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Disclosures

- **Speakers Bureau** - SunPharma/Ranbaxy, LEO, Abbvie, Novartis, Janssen, Celgene, Galderma, Lilly

- **Advisory Board** – Lilly

- **Stockholder** – TopMd
Objectives

- Review and characterize the clinical features of atopic dermatitis (AD)
- Discuss the current immune pathophysiology of AD
- Identify strategies for comprehensive treatment of atopic dermatitis in pediatric and adult populations
- Update and position new and emerging topical therapies as well as targeted biologic agents as a new treatment option for patients with AD
ITCH, ITCH, ITCH... SCRATCH, SCRATCH... ITCH...
Atopic Dermatitis
AD - The Dermatologist’s “Working” Definition

**Atopic dermatitis (AD)** is characterized by a pruritic eruption that follows a chronically relapsing course, with a predilection for specific body areas depending on the age of the patient.

- Also called “atopic eczema”, “flexural eczema”, “disseminated neurodermatitis”, “prurigo diasthésique”
  - **Eczema** from Greek *ekzein* (to boil over)
  - Associated with a personal or FH of *atopy*
Epidemiology, Comorbidities and Burden of Disease

- AD is the most common chronic skin disease of children (onset < 1 yr 60% / > 5yrs 85%)
- Persists into adulthood in in 10-30% of cases
- 2-3% of young adults
- All races affected (some increase if African American)
- Increased prevalence noted in industrialized countries (appears to coincide w increasing prevalence of asthma)
Atopic Dermatitis – Multiple Pathogenic Factors

Factors Contributing to the Pathogenesis of Atopic Dermatitis

- Genetics
- Environmental
- Immunology
- Epidermal Barrier Dysfunction

"Atopy" means "out of place" or "strange"

**Atopic Triad** –

1. Asthma
2. Allergies (allergic rhinitis)
3. Atopic dermatitis
Atopic March: 3 FOLD RISK IN ATOPICS and INCREASES OVER TIME

Common Allergic Childhood Diseases

- Rhinitis
- Asthma
- Eczema
- Food Allergy

Reprinted with permission from Barnetson RSC and Rogers M. BMJ. 2002;324:1376-1379.
Genetics of Atopic Dermatitis$^{1,2}$

- Autosomal dominant inheritance
- If one parent has an atopic diathesis
- 60% chance of child being atopic
- Increases to 80% if both parents are affected

Non Allergic Co-morbidities of AD

- Mental Health Disorders (Depression, Anxiety, Autism, ADHD)
- HTN
- Obesity
- Infections
- Prevalence of co-morbid conditions is related to underlying disease severity
- Sleep disturbances (60% - 83% Exacerbations) – persist even in periods of remission
New Evidence for Additional Co-morbidities in AD

- Obesity
- Osteoporosis, Fractures
- More accident prone
- Vitiligo
- Alopecia areata
- Visual Problems
- Dental issues
Pathophysiology – The basics

- Genetics is important
  - Excessive T-cell response to antigen/trigger factors
  - Langerhans’ cells are thought to play a major role in immunologic mechanisms
  - Superantigens from staph colonization are thought to help stimulate T cells in atopic patients

- Non-immunologic mechanisms can be triggers of eczema
  - Itch-scratch cycle
  - Environmental factors

Immunopathogenesis of Atopic Dermatitis

- ↑ T-cell activation
- Hyperstimulating dendritic cells
- Th1/Th2 cytokine imbalance
- ↑ IgE production

Complex interaction of:
- keratinocytes
- endothelial cells
- mast cells
- eosinophils
- Langerhans’ cells
- T-cells
- Numerous cytokines and inflammatory mediators, including histamine and interleukins

What are the New Theories Regarding the Immune Pathophysiology of Atopic Disease?
Out or Outside In: Does Atopic Dermatitis Disrupt Barrier Function or Does Disruption of Barrier Function Trigger Atopic Dermatitis?

Atopic dermatitis (AD) is a multifactorial disease associated with barrier disruption and intense systemic inflammation. While the immunologic features of AD are well established, controversy remains as to whether AD is caused by systemic inflammation triggering barrier dysfunction (the “inside-out” hypothesis) or from the epidermal skin barrier disruption triggering immunologic imbalance (the “outside-in” hypothesis).


