

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.

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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

Faculty/Steering Committee

Faculty/steering committee reported the following relevant financial relationships that they or their spouse/partner have with commercial interests:

Joel M. Gelfand, MD, MSCE – *Consultant/Independent Contractor:* Abbvie, Coherus, Janssen, Merck, Novartis, Pfizer, Valeant; *Research Support/Grants:* AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, Regeneron, Sanofi; *Other:* Co-patent holder for Resiquimod

Jonathan M. Spergel, MD, PhD – *Consultant/Independent Contractor:* Dannone, DBV Technology; *Research Support/Grants:* Aimmune Therapeutics; *Stock Shareholder:* DBV Technology

Non-faculty Content Contributors

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Carole Drexel, PhD, CHCP; Barry Watkins, PhD; Blair St. Amand; Thomas Sullivan; Lindsay Scott, PT, DPT, ATC: Nothing to disclose

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Disclosures Slide

Our disclosures are as shown on this slide.

Educational Objectives

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

- Recognize the importance of targeting the underlying pathophysiology of atopic dermatitis (AD) that is driven by abnormal type 2 immune responses
- Summarize the role of type 2 immune response in the pathophysiology of AD and the atopic march
- Recognize hallmark signs and symptoms of AD to ensure early diagnosis
- Apply appropriate assessments to determine disease severity
- Explain how emerging systemic treatments for AD can improve management of the disease and its comorbidities, while considering MOAs, safety and efficacy profiles, indications, and impacts on AD biomarkers and disease progression

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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.

Section I: Welcome and Introduction

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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

- Impact goes beyond the physical signs and symptoms – AD negatively impacts people's lives socially and psychologically
- Pathophysiology is complex and new insights have led to the new FDA-approved systemic agents for AD
- New directed therapies should be incorporated in a multimodal approach to management, along with concomitant continuous or intermittent use of standard therapies

Friedlander SF et al. *Semin Cutan Med Surg*. 2016;35(5 Suppl):S88-S99.
New Survey Reveals the Widespread and Serious Impact of Moderate-to-Severe Atopic Dermatitis on People Living with the Disease. Available at: <http://www.streetinsider.com/Press+Releases/New+Survey+Reveals+the+Widespread+and+Serious+Impact+of+Moderate-to-Severe+Atopic+Dermatitis+on+People+Living+with+the+Disease/12104737.html>. Accessed November 30, 2016.


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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 Health-Related QoL

- Survey of 505 US adults (≥18 years of age) with moderate-to-severe AD
 - 82% have made lifestyle modifications
 - 70% often or sometimes experience flares while on treatment
 - 55% have decreased confidence
 - 49% have moderate to significant sleep disruption
 - 23% feel depressed and 28% feel anxious
 - 20% report that AD has impacted their ability to maintain employment

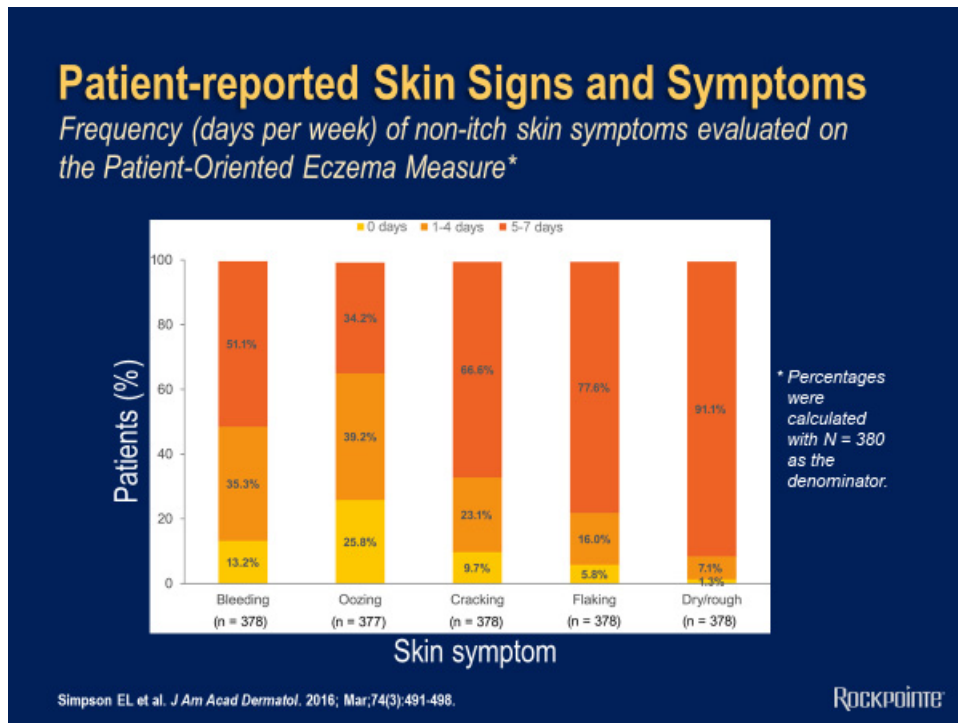


New Survey Reveals the Widespread and Serious Impact of Moderate-to-Severe Atopic Dermatitis on People Living with the Disease. Accessed November 30, 2016. Available at: <http://www.streetinsider.com/Press+Releases/New+Survey+Reveals+the+Widespread+and+Serious+Impact+of+Moderate-to-Severe+Atopic+Dermatitis+on+People+Living+with+the+Disease/12104737.html>.

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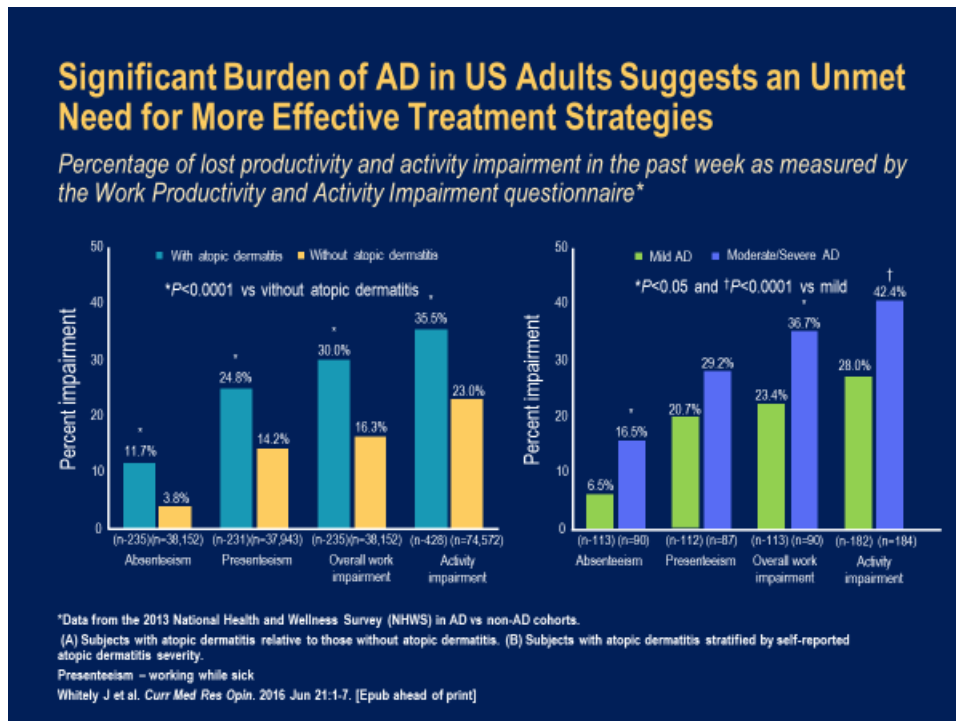
Impact of AD on HRQoL

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.



