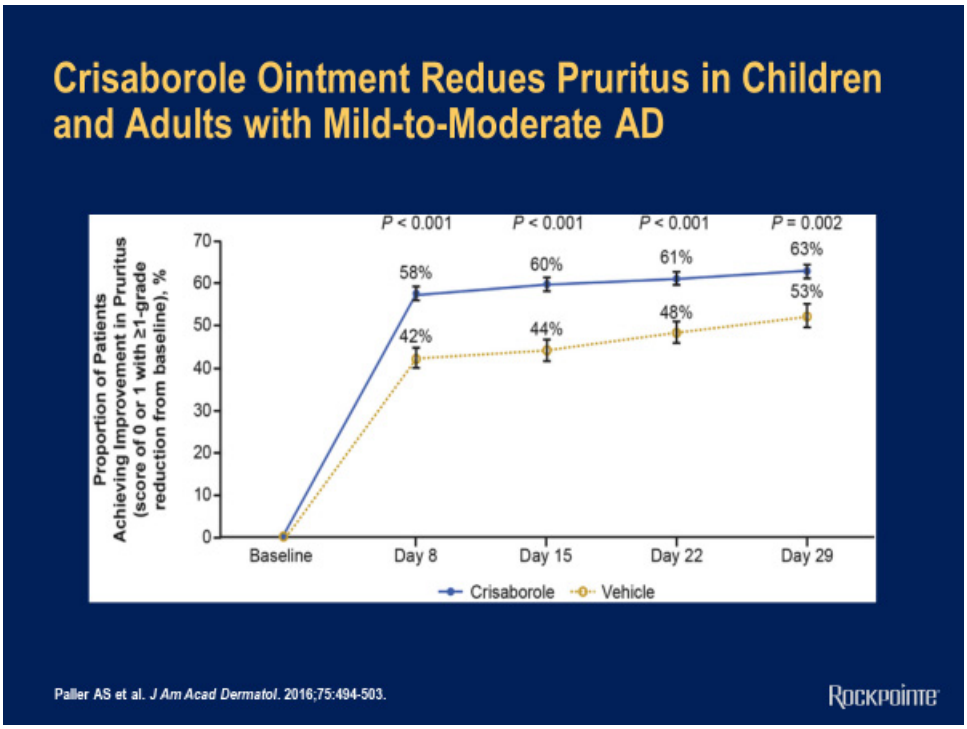
Inhibition, which is seen on the right now with the new topical agent, leads to activation of intracellular AMP, which then leads to inhibition of the NFAT and NF-kB pathway, which is responsible for the inflammatory cytokines and any associated inflammation.



Crisaborole Ointment Improves Disease Severity and Pruritus in Children and Adults with Mild-to-Moderate AD

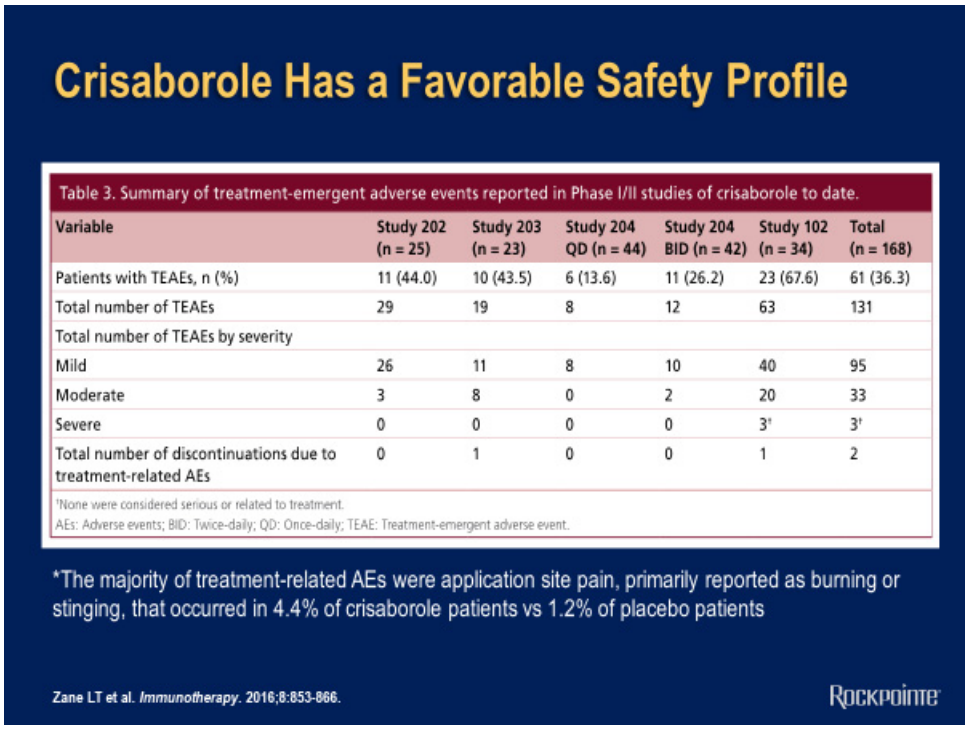
There were two clinical trials that were published looking at children and adults with mild-to-moderate atopic dermatitis. They looked at Investigator Global Assessments it's called ISGA instead of IGA, but it's a very similar score. After 29 days, there's an improvement with the skin therapy compared to placebo. This is looking at the yellow bar is placebo, or the vehicle alone, and the other is the active therapy, so you get improvement from, basically, 25 to 32, and 18 to 31.