Nanette B. Silverberg, MD; Jonathan I. Silverberg, MD, PhD, MPH
INSIDE OUT or OUTSIDE IN???

- Primary defect of the epidermal barrier leading to secondary immune dysregulation and inflammation ("Outside In" hypothesis) *or*....

- Primary Immune dysfunction (cytokine upregulation) leading to IgE sensitization and epithelial barrier disturbances ("Inside Out " hypothesis)
Outside In Hypothesis

- 2006 discovery of Filaggrin (*FLG*) mutation gene (9% of Europians are heterozygous for this mutation)

- FLG mutation associated with early onset AD and often more persistent and debilitating RAD (only with AD)
- Fewer filaggrin repeats correlate with dry skin

- FLG – precursor to NMF – breakdown products include urocanic acid & pyrrolidione carboxylic acid (humectants) – retain H2O at low pH, reduce bacteria

- Reduction of skin integrity and greater TEWL

- Reduction and dysfunction of both skin surface proteins and ceramides (DRY SKIN/HLpalms)
Inside Out Hypothesis:

- AD associated with immune abnormalities – T helper cell dysregulation, mast cell hyperactivity, and IgE production (80% (2dary?)

Imbalance in T cell subsets:

- Th2 predominance (IL-4/IL-5/IL-13) acute /chronic AD
- IL-31 plays a role as a pruritus specific cytokine
- Decreased IFN gamma
Inside Out Hypothesis:

- In chronic forms of AD – Th2 activity persists yet there is upregulation of Th1 cytokines

- Role of Th17 in AD still not completely elucidated – seen more commonly in intrinsic AD and in the Asian population
Inside Out Hypothesis:

- Th-22 cells are activated in both acute & chronic AD (specifically in adults)

- Th2 cytokines downregulate expression of proteins of epidermal differentiation (eg., FLG) and skin surface lipids
AD - Immunopathophysiology

- **Initial**
  - Decreased ceramide, filaggrin, and antimicrobial peptides
  - Damaged skin barrier

- **Early**
  - Pruritus, Inflammation
  - B cells
  - Eosinophilia

- **Ongoing**
  - Allergens, Pathogens

**Diagram Key:**
- \( \text{Dentritic cell} \)
- \( \text{Naïve T cell} \)
- \( \text{Type 2 helper cell} \)
- \( \text{B cell} \)
- \( \text{Mast cell} \)
- \( \text{Eosinophil} \)
- \( \text{Basophil} \)

**Cells and Processes:**
- \( T_{0} \): Naïve T cell
- \( T_{h2} \): Type 2 helper cell
- \( B \): B cell
- \( M \): Mast cell
- \( E \): Eosinophil
- \( Ba \): Basophil
New Thinking: Role of Phosphodiesterase (PDE) in AD

- PDE increased in peripheral blood leukocytes in associated with the characteristic immunologic and inflammatory hyperactivity seen in AD (allergic triad: AD, Asthma, AR) \{Hanifin\}

- Peripheral cord blood samples of newborns w elevated PDE from atopic parents

- Inhibitors of PDE increase IC cAMP and reduce inflammatory cytokines upregulated in AD
Lesional and nonlesional skin in AD is often heavily colonized with *S. aureus*, contributing to skin barrier dysfunction via enterotoxin enzyme activity (e.g. ceramidase).

The cycle of events incited by the AMP deficiency → bacterial colonization → skin barrier dysfunction represents an opportunity for therapeutic intervention in the treatment of AD.
Antimicrobial peptides (AMPs) are a family of naturally occurring “antibiotics” found in keratinocytes and adnexa that represent a first line of innate immune defense against microbial invasion.

In atopic dermatitis (AD), there is a deficiency of AMPs such as cathelicidin. Such deficiencies may predispose atopic skin to colonization with microorganisms (e.g. S aureus) and increase the risk of skin infection.
In summary, moderate-to-severe AD is now being viewed as a systemic inflammatory disease characterized by an immune response with specific roles for T-cell subsets and cytokines involved in initiating and maintaining this immune response.