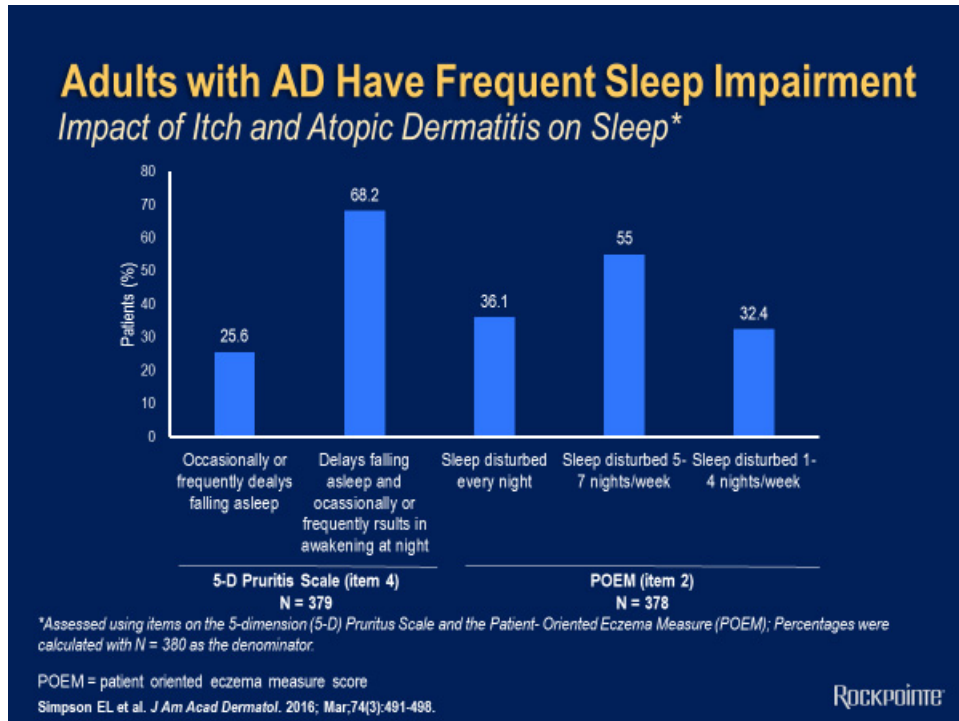
Patient-reported Skin Signs and Symptoms

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



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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

- Recognize the importance of making accurate diagnosis
- Recognize hallmark signs and symptoms of AD to ensure early diagnosis
- Apply appropriate assessments to determine disease severity

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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*

| ESSENTIAL FEATURES | IMPORTANT FEATURES | ASSOCIATED FEATURES |
|--|--|--|
| Both must be present 1. Pruritus 2. Eczema (acute, subacute, chronic) <ul style="list-style-type: none"> a. Typical morphology and age-specific patterns <ul style="list-style-type: none"> • Infants/children: facial, neck and extensor involvement • Any age group: current or previous flexural lesions • Sparing the groin or b. Chronic or relapsing history | Add support to the AD diagnosis, present in most cases 1. Early age of onset 2. Atopy <ul style="list-style-type: none"> a. Personal and/or family history b. IgE reactivity c. Xerosis | Suggestive of AD but too nonspecific to be used for defining or detecting AD in studies 1. Atypical vascular response (eg, facial pallor, white dermographism, delayed blanch response) 2. Keratosis pilaris/pityriasis alba/hyperlinear palms/ ichthyosis 3. Ocular/periorbital changes 4. Other regional findings (eg, perioral changes/periauricular lesions) 5. Perifollicular accentuation/lichenification/prurigo lesions |
| EXCLUSIONARY CONDITIONS | | |
| <ul style="list-style-type: none"> • Scabies • Psoriasis • Ichthyoses | <ul style="list-style-type: none"> • Seborrheic dermatitis • Contact dermatitis (irritant or allergic) • Cutaneous T-cell lymphoma | <ul style="list-style-type: none"> • Photosensitivity dermatoses • Immune deficiency diseases • Erythroderma of other causes |

*Adapted from Eichenfield LF et al. Consensus Conference on Pediatric Atopic Dermatitis. *J Am Acad Dermatol.* 2003;49(6):1088-1095.
Eichenfield LF et al. *Pediatrics.* 2015;138:554-565.

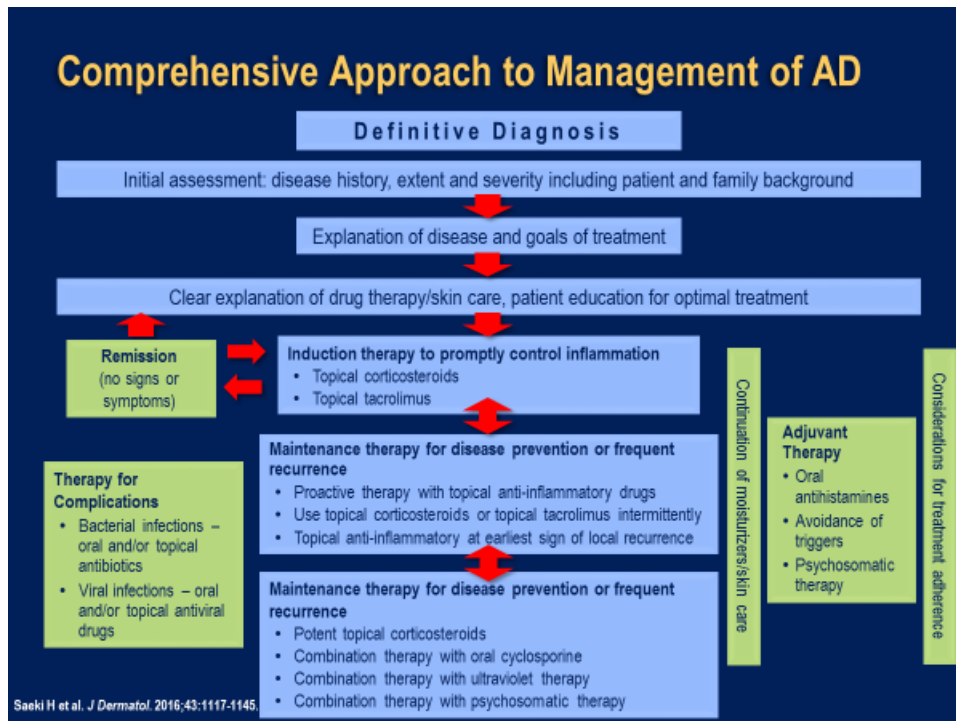
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AD Diagnostic Criteria*

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

In order to be diagnosed with atopic dermatitis according to the UK Working Party diagnostic criteria, patients must have a history of itchy skin plus at least 3 of the following:

- History of a flexural involvement (antecubital or popliteal fossa, front of ankles, wrists, or neck)
- Visible flexural dermatitis
- Personal history of asthma or hay fever (or history of atopic disease in parents or siblings if the patient is younger than 4 years of age)
- History of a generally dry skin in the last year
- Onset under the age of 2

Atopic Dermatitis Diagnostic Criteria. Available at: <http://bestpractice.bmj.com/best-practice/monograph/87/diagnosis/criteria.html>.