And you can see on the Panel B, again, there's improvement. You get improvement after the first week, and it continues to improve throughout the 30 days of the therapy. In this, they were told to put this on twice a day, and this is looking, at a percentage of patients cleared.



Crisaborole Ointment Improves Pruritus in Children and Adults with Mild-to-Moderate AD

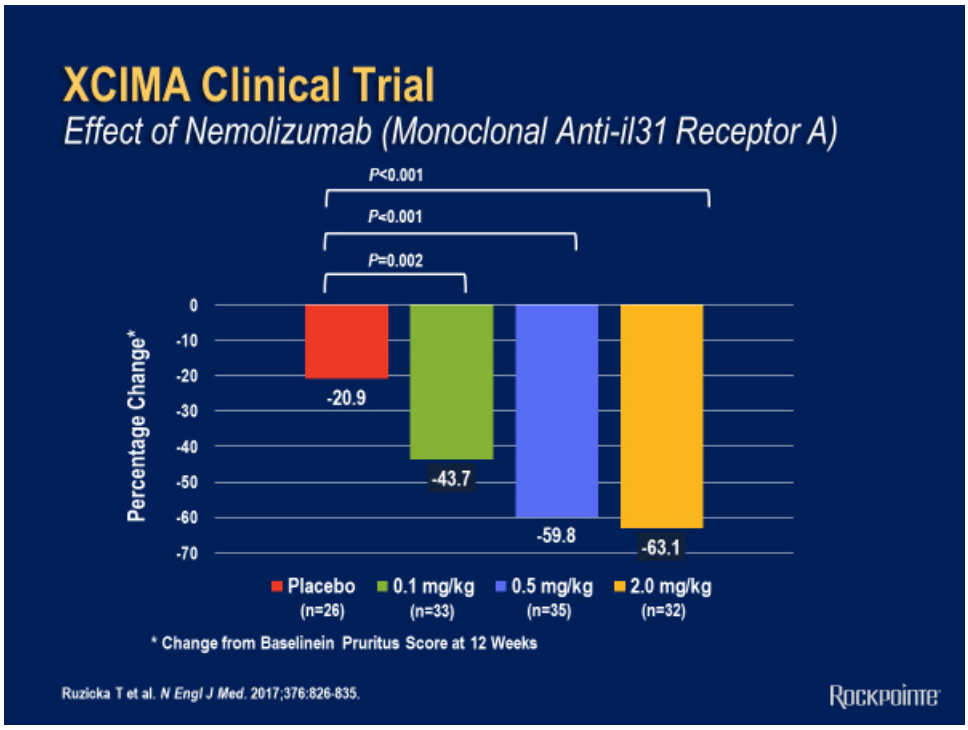
It's important because pruritus, or itching, is sort of this main feature which really keeps people up at night, and so if you ask any patient with atopic dermatitis, this is the key thing. And you see with the PDE4 inhibitor, a significant improvement by one week compared to a placebo of basically 60% to 40% in the placebo group, and this is able to maintain throughout the study.