The level of AD disease activity has been shown to positively correlate with lesional and nonlesional skin expression of Th2 and Th22 mediators.
“An Evolution of New Models of immunopathophysiologic mechanisms has led to a better understanding of AD as well as the development of a host of targeted therapeutic options…”

(Paller, IEC 1st Annual Meeting 3-3-2016)
Common Triggers of Atopic Dermatitis

- Anxiety/stress
- Climatic factors
  - Temperature
  - Humidity
- Irritants
  - Hard water, detergents, solvents
  - Wool or other rough material
- Contact or inhaled antigens and, occasionally food allergies
- Microbial organisms (STAPH)
Colonization with *S. aureus* (74% in acute lesional AD skin – 38% chronic les AD skin – 3% controls)

Increased susceptibility to secondary bacterial infections including *S. aureus*

More Staph colonization w increased age/severity of diseases
Frequent nasal carriage and possible self/re-colonization from reservoir sources eg., fingers

Multiple varying strains may exist in both lesional and uninvolved skin

Severity of AD correlates with the amount skin bacteria and environmental S aureus burden (65% AD parents also carry)
Why is Staph such a major trigger of AD?

- Scratching results in greater bacterial adhesion

- Decreased innate immune responses/defenses (decreased FLG, increased proteases) – decreased AMPs – Th2 upregulation suppresses cAMP (increased PDE)

- Microbiome shifts – disease flares w increasing Staph and less diversity of normal flora
CLINICAL FEATURES & DIAGNOSTIC CONSIDERATIONS
A Diagnosis Based on Clinical Assessment

- 3 major features
  - Clinical criteria
  - Family and past medical history
  - History of the present illness

- Given the absence of any pathognomonic skin lesions or laboratory tests, diagnosis of acute dermatitis depends solely on clinical assessment and medical history.

- This assessment depends on skin lesions consistent with eczema (e.g., eczema-like morphology, distribution, and duration of lesions) as well as pertinent features of past medical and family history.
Who Gets Atopic Dermatitis?
Clinical Features of Atopic Dermatitis

- Commonly affected areas:
  - Infants – face and extensor surfaces of limbs
  - Children - flexural areas
  - Adults – variable; often localized

- Signs and symptoms of active AD
  - Pruritus (#1 cardinal feature of AD)
  - Eczematous dermatitis
  - Xerosis (“Dry skin”)
  - Urticarial eruptions may occur

- Itch-scratch cycle

- Lichenification develops at sites of chronic scratching and/or rubbing

- AD characterized by remissions and exacerbations (“flares”)
  - Tendency for eczema flare is inherent in xerotic and in normal-appearing atopic skin

Clinical Features of Atopic Dermatitis

Atopic Dermatitis
Typical areas of involvement

Before Age 2

After Age 2
Diagnosing AD: Clinical Presentation

Signs and Symptoms

- Dry, itchy, flaky skin
- Scaling
- Edema
- Oozing, weeping, fissuring
- Papulation
- Erythema
- Excoriation
- Lichenification
Signs and Symptoms

Pruritus, Erythema, Edema
Signs and Symptoms

Erythema, excoriation
Signs and Symptoms

Lichenification
AD VARIANTS
Localized Atopic Dermatitis

- Palmar/plantar dermatitis
- Eyelid dermatitis
- Hand dermatitis
- Nipple dermatitis
- Cheilitis

Atopic Dermatitis

- In African-American patients:
  - More papular
  - More follicular ("follicular prominence")
  - More postinflammatory hyperpigmentation

Associated Findings with Atopic Dermatitis

- Xerosis
- Ichthyosis vulgaris
- Hyperlinearity of palms & soles
- Keratosis pilaris
- Pityriasis alba
- Morgan-Dennie folds
- Transverse nasal crease
- Eye/periorbital findings

Diagnosis & Assessment : DDX

- Allergic contact dermatitis (ddx or exacerbant)
- Nutritional, metabolic and immunologic ds in children
- Nummular eczema
- Psoriasis
- CTCL in adults
- Scabies
- Seborrheic dermatitis
- Dermatophytosis
- Ichthyosis
- Darier’s Dz (keratosis follicularis)
- Dermatitis herpetiformis