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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

| EASI* | SCORAD** |
|---|---|
| <ul style="list-style-type: none"> • Only AD scoring system that meets standardization criteria • Well-validated composite score based on 4 body regions: <ul style="list-style-type: none"> • Head and neck • Trunk (including genital area) • Upper limbs • Lower limbs (including buttocks) • Total area of involvement in each region graded on a scale of 0 to 6 • AD severity graded as composite of 4 parameters (ranked on a scale of 0–3), including redness, thickness, scratching, and lichenification • Surface area of each region relative to body size is multiplying factor, resulting in the following severity strata: <ul style="list-style-type: none"> • 0=clear • 0.1–1.0=almost clear • 1.1–7.0=mild • 7.1–21.0=moderate • 21.1–50.0=severe • 50.1–72.0=very severe | <ul style="list-style-type: none"> • Older less frequently used eczema score • Addresses surface area by rule of nines and severity of 6 features by region on a scale of 0 to 3 <ul style="list-style-type: none"> • Redness • Swelling • Oozing/crusting • Scratch marks • Skin thickening (lichenification) • Dryness (assessed in an area with no inflammation) • Subjective symptom parameter for itching and sleeplessness helps in gauging disease activity and impact on a child's life |

*EASI = Eczema assessment and severity index scoring system
 **SCORAD = Severity Scoring of Atopic Dermatitis Index
 Silverberg NB. *Cutis*. 2016;97:326-329.

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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



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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

- Disruption of skin barrier is a central feature of AD¹
 - Transepidermal water loss and xerosis
 - Diminished levels of ceramide reduce water-binding capacity
- Use of occlusive emollients reduces requirement for topical and systemic immunosuppressants¹
- Use of emollients in at-risk infants significantly reduced risk for developing AD²
- Soak and seal: Regular daily 15-minute soaking baths in lukewarm water (showers not as effective) and immediate application of occlusive ointment^{1,3}
- Re-application of occlusive emollients throughout the day^{1,3}

1. Lyons JJ et al. *Immunol Allergy Clin North Am*. 2015;35:161-183; 2. Horimukai K et al. *J Allergy Clin Immunol*. 2014;134:824-830; 3. AAD 2014 Guidelines. <https://www.aad.org/media/news-releases/american-academy-of-dermatology-s-newest-guidelines-for-the-management-of-atopic-dermatitis-focus-on-treatments>.

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.

American Academy of Dermatology: 2014 Recommendations for AD Treatment

| RECOMMENDATION | STRENGTH OF RECOMMENDATION | LEVEL OF EVIDENCE |
|--|----------------------------|-------------------|
| Phototherapy (all forms) | B | II |
| Cyclosporine | B | I-II |
| Azathioprine | B | II |
| Methotrexate | B | II |
| Mycophenolate mofetil | C | III |
| Interferon gamma | B | II |
| Systemic steroids | B | II |
| Systemic antibiotics | | |
| • None, if noninfected AD | B | II |
| • For infected AD | A | II |
| • Concurrent topical steroid during oral antibiotic course | C | III |
| Systemic antivirals for eczema herpeticum | C | II |
| Against use of antihistamines | | |
| • Sedating | C | III |
| • Nonsedating | A | II |

Sidbury R et al. *J Am Acad Derm.* 2014;71:327-349.

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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

| | |
|---|--|
| <h3>TOPICAL CALCINEURIN INHIBITORS (TCI) [tacrolimus or pimecrolimus]^{1,2,3}</h3> <ul style="list-style-type: none">• Recommended if no relief from 1st-line treatments (moisturizing, bathing, wet wrap therapy or TCS or when the use of TCS is not advisable)• Used to treat active inflammation and itch and to prevent future disease flares• Favored vs TCS in delicate body areas (face, genitals, axillae, groin)• Antiinflammatory and antipruritic effects without AEs of TCS (ie, skin atrophy)• Most frequent AE transient burning at application site during the first days | <h3>TOPICAL CORTICOSTEROIDS (TCS)^{1,2,3}</h3> <ul style="list-style-type: none">• Treat active inflammation and itch and to prevent future disease flares• Available over the counter and in increasing prescription strengths and in several formulations (ointments, creams, foams, gels, and lotions) <p>Concerns about skin atrophy with long-term use</p> <h3>WET WRAP THERAPY¹</h3> <ul style="list-style-type: none">• Quickly reduce AD flares<ul style="list-style-type: none">– Increase penetration of moisturizers and prescription topical medications– Decrease water loss– Provide a physical barrier against scratching |
|---|--|

1. AAD 2014 Guidelines. <https://www.aad.org/media/news-releases/american-academy-of-dermatology-s-newest-guidelines-for-the-management-of-atopic-dermatitis-focus-on-treatments>. 2. Wollenberg A, et al. for the European Task Force on Atopic Dermatitis/EADV Eczema Task Force. *J EADV*. 2016; 30, 729–747. 3. Lyons JJ et al. *Immunol Allergy Clin North Am*. 2015;35(1):161-83.

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 topical 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 | |
|---|--|
| Treatment of AD – Adult <ul style="list-style-type: none"> For every phase, <i>additional</i> therapeutic options are given Add antiseptic/antibiotics in cases of superinfection Consider compliance and diagnosis, if therapy has no effect Refer to full text for restrictions, especially for treatment marked with an * | Treatment of AD – Children <ul style="list-style-type: none"> For every phase, <i>additional</i> therapeutic options are given Add antiseptic/antibiotics in cases of superinfection Consider compliance and diagnosis, if therapy has no effect Refer to full text for restrictions, especially for treatment marked with an * |
| SEVERE: SCORAD >50/or persistent eczema | Hospitalization, systemic immunosuppression: short course of oral glucocorticosteroids, cyclosporin A, methotrexate, azathioprine, mycophenolate mofetil, PUVA*, Alectrion |
| MODERATE: SCORAD >25-50/or recurrent eczema | Proactive therapy with topical tacrolimus or class II or class III topical glucocorticosteroids, wet wrap therapy, UV therapy (UVB 311 nm, medium dose UVA 1), psychosomatic counseling, climate therapy |
| MILD: SCORAD <25/or transient eczema | Reactive therapy with topical glucocorticosteroids or depending on local cofactors: topical calcineurin inhibitors, antiseptic incl. silver/AEGIS underwear* |
| BASELINE Basic Therapy | Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests) |

Wollenbyrg A. J EADV, 2016, 30, 729-747. Rockpointe

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

- Ultraviolet (UV) light may be prescribed to treat patients with acute AD or as a maintenance therapy
- Ultraviolet B (UVB), ultraviolet A (UVA), or a combination of UVB and UVA may be used
- Most commonly used for chronic AD (infrared energy can exacerbate acute AD)
- Can be used alone or in combination with TCS and moisturizers
- Short-term risks: itch and acute burns
- Long-term risk: possible increased risk for skin cancer
- Ability to maintain the treatment regimen, with visits 2 to 3 times a week, may be challenging

AAD 2014 Guidelines. <https://www.aad.org/media/news-releases/american-academy-of-dermatology-s-newest-guidelines-for-the-management-of-atopic-dermatitis-focus-on-treatments>.

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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 do not achieve adequate control of AD with topical therapies or phototherapy or those who have been unable to control their symptoms despite adherence to recommended treatment plans
- May also be used when a patient's AD negatively affects their medical, physical, and emotional well-being
- Are off-label for treating AD
- Cyclosporine, methotrexate, mycophenolate, and azathioprine can be effective treatments for unresponsive AD
- Once disease is better controlled, use of systemic immunomodulators is slowly decreased

AAO 2014 Guidelines. <https://www.aad.org/media/news-releases/american-academy-of-dermatology-s-newest-guidelines-for-the-management-of-atopic-dermatitis-focus-on-treatments>.

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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.