Crisaborole Has a Favorable Safety Profile

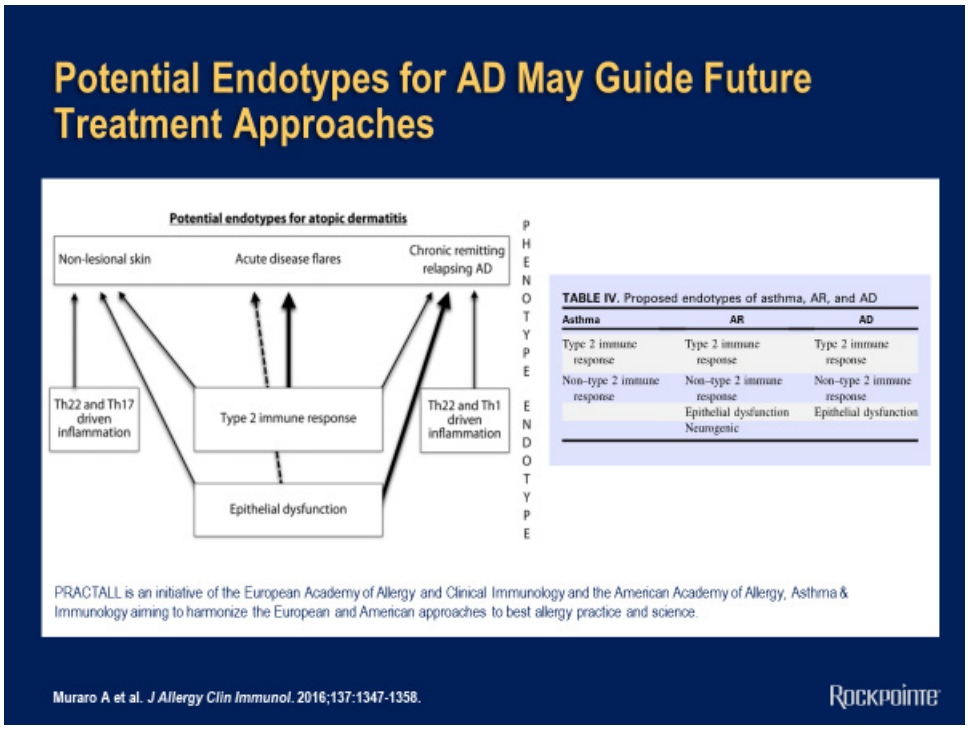
Again, we need to also look at adverse events throughout the study. There was no significant major issues. Two patients stopped the therapy due to treatment-related events.

4% of the patients on crisaborole, or the active therapy, had some itching and burning compared to about 1% of the placebo.



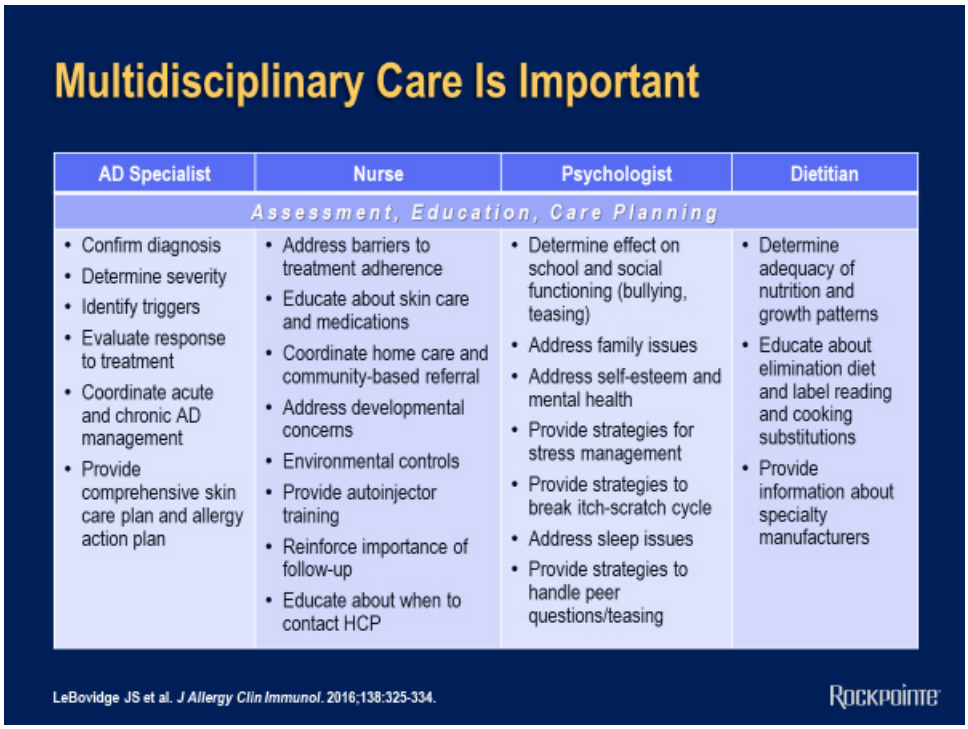
XCIMA Clinical Trial

There's been a recent publication of positive phase 2 data for Anti IL31, which is the agent called nemolizumab. And AntiIL31 is an agent used primarily in pruritus. This recent paper published in the New England Journal of Medicine showed a positive dose effect as you can see on this slide, as they moved up in doses from .1 to .5 to 2 mg you saw a significant improvement in pruritus in these patients as well as improvement in general atopic dermatitis studies. Again this will need to be shown in additional studies before being able to be used in patients.