*Degree of itch, impact on ADLs, disease persistency – be on look out for other disorders concomitant to AD or a known co-morbid factors – food allergies, asthma, AR (eg., sleep disturbances, depression)*
COMPLICATIONS AND SECONDARY FACTORS ASSOCIATED WITH ATOPIC DERMATITIS
Herpes Simplex Virus (Eczema Herpeticum) and Atopic Dermatitis (KVE)

- Eczema herpeticum, or Kaposi's varicelliform eruption
- Presents with acute onset of fever with clustered vesicles, vesiculopustules, and tender erosions in areas of AD
- Usually primary HSV infection
- Treat with oral antiviral agent and supportive care

Is There a significance of Food Allergies?

- Increased rates of environmental and food allergies in AD patients (assess during H/P) – Mild AD – 10-15% Mod/severe 45%
- Consider early on < 5y/0 when persistent AD despite optimal tx OR validated allergic rxn
- If true allergens ID (w documented urticaria) – evaluate for soy, wheat, egg, peanut, milk allergy (new evidence re early peanut administration may actually prevent peanut allergy – NIAID Consensus 2015)
- NOTE – ALLERGY TESTING INDEPENDENT OF Hx NOT RECOMMENDED
Natural Course of Atopic Dermatitis

- Variable and difficult to predict
- “The itch that rashes”
- Cutaneous hyperreactivity
- Seasonal flares — worse in winter
- Other triggers

NO REALLY EFFECTIVE TXs
Management of Eczema
Management of Atopic Dermatitis

- Multifactorial
- Education vital
Goals of Therapy

- Control Flares
- Minimize and/or eradicate infections
- Relieve pruritus

- Non pharmacologic measures (lifestyle adjustments/ Behavior modifications)
- Patient/care provider education

- Topical Therapies (TCC, TCIs, new & emerging Txs):
  - Generally treat a few days beyond observed clinical improvement
  - Ongoing strategies to decrease Staph colonization
  - Refractory AD: systemic therapies
Goals of Therapy

- Treat active inflammation with appropriate medication
  - Develop good skin care routines (moisturization)
  - Identify and avoid eczema triggers
  - Treat skin infections appropriately
- Proactively manage the disease long term
Goal = Eczema Control

To go from this

Flare
Well-Established Inflammation
First Signs and Symptoms
No Flare

To this
Good Skin Care Routines

- Frequent bland emollient use
- Avoid harsh/scented soaps/detergents, bath oils, chemical irritants, and known allergens

- Adopt proper bathing techniques
  - Lukewarm baths to cleanse/moisturize skin
  - Apply cream/ointment to “seal in” moisture immediately after bathing (“SOAK & SEAL”)
  - Cold compresses can relieve dry, itchy skin
Current Therapies for Atopic Dermatitis

- Non-medication
  - Baths, bathing rituals
  - Emollients
  - Herbal preparations (Chinese herbal teas)
  - Alternative medicine (Virgin coconut oil - Int J Dermatolol 2014)
  - Dietary intervention
  - Environmental intervention
  - Wet wrap therapy

References:
Wet Wrap Therapy

- Soaking Three Times a Day

- One of the keys to wet wrap therapy is soaking in a lukewarm bath for approximately 15 minutes, three times a day.

- This patient is covered in wet towels to ensure that his skin remains moist.

- NIAID researchers have determined that long soaks are vital to allowing topical medicines (applied after each bath) to penetrate the outer layer of the skin. In severe cases, bleach may be added to the water to combat skin infections.
Treatment

- **Bathing**\(^1\)
  - Daily is desirable, 10 minutes or less
  - Avoid harsh soaps or cleansers
  - Decreased bacterial load
  - Hydration of stratum corneum, accentuated penetration of topical medicines

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Moisturizers or Emollients$^{1,2}$

- The most important aspect in therapy and prevention of AD
- Ointments preferred over creams, lotions
- Ointments during winter, creams or lotions during summer
- Can apply over topical steroids, throughout day