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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

- Combination of predefined, long-term, low-dose, anti-inflammatory applied to previously affected areas of skin, in combination with use of daily emollients on the entire body and a predefined appointment schedule for clinical control examinations
- Proactive (usually 2x week) topical treatment started only after all visible lesions have successfully been treated
- Clinical trial data available for methylprednisolone aceponate and fluticasone propionate for up to 3 months and for tacrolimus ointment for up to 1 year
- Barrier disruption is lower with proactive therapy vs daily application and with topical corticosteroids vs topical calcineurin inhibitors

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

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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

- Systemic corticosteroids not recommended
 - Potential for short- and long-term health risks
 - Frequently lead to AD flares upon discontinuation that may be worse than the initial flare
- Topical antihistamines not recommended
- Non-sedating antihistamines not recommended unless other atopic conditions
- Sedating antihistamines may be used to relieve AD itchiness that leads to sleeplessness on a short-term intermittent basis but should not be substituted for topical therapies
- Systemic antibiotics not recommended unless signs of a bacterial infection
- Topical antimicrobial and antiseptic treatments (soaps or bath additives) not recommended and can increase the risk of a patient developing contact dermatitis

AAD 2014 Guidelines. <https://www.aad.org/media/news-releases/american-academy-of-dermatology-s-newest-guidelines-for-the-management-of-atopic-dermatitis-focus-on-treatments>.

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

- I. Is the diagnosis of AD correct?¹
- II. Does the patient have a good understanding of AD?¹
 - ✓ Chronic disease exacerbations and remissions
 - ✓ No cure
 - ✓ Appropriate general measures
- III. Is current treatment optimum?^{1,2}
 - ✓ Adherence
 - ✓ Under-treatment: hydration, inadequate prescription of corticosteroid, cost constraints
 - ✓ Topical therapy not applied properly
 - ✓ Consider treatment targeting specific immune components that drive AD
- IV. Are there any trigger factors?¹
 - ✓ Infection: bacterial (*Staphylococcus aureus*), viral (herpes simplex), fungal (tinea corporis)
 - ✓ Allergens: foods, aeroallergens
 - ✓ Irritants: detergents, soaps, chemicals, preservatives, clothing, heat
- V. Are there any psychosocial disturbances?¹
 - ✓ Emotional stress: anger, frustration, anxiety, family dysfunction, bullying

1. Arkwright PD et al. *J Allergy Clin Immunol: In Practice*. 2013;1:142-151.
2. Wang D et al. *Am J Clin Dermatol*. 2016;17:425-443.

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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

- Establish the correct diagnosis (rule out exclusionary conditions)¹
- Successful AD treatment requires a multipronged approach eliminating triggers, improving skin barrier function, and proactive anti-inflammatory therapy²
- Treatment should be individualized based on standardized assessment of AD severity and treatment goals^{2,3}
- Topical corticosteroids and calcineurin inhibitors for control of flares^{2,3}
- Maintaining barrier function is the cornerstone of maintenance treatment³
- Proactive therapy with topical corticosteroids or topical tacrolimus intermittently is effective²
- Phototherapy or systemic immunosuppressive medications may be required for control of severe AD²

1. Eichenfield LF et al. *Pediatrics*. 2015;138:554-565.

2. Leung DY. *Curr Opin Pediatr*. 2016;28:456-462.

3. Saeki H et al. *J Dermatol*. 2016;43:1117-1145.

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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

- 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 response in the pathophysiology of AD and the atopic march
- Explain how emerging systemic treatments for AD can improve management of the disease and its comorbidities, while considering MOAs, safety and efficacy profiles, indications, and impacts on AD biomarkers and disease progression

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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?

Inside Out – *Cutaneous inflammation precedes barrier impairment and results in an impaired skin barrier*

- Filaggrin plays essential role in skin barrier function and moisturizing
- Inflammation weakens skin barrier by downregulating Filaggrin
 - Transcutaneous penetration of allergens
 - Increased *Staph. aureus* counts
- Mutations and polymorphisms of inflammatory genes linked to AD

Implications for Treatment

- New therapeutic agents targeting systemic Th2 inflammation that occurs in severe AD
 - Anti-IL-4/13 receptor antibody
 - Anti-IL-13 antibodies
 - Biologics targeting IL-12/23, IL-22, and IL-31 receptors

Outside In – *Impaired skin barrier precedes AD and is required for immune dysregulation*

- Filaggrin gene mutations associated with persistent AD
- Skin barrier disruption results in increased cutaneous and systemic Th2 responses (ie, IL-4/13)
- Inflammatory Th2 may predispose to development of allergic diseases in (Atopic March) or progression of AD to other forms of atopy (eg, food allergy, asthma)

Implications for Treatment

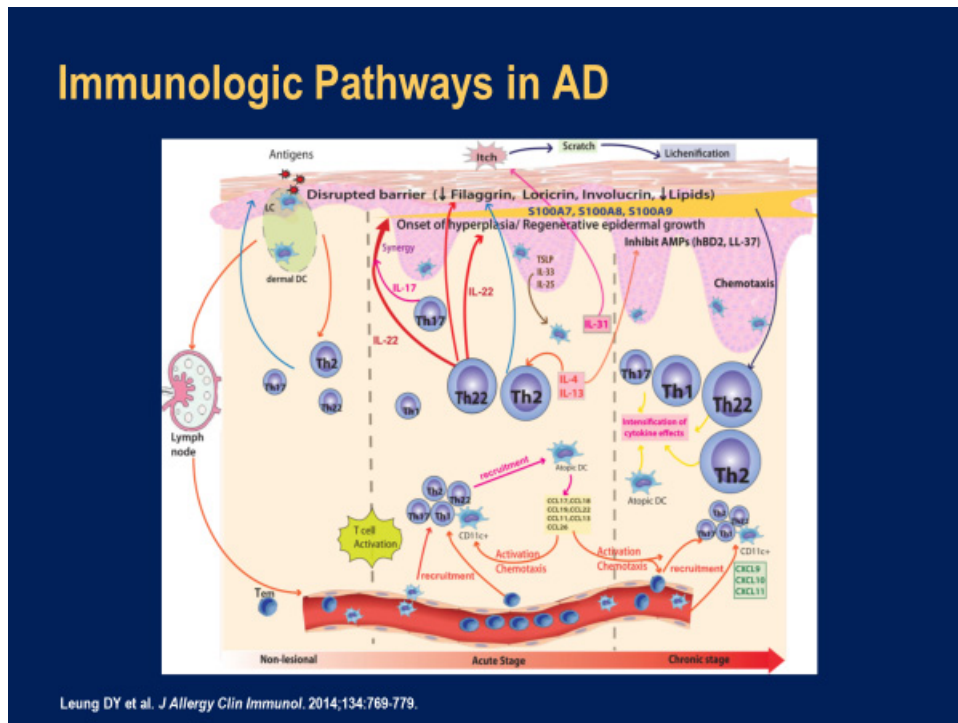
- Risk of developing AD reduced by 50% in newborns at high treated with emollients

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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