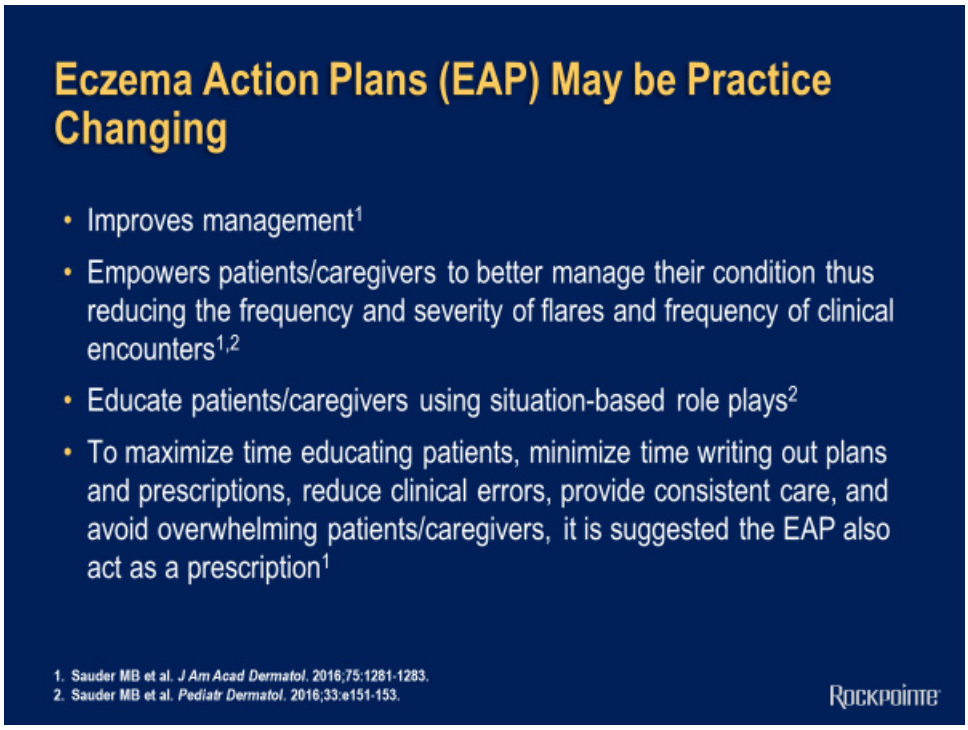
Potential Endotypes for AD May Guide Future Treatment Approaches

What does this really bring this down to? When we think about atopic dermatitis, we know it's not just a disease of the skin; this is some recommendations from the PRACTALL. The PRACTALL is a European and American allergy group with a generalized approach to disease. The idea is, where can we start to treat these things by controlling this epithelial barrier dysfunction? We talked about emollients, getting this Th2 pathway under control. It's potentially some of these new biologics or the topical steroids and the topical calcineurin inhibitors. The Th1 general information, again, is along the same lines.