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<tr>
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<td>VaniCream</td>
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Impaired barrier function limits treatment results

Current research suggests that lipid bilayer deficiencies compromise the integrity of the skin barrier\textsuperscript{1-4}

- Reduction of ceramides, fatty acids, and cholesterol impede skin's protective function\textsuperscript{1}
Appropriate Regimen Can Repair Barrier

- Proper ingredients needed to correct lipid deficiency
  - ↑ Ceramides
  - Moisture balance restored

- Vicious cycle blocked
  - Cytokines not released
  - Reduced inflammation

- Underlying condition can be more effectively treated
  - Skin barrier retains moisture
  - Itch-scratch-itch halted
  - Fewer/shorter treatment times
  - Reduced need for steroids

REF: Clinics in Dermatology 2003
Stepwise Therapy in AD

- **Step 1**: Dry skin only
  - Basic treatment: Skin hydration, emollients, avoidance of irritants, identification and addressing of specific trigger factors

- **Step 2**: Mild to moderate AD
  - Low-mid potency TCS and/or TCI

- **Step 3**: Moderate to severe AD
  - Mid-high potency TCS and/or TCI

- **Step 4**: Recalcitrant, severe AD
  - Systemic therapy (e.g., CyA) or UV therapy

* TCS = Topical corticosteroids, TCI = Topical calcineurin inhibitors, CyA = Cyclosporine A
* Over the age of 2 years
OTC/Rx topical corticosteroids
- Topical calcineurin inhibitors (pimecrolimus and tacrolimus)
- Oral/topical anti-infectives
- Antihistamines
- Systemic immunosuppressants, including oral corticosteroids
- Phototherapy
Guidelines for Selection of Topical Corticosteroids

- Match potency to disease severity. Potency may depend on several factors, including:
  - inherent activity of the steroid molecule
  - concentration of the active ingredient
  - duration of treatment
  - nature of vehicle

- Prescribe the least potent steroid possible

- Use special care in treating children with topical steroids

- Monitor patients using moderate and higher potency steroids for local and systemic side effects

The Benefits and Risks of Topical Corticosteroids

- **Benefits**
  - Fast and effective short-term treatment

- **Risks**
  - **Cutaneous**
    - Skin atrophy/striae
    - Telangiectasia, pigmentation abnormalities
    - Acneform, rosacea-like eruptions
    - Secondary infections, delayed wound healing
    - Hypertrichosis
  
  - **Systemic**
    - HPA axis suppression
    - Growth retardation
    - Cushing’s syndrome
    - REBOUND

- Tachyphylaxis (loss of efficacy with use)
- Ocular toxicity

- LIMIT IRRATIONAL STEROID a PHOBIA (Eichenfeld)
Topical Corticosteroids (MOA)

- Topical Corticosteroids
  - Anti-inflammatory
  - Antimitotic
  - Immunosuppressant
  - Vasoconstrictive
Steroid Side Effects

Striae
Steroid Side Effects

Acne/Folliculitis
Steroid Side Effects

Atrophy
Treatment

- Severe or Refractory Disease
  - Systemic steroids - rarely, in severe cases, as a “jump start”
  - Systemic immunosuppressants - recalcitrant therapy
Steroid Side Effects

- Systemic effects:
  - Cataracts, glaucoma
  - Loss of bone density - osteoporosis
  - Adrenal (Hypothalamic-Pituitary-Adrenal axis) suppression
  - Growth retardation
  - Cushing’s syndrome
  - Hypertension
Antimicrobial Therapy

- **Antibiotics**
  - When indicated
  - Cephalexin, dicloxacillin, doxy, TMP-SMZ
  - Topical mupirocin
  - Remember MRSA – culture – culture – culture (if no response)

Treatment

- **Phototherapy**
  - Ultraviolet light therapy - UVA/UVB/NBUVB/PUVA
  - Successful for chronic disease
  - Requires multiple office visits
  - Potential risk for skin cancer with long-term use
TCI’s
Atopic Dermatitis Treatment

- Conventional therapies (TCS)
  - concerns about side effects
  - long-term use or application site restrictions