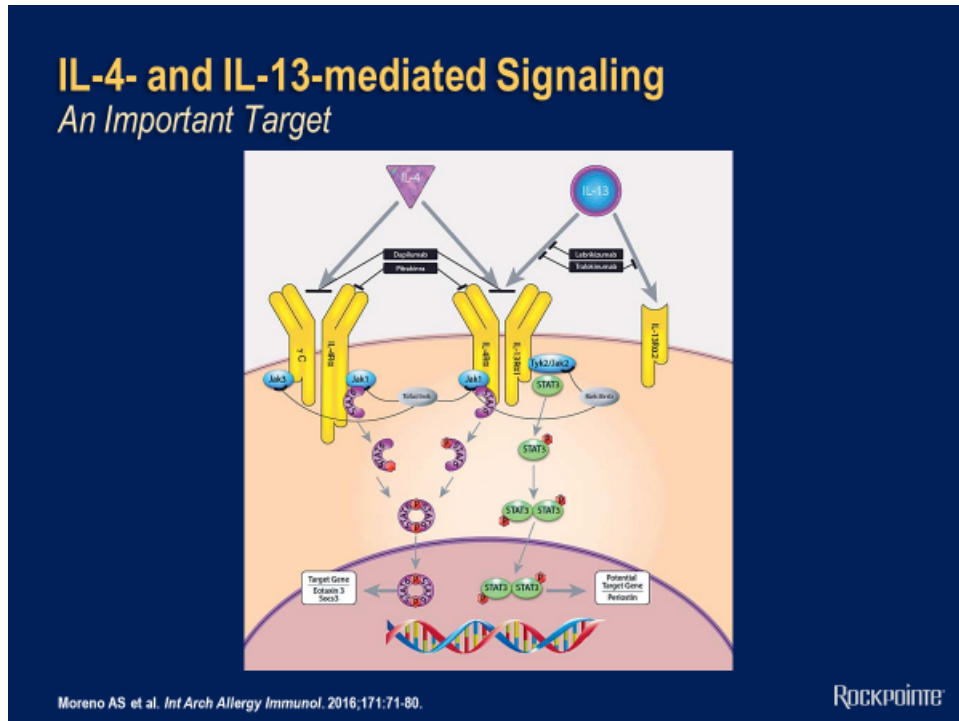
- Skin is characterized by a predominant T helper 2 (Th2) environment¹
- Itching and mechanical disruption of the skin barrier play a central role¹
- Most patients with AD present with increased Th2 pathway activation¹
 - Increased serum immunoglobulin IgE
 - Blood eosinophilia
 - Allergen sensitization
- Chronic AD lesions display a mixed Th1 and Th2 response¹
- IL-22 released from Th17 and Th22 T cells^{1,2}
 - Has a unique role in AD by mediating keratinocyte proliferation and epidermal hyperplasia
 - Suggests that a transition from Th17 to Th22 is associated with chronic disease
 - May differentiate AD from psoriasis and is an emerging target for treatment
- Th2 cytokines (IL-4, IL-5, and IL-13) play a central role in pathogenesis¹
 - Activate inflammatory pathways in multiple cell types
 - Impair epidermal barrier structure and function
 - Induce allergen sensitization

1. Moreno AS et al. *Int Arch Allergy Immunol*. 2016; 171:71-80. 2. Nograles KE et al. *J Allergy Clin Immunol*. 2009;123:1244.e2.

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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 tralokinumab. 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

- Onset of AD followed by atopic march¹
- Like psoriasis, AD skin lesions accompanied by epidermal hyperplasia, T-cell and dendritic cell infiltrates, and increased production of inflammatory products¹
- Th1 and Th17 responses in psoriasis; IBD and RA implicated in transition to chronic inflammation in AD¹

AD associated with increased risk for^{1,2,3}

- ESTABLISHED
 - Asthma
 - Allergic rhinitis
 - Food allergy
- POSSIBLE
 - Depression
 - Anxiety

IBD = inflammatory bowel disease
RA = rheumatoid arthritis

1. Brunner PM et al. *J Invest Dermatol.* 2016 Oct 20. pii: S0022-202X(16)32366-1.
2. Ewald DA et al. *BMC Medical Genomics.* 2015;8:60. 3. Schmitt J et al. *J Allergy Clin Immunol.* 2016;137:130.

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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



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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

- Systemically modulate inflammatory pathways associated with AD pathogenesis to enhance disease control and tolerability
- Control symptoms and improve QoL
- Prevent adverse events and long-term complications

1. Saeki H et al. *J Dermatol*. 2016;43:1117-1145.
2. Moreno AS et al. *Int Arch Allergy Immunol*. 2016;171:71-80.

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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 and Emerging Treatments that Target the T Helper 2 Inflammatory Axis

| Immunologic Target | Agent | Route of Administration |
|--------------------|--------------|-------------------------|
| IL-4R α | Dupilumab* | Subcutaneous |
| | Pitrakinra | Subcutaneous |
| IL-5 | Mepolizumab | Subcutaneous |
| IL-13 | Tralokinumab | Subcutaneous |
| | Lebrikizumab | Subcutaneous |
| IgE | Omalizumab | Subcutaneous |
| | Ligelizumab | Subcutaneous |
| IL-31 | Nemolizumab | Subcutaneous |
| JAK1/JAK3 | Tofacitinib | Oral |
| JAK1/JAK2 | Baricitinib | Oral |
| TSLP/TSLPR | Tezepelumab | Subcutaneous |

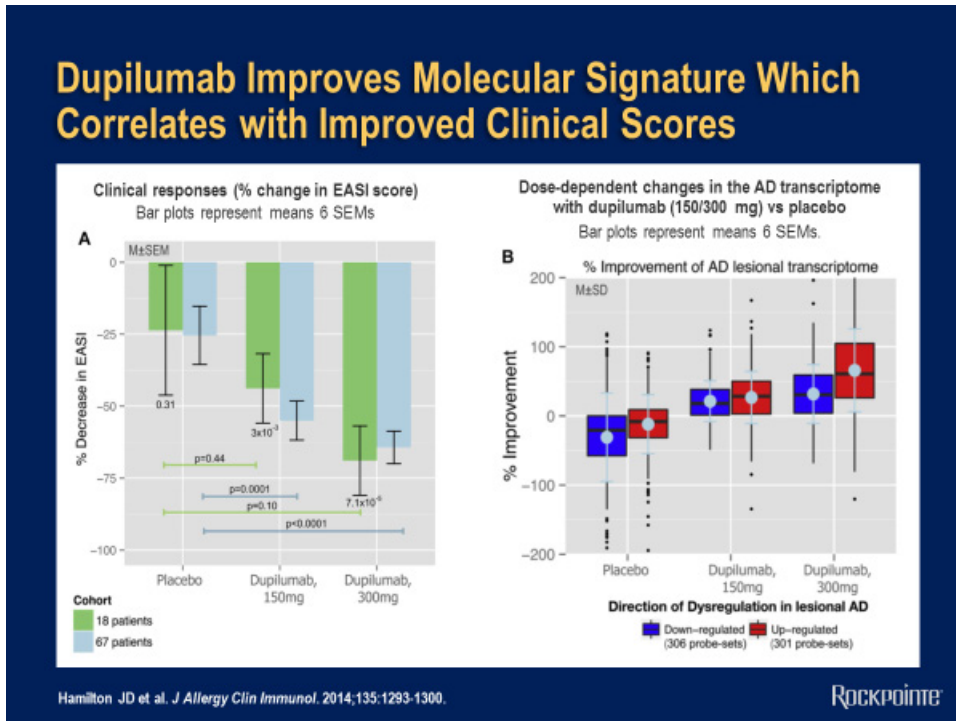
*Dupilumab was FDA approved on March 28, 2017

Moreno AS et al. *Int Arch Allergy Immunol.* 2016;171:71-80.

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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. Dupilumab, 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

- Independent 16-week randomized, double-blind, placebo-controlled, parallel-group trials
- Adults with moderate-to-severe AD
 - SOLO 1 (N=671)
 - SOLO 2 (N=708)
- Patients randomized in 1:1:1 ratio to subcutaneous dupilumab (300 mg) or placebo weekly or the same dose of dupilumab every other week alternating with placebo
- Primary outcome: Proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator's Global Assessment and a reduction of 2 points or more in that score from baseline at week 16