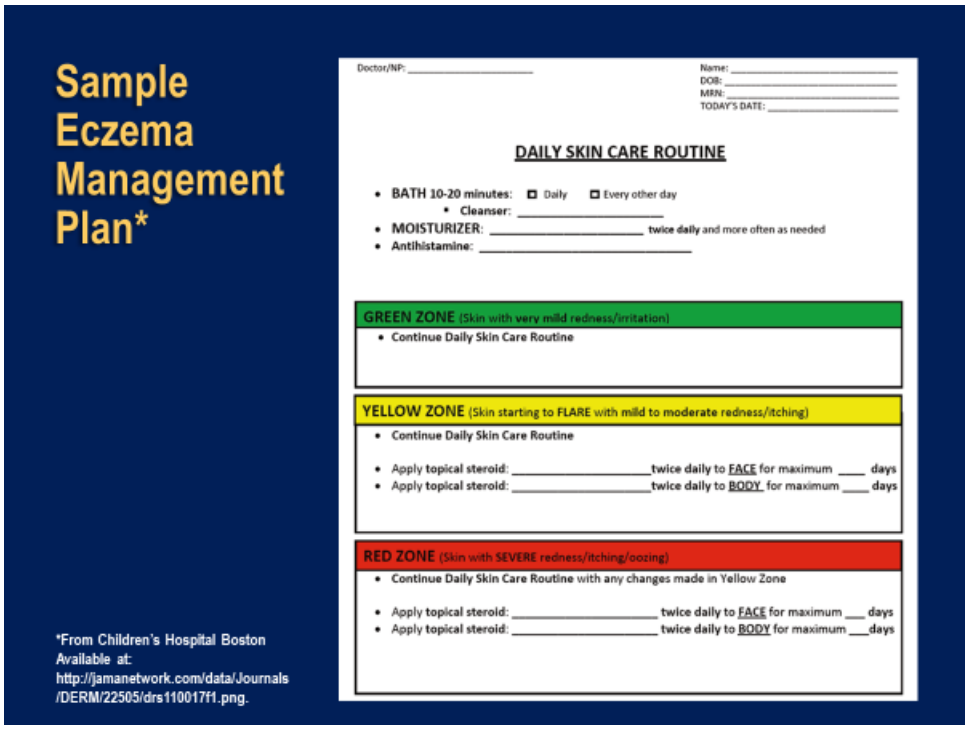
Multidisciplinary Care is Important

This leads to a multiple generalized approach, not only involving atopic dermatitis specialists, making sure we have the diagnosis, treating the disease, coming up with a good skincare plan. You need good education, especially by a nurse or other healthcare providers to help you with that, getting good care of the skin, teaching them how to do it, working on therapies and helping along those lines. A lot of these patients, as we talked about, have anxiety and depression, and sleep issues. A lot of patients have visual atopic dermatitis, get bullied and have stress. The young children who have dietary or multiple food allergies need to see a dietitian to make sure they're growing well.



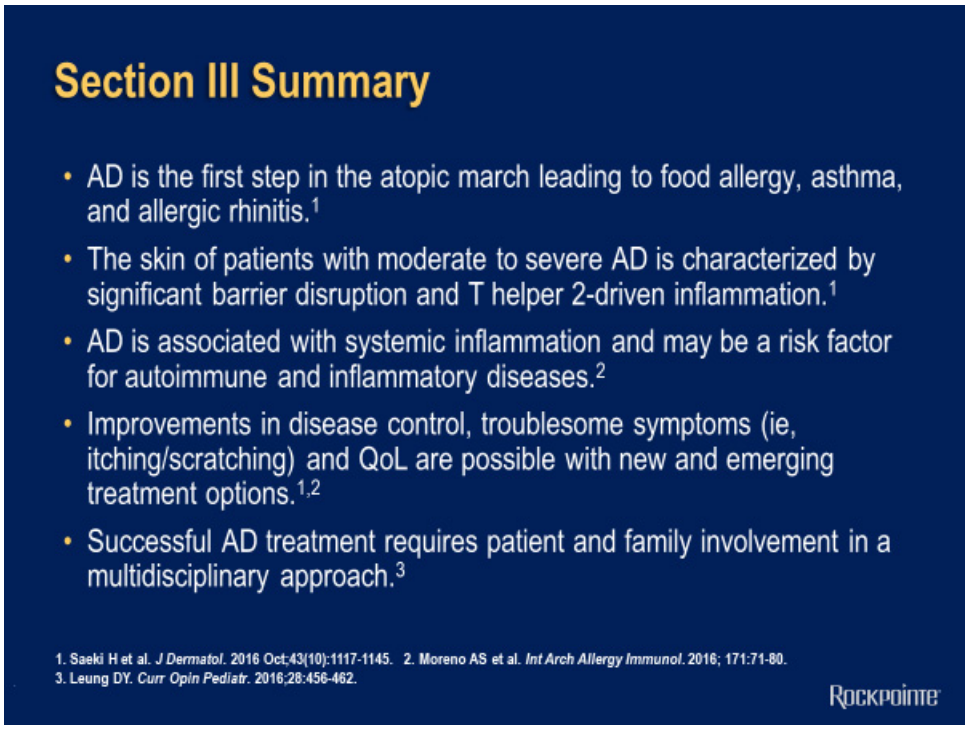
Eczema Action Plans (EAP) May be Practice Changing

What's been shown to play a role are these eczema action plans, similar to what's been done for asthma. And these eczema plans basically improve management and helps the patients help themselves. They come up with a basic therapy: this is what to do when you begin to get sick, and this is what to do when things get worse.