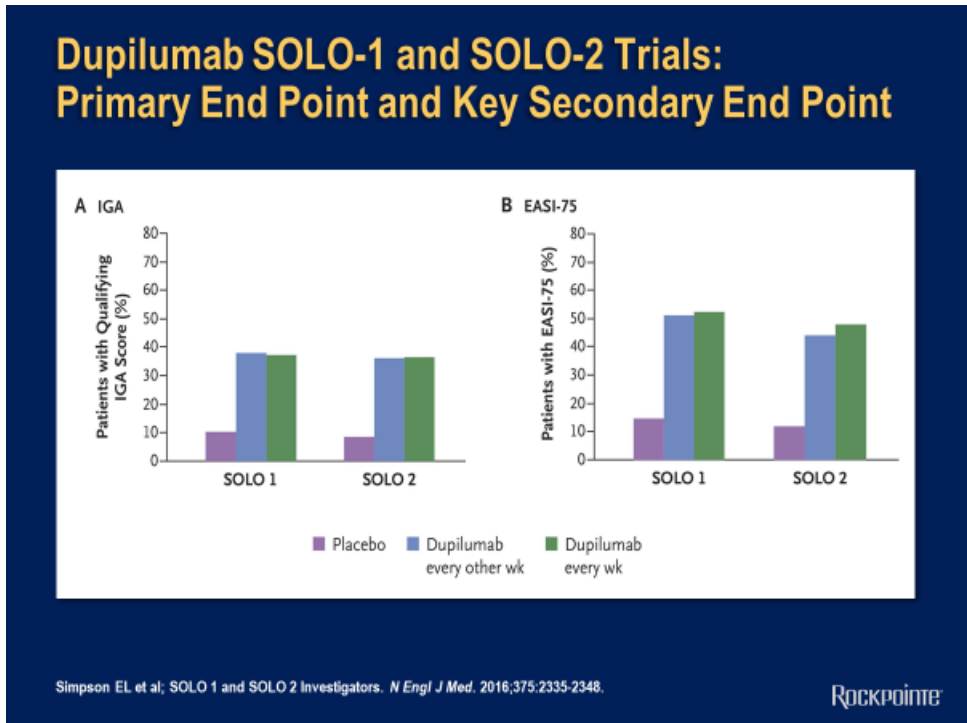
Simpson EL et al; SOLO 1 and SOLO 2 Investigators. *N Engl J Med.* 2016;375:2335-2348.

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Two Phase 3 Trials of Dupilumab

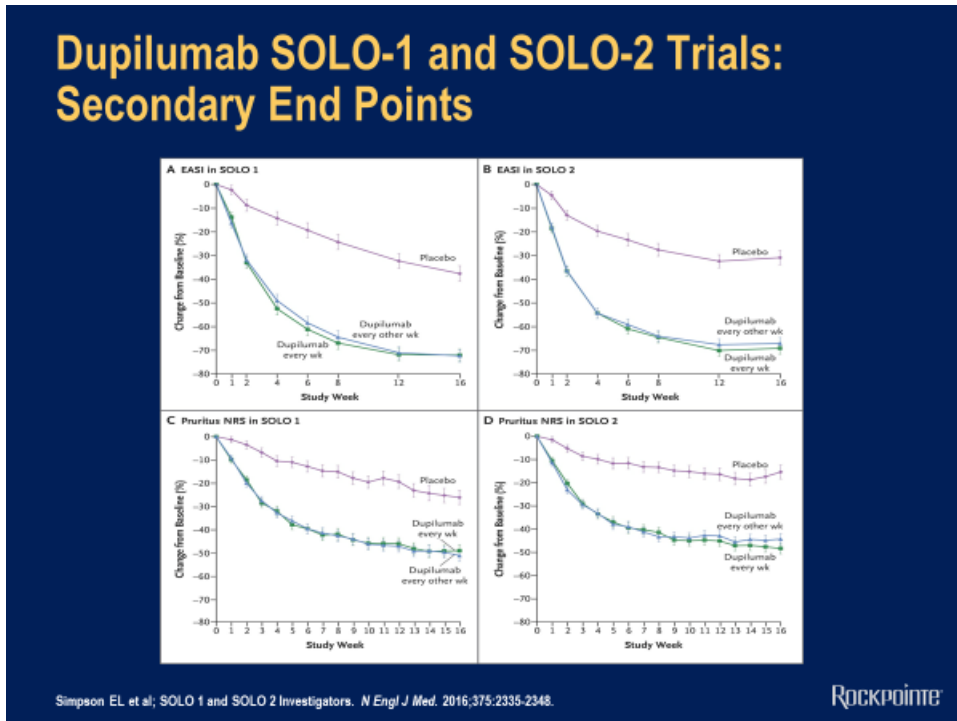
They did two Phase III clinical trials which were published in *The New England Journal of Medicine*; these were two independent trials. They're called SOLO Trial 1 and 2, and the patients were randomized in three groups: one to dupilumab weekly, or the one with every other week, and the third group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

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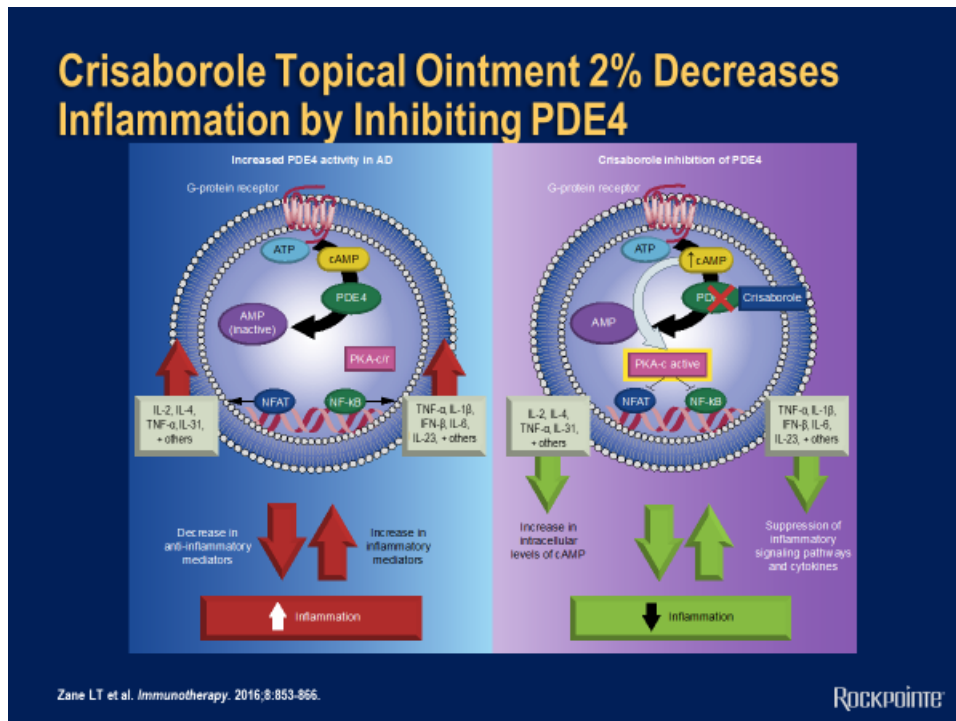
Dupilumab Adverse Events

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.

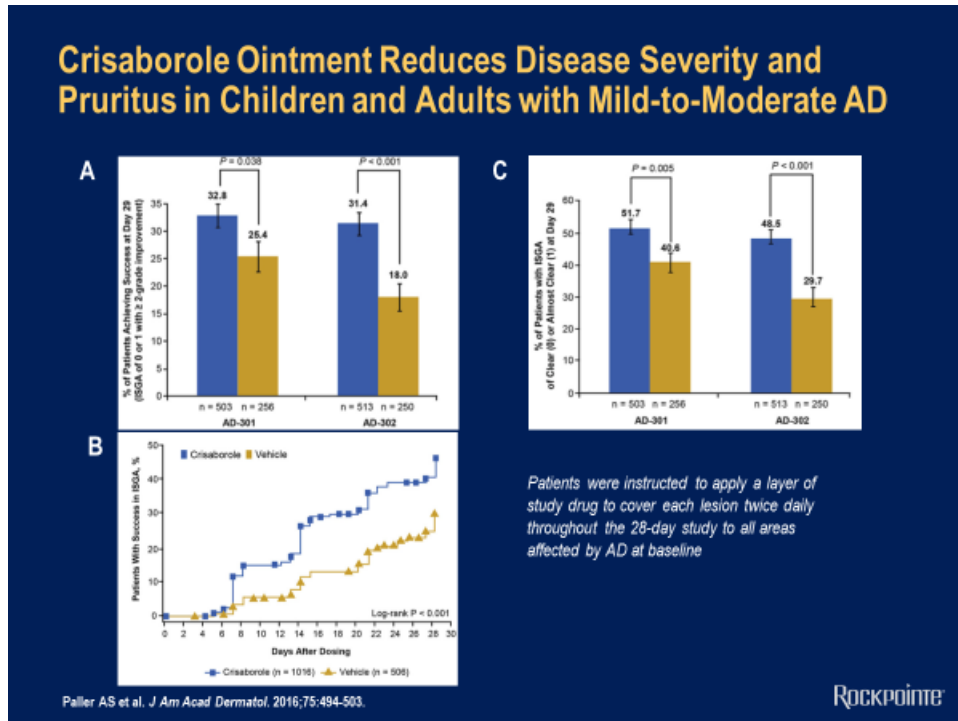
There were some injection-site reactions, slightly higher in the patients taking dupilumab weekly compared to every other week. Eczema exacerbations, not surprisingly, were less. And along those therapies, the rate of skin infections were similar in both placebo and active two therapy groups.



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.

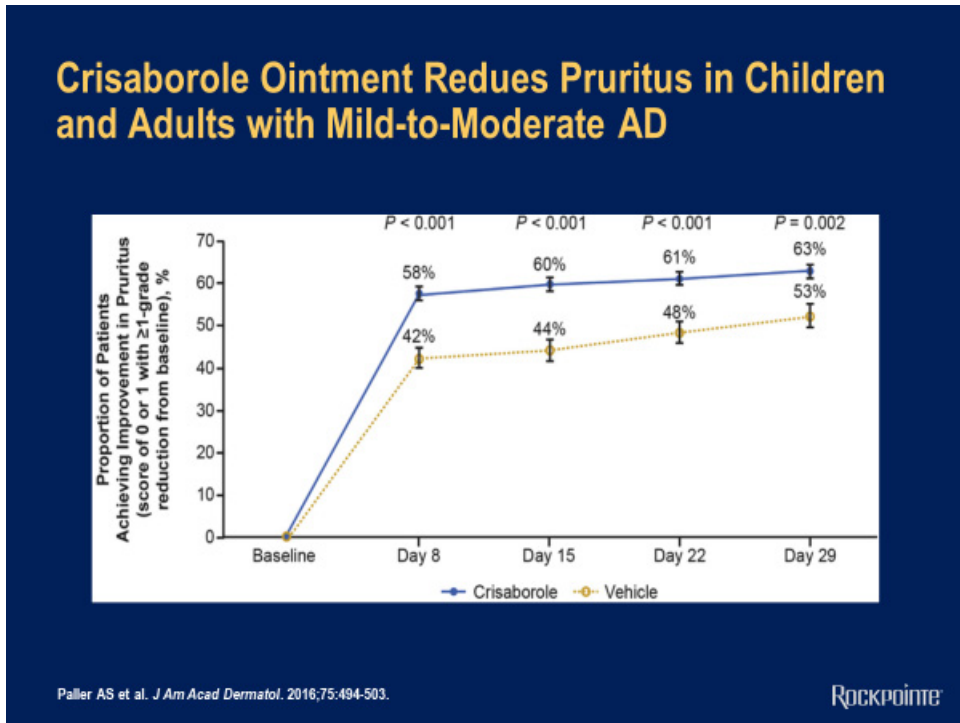
Inhibition, which is seen on the right now with the new topical agent, leads to activation of intracellular AMP, which then leads to inhibition of the NFAT and NF-κB pathway, which is responsible for the inflammatory cytokines and any associated inflammation.



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

| Variable | Study 202 (n = 25) | Study 203 (n = 23) | Study 204 QD (n = 44) | Study 204 BID (n = 42) | Study 102 (n = 34) | Total (n = 168) |
|---|-----------------------|-----------------------|--------------------------|---------------------------|-----------------------|--------------------|
| Patients with TEAEs, n (%) | 11 (44.0) | 10 (43.5) | 6 (13.6) | 11 (26.2) | 23 (67.6) | 61 (36.3) |
| Total number of TEAEs | 29 | 19 | 8 | 12 | 63 | 131 |
| Total number of TEAEs by severity | | | | | | |
| Mild | 26 | 11 | 8 | 10 | 40 | 95 |
| Moderate | 3 | 8 | 0 | 2 | 20 | 33 |
| Severe | 0 | 0 | 0 | 0 | 3 [†] | 3 [†] |
| Total number of discontinuations due to treatment-related AEs | 0 | 1 | 0 | 0 | 1 | 2 |

[†]None were considered serious or related to treatment.
AEs: Adverse events; BID: Twice-daily; QD: Once-daily; TEAE: Treatment-emergent adverse event.

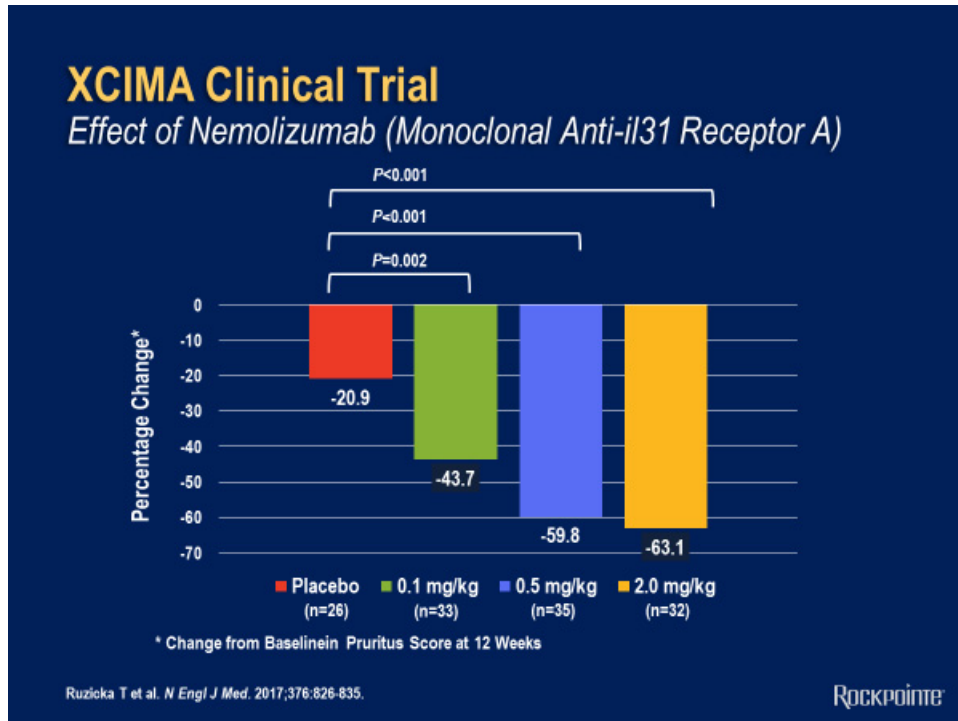
*The majority of treatment-related AEs were application site pain, primarily reported as burning or stinging, that occurred in 4.4% of crisaborole patients vs 1.2% of placebo patients

Zane LT et al. *Immunotherapy*. 2016;8:853-866. Rockpointe

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

Potential endotypes for atopic dermatitis

```

graph TD
    subgraph Endotypes
        T2[Th22 and Th17 driven inflammation]
        T2I[Type 2 immune response]
        ED[Epithelial dysfunction]
    end
    subgraph Phenotypes
        NLS[Non-lesional skin]
        ADF[Acute disease flares]
        CRA[Chronic relapsing AD]
    end
    T2 --> NLS
    T2 --> ADF
    T2 --> CRA
    T2I --> ADF
    T2I --> CRA
    ED --> NLS
    ED --> ADF
    ED --> CRA
    
```

TABLE IV. Proposed endotypes of asthma, AR, and AD

| Asthma | AR | AD |
|----------------------------|--------------------------------------|----------------------------|
| Type 2 immune response | Type 2 immune response | Type 2 immune response |
| Non-type 2 immune response | Non-type 2 immune response | Non-type 2 immune response |
| | Epithelial dysfunction Neurogenic | Epithelial dysfunction |

PRACTALL is an initiative of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology aiming to harmonize the European and American approaches to best allergy practice and science.