Sample Eczema Management Plan*

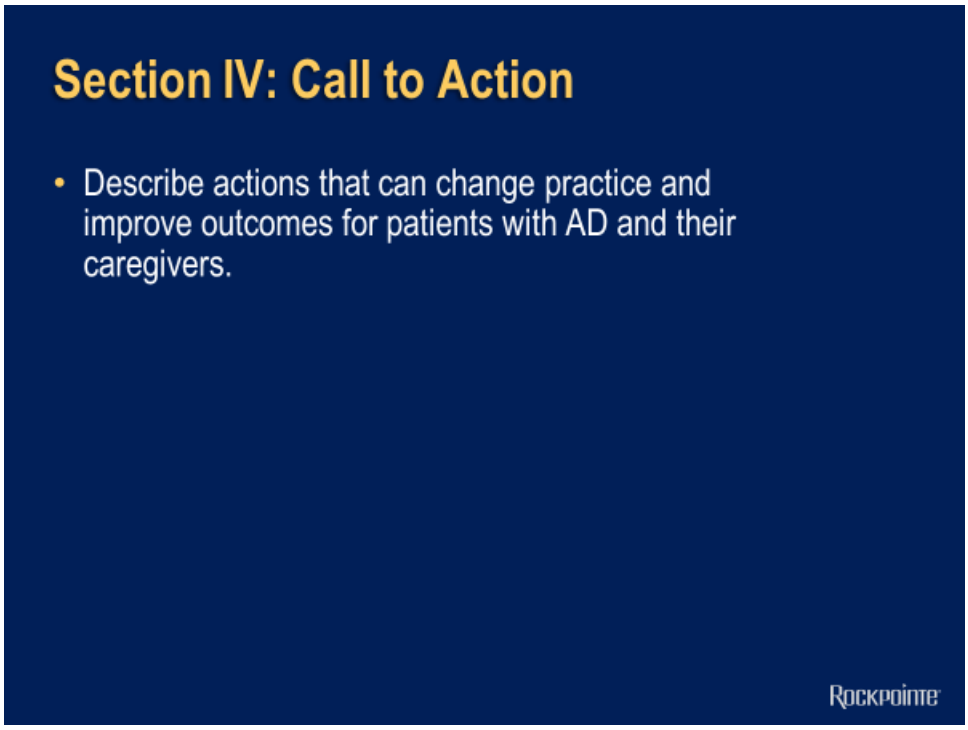
This is an example of an action plan for atopic dermatitis, this one is from Children's Hospital of Boston. There are different spots for treating for the face and the body. When someone has more chronic disease there is maintenance therapy which is the green zone, which you're going to have proactive therapy. Also, this is where the new biologics will be able to be fit in as well.



Section III Summary

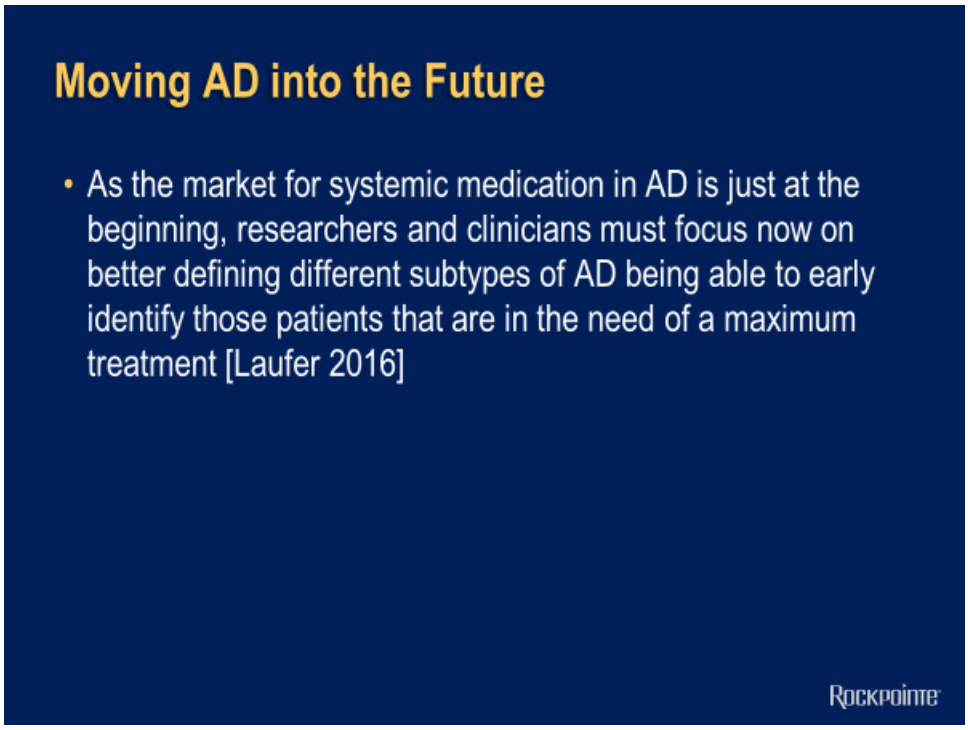
Just to summarize, we talked about atopic dermatitis, the beginning the atopic march; patients with atopic dermatitis are at risk to develop asthma and allergic rhinitis. The thought is that we can prevent things happening if we control the atopic dermatitis early on.