Muraro A et al. *J Allergy Clin Immunol*. 2016;137:1347-1358. Rockpointe

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

| AD Specialist | Nurse | Psychologist | Dietitian |
|--|--|--|--|
| <i>Assessment, Education, Care Planning</i> | | | |
| <ul style="list-style-type: none"> • Confirm diagnosis • Determine severity • Identify triggers • Evaluate response to treatment • Coordinate acute and chronic AD management • Provide comprehensive skin care plan and allergy action plan | <ul style="list-style-type: none"> • Address barriers to treatment adherence • Educate about skin care and medications • Coordinate home care and community-based referral • Address developmental concerns • Environmental controls • Provide autoinjector training • Reinforce importance of follow-up • Educate about when to contact HCP | <ul style="list-style-type: none"> • Determine effect on school and social functioning (bullying, teasing) • Address family issues • Address self-esteem and mental health • Provide strategies for stress management • Provide strategies to break itch-scratch cycle • Address sleep issues • Provide strategies to handle peer questions/teasing | <ul style="list-style-type: none"> • Determine adequacy of nutrition and growth patterns • Educate about elimination diet and label reading and cooking substitutions • Provide information about specialty manufacturers |

LeBovidge JS et al. *J Allergy Clin Immunol.* 2016;138:325-334. Rockpointe

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

- Improves management¹
- Empowers patients/caregivers to better manage their condition thus reducing the frequency and severity of flares and frequency of clinical encounters^{1,2}
- Educate patients/caregivers using situation-based role plays²
- To maximize time educating patients, minimize time writing out plans and prescriptions, reduce clinical errors, provide consistent care, and avoid overwhelming patients/caregivers, it is suggested the EAP also act as a prescription¹

1. Sauder MB et al. *J Am Acad Dermatol*. 2016;75:1281-1283.
2. Sauder MB et al. *Pediatr Dermatol*. 2016;33:e151-153.

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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*

Doctor/NP: _____ Name: _____
DOB: _____
MRN: _____
TODAY'S DATE: _____

DAILY SKIN CARE ROUTINE

- BATH 10-20 minutes: Daily Every other day
 - Cleanser: _____
- MOISTURIZER: _____ twice daily and more often as needed
- Antihistamine: _____

GREEN ZONE (Skin with very mild redness/irritation)

- Continue Daily Skin Care Routine

YELLOW ZONE (Skin starting to FLARE with mild to moderate redness/itching)

- Continue Daily Skin Care Routine
- Apply topical steroid: _____ twice daily to **FACE** for maximum ____ days
- Apply topical steroid: _____ twice daily to **BODY** for maximum ____ days

RED ZONE (Skin with SEVERE redness/itching/oozing)

- Continue Daily Skin Care Routine with any changes made in Yellow Zone
- Apply topical steroid: _____ twice daily to **FACE** for maximum ____ days
- Apply topical steroid: _____ twice daily to **BODY** for maximum ____ days

*From Children's Hospital Boston
Available at:
<http://jamanetwork.com/data/Journals/DERM/22505/drs110017f1.png>.

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

- AD is the first step in the atopic march leading to food allergy, asthma, and allergic rhinitis.¹
- The skin of patients with moderate to severe AD is characterized by significant barrier disruption and T helper 2-driven inflammation.¹
- AD is associated with systemic inflammation and may be a risk factor for autoimmune and inflammatory diseases.²
- Improvements in disease control, troublesome symptoms (ie, itching/scratching) and QoL are possible with new and emerging treatment options.^{1,2}
- Successful AD treatment requires patient and family involvement in a multidisciplinary approach.³

1. Saeki H et al. *J Dermatol*. 2016 Oct;43(10):1117-1145. 2. Moreno AS et al. *Int Arch Allergy Immunol*. 2016; 171:71-80.
3. Leung DY. *Curr Opin Pediatr*. 2016;28:456-462.

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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

- Describe actions that can change practice and improve outcomes for patients with AD and their caregivers.

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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

- As the market for systemic medication in AD is just at the beginning, researchers and clinicians must focus now on better defining different subtypes of AD being able to early identify those patients that are in the need of a maximum treatment [Laufer 2016]

Росквітте

Moving AD into the Future

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

Questions & Answers and Concluding Remarks

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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.

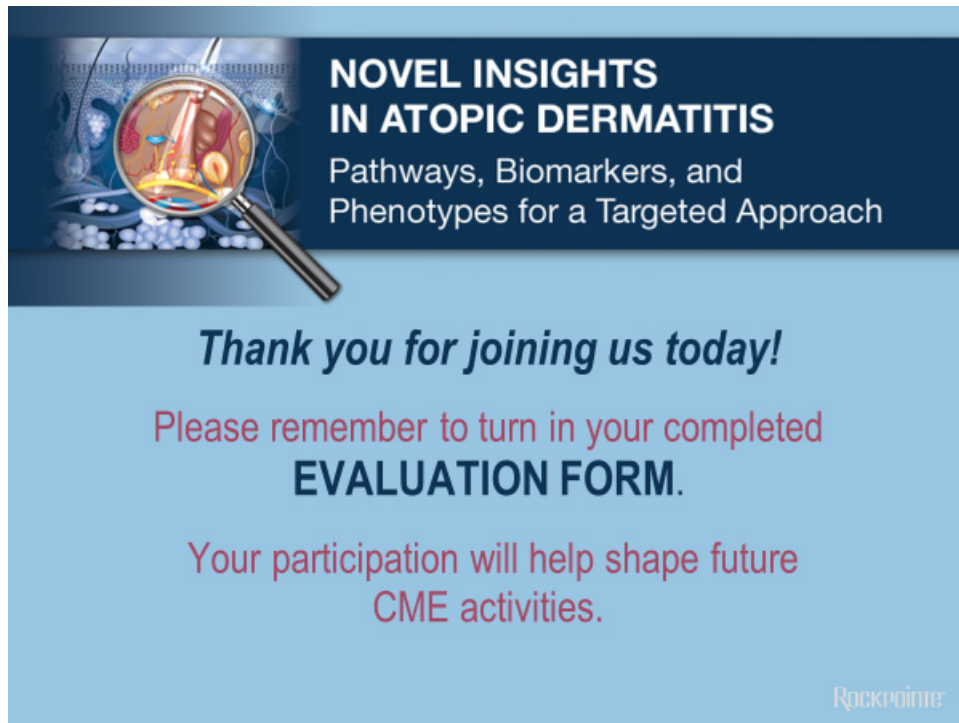
Now, crisaborole, the PDE4 inhibitor, seems to be more for the mild-to-moderate, so it may be something to be used like the topical calcineurin inhibitors tacrolimus and pimecrolimus, sort of a second agent after failing topical steroids. We'll need additional studies to see what all the safety issues 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.



**NOVEL INSIGHTS
IN ATOPIC DERMATITIS**
Pathways, Biomarkers, and
Phenotypes for a Targeted Approach

Thank you for joining us today!

Please remember to turn in your completed
EVALUATION FORM.

Your participation will help shape future
CME activities.

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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.