The atopic dermatitis is a Th2-driven disease. There is also increase Th1 phenotype of overall inflammation. Therefore, it's really important to control our atopic dermatitis and have improvement in quality of life, and this involves not only whether we use the new therapies or new therapies that'll be coming out in the future, but a general team approach to involving the patient with these eczema care plans, as well as other healthcare providers.



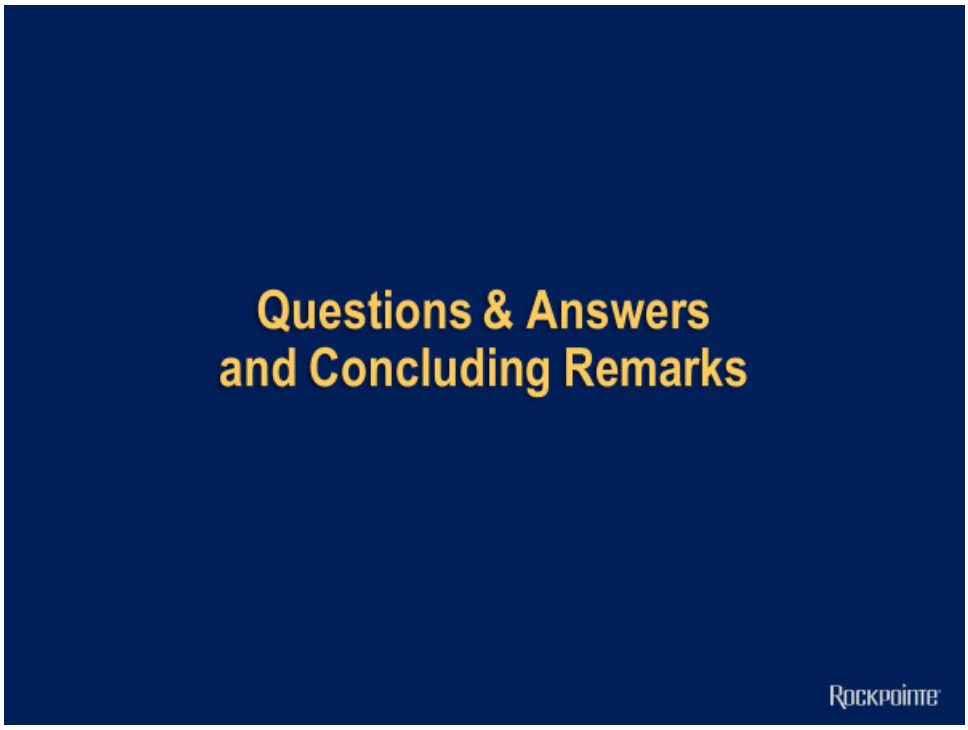
Section IV: Call to Action

What do we need to do? We need to think about what we can do to help control atopic dermatitis. This is an area that really needs additional therapy. This is the bottom line – we want to make our patients happier.



Moving AD into the Future

And now things have changed. There will be new therapies, potentially, use the new biologics, indentify who is the right patient, moderate or severe patient? It's beginning to get more personalized medicine to help control atopic dermatitis.



Q&A

Joel M. Gelfand, MD, MSCE: Thank you, Dr. Spergel. With all of these advances in atopic dermatitis therapies becoming available for us, where do you see them playing a role in the current treatment paradigm of these patients, from your perspective?

Jonathan M. Spergel, MD, PhD.: Dr. Gelfand, the very interesting question is where to put on these newer agents in the treatment of atopic dermatitis. Thinking about the clinical trials of what's been published, dupilumab appears to be more for the moderate/severes. In my mind, this will take place where we currently use phototherapy and cyclosporine, potentially, the patients who are failing their topical steroids and topical calcineurin inhibitors. And maybe, also, because it's blocking the general atopic pathway, with a patient who has moderate disease and lots of other atopic features, asthma and allergic rhinitis.

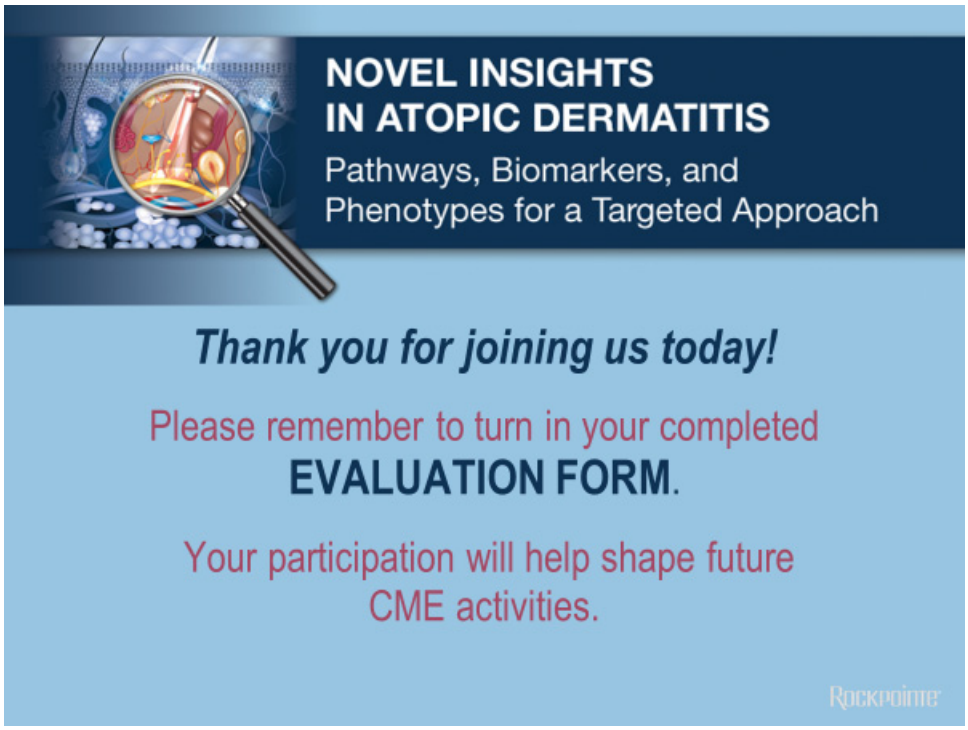
Now, crisaborole, the PDE4 inhibitor, seems to be more for the mild-to-moderate, so it may be something to be used like the topical calcineurin inhibitors tacrolimus and pimecrolimus, sort of a second agent after failing topical steroids. We'll need additional studies to see what all the safety issues are comparing those three agents. But, in my mind, based on what we're seeing, it seems to be another topical medication.

Joel M. Gelfand, MD, MSCE: Well, from my perspective as a dermatologist, the most striking advances are in the systemic therapy arena. Patients with atopic dermatitis, essentially, have had no good options for managing their disease. The patients who have severe atopic eczema will probably need to consider the newer biologics such as dupilumab as a first-line agent for managing their disease.

Of course, insurance issues may be a concern in this circumstance, but, in my view, patients who are not adequate control with topical therapies or not controlled with very short courses of

prednisone are people that we have to consider, these more effective therapies that have better safety profiles than our existing treatments we use, such as cyclosporine or, of course, oral prednisone.

Some of the newer topical therapies for atopic dermatitis, are a welcome addition to our therapeutic armamentarium. Certainly, topical steroids – we are concerned about their impacts of atrophy on the skin over time. And, of course, the topical new modulators, pimecrolimus and tacrolimus both carry black box warnings, which sometimes create safety concerns for providers and patients. Therefore, having additional options, non-steroidal, are certainly going to be welcome to managing this chronic disease.



Thank you

I want to thank you, Dr. Spergel, for sharing your insights with us in this educational program.

And I want to thank you, the audience, for joining us, and learning about atopic dermatitis and the expanding therapeutic paradigm we now have available to us.

And I want to remind you to please complete the CME survey at the end of this educational activity.