- Recent therapeutic options - Topical ImmunoModulators (TIMs)
  - safe and effective
  - topical
  - long-term use potential
  - no application site restrictions
In a Public Health Advisory issued March 10, 2005, FDA recommended physicians to consider:

- Topical calcineurin inhibitors (TCIs) are second-line agents
- TCIs should not be used in children younger than 2 years of age
- TCIs should be used for short periods of time, not continuously; long-term safety unknown
- TCIs should not be used in patients with weakened/compromised immune systems
- The minimum amount of product needed to control the patient’s symptoms should be used
Pimecrolimus

- Reduces number of flares requiring a corticosteroid
- Significantly delays first flare
- Reduces the number of days of corticosteroid use
- Provides sustained improvement in disease extent and severity

Pimecrolimus Patients Spent Fewer Days on Corticosteroids

Days on topical corticosteroid therapy over 12 months (% subjects)

ELIDEL (n=474)
- 57% 0 Days
- 23% 1–21 Days
- 20% 22+ Days

Placebo Cream (n=237)
- 32% 0 Days
- 40% 1–21 Days
- 28% 22+ Days

Data on file, Novartis Pharmaceuticals Corporation.
Can Manage Eczema Avoiding the potential consequences of topical corticoids

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<tr>
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<td>NO</td>
<td>Telangiectasia</td>
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<td>Hypopigmentation</td>
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- TCIs may be used on all skin surfaces, including the face, around the eyes, neck, hands, and other sensitive skin areas

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<td>Vasoconstriction</td>
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<td>NO</td>
<td>HPA axis suppression</td>
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Overview of Outcomes with Pimecrolimus & Tacrolimus Ointment

- No clinical evidence for increased risk of malignancies in adults or children
- Reporting rates for lymphoma and skin cancer are not higher than the expected incidence in the general population
- No impairment of local or systemic immunocompetence
- Ongoing safety monitoring programs
Education About TCIs

**Safety Data**
- Postmarketing registries (APPLES and PEER)
- > 5000 pediatric patients in each registry
- No increase in lymphoma

**Eczema Action Plan**
- Matches dynamic therapy to child's dynamic state
- Allows parents to respond to current treatment needs

**Maintenance Treatment**
- Treat more aggressively if flaring
- Maintain basic care when not flaring

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Emerging Topical Therapies
Need for New and Emerging therapies:

- Topical phosphodiesterase (PDE) inhibitors
- Janus Kinase (JAK) Inhibitors
- Calcineurin inhibitor (new)
Boron Based PDE-4 Inhibitor - Crisaborole

- Integrates a boron ring into the cyclic structure of the molecule allowing for greater stability, effective target binding capacity/selectivity, and enhanced physiologic activity without compromise to the therapeutic response.

- Favorable safety.

- Naturally occurring agent – present in many foods.

- Its low molecular weight allows for easy penetrability through the skin – with great access to target cells.

- Boron-based PDE-4 inhibitors (intracellular enzyme – degrades cAMP via production of inflammatory cytokines).

- Boron is essential for crisaborole’s inhibition of PDE4.
Results From Two Phase 3 Studies in Children and Adults With Mild to Moderate Atopic Dermatitis Treated With Crisaborole Topical Ointment, 2%, a Novel, Investigational, Nonsteroidal, Topical, Anti-inflammatory, Phosphodiesterase 4 Inhibitor
Primary Efficacy Endpoint: Proportion of Patients Achieving Success in ISGA at Day 29 (Clear [0] or Almost Clear [1] With ≥2-Grade Improvement From Baseline)

- Significantly more patients achieved Success in ISGA with crisaborole than vehicle at Day 29 ($P = 0.038$ for 301 and $P < 0.001$ and 302)

![Bar chart showing success rates in ISGA at Day 29]
Photographs of Primary Efficacy Endpoint Successes in Patients Treated With Crisaborole

Baseline, ISGA = 3

Day 29, ISGA = 0

Baseline, ISGA = 3

Day 29, ISGA = 1

ISGA, Investigator’s Static Global Assessment
No treatment-related serious adverse events (AE’s) among patients treated with crisaborole.

The majority of AEs in crisaborole-treated patients were mild in severity.

On a pooled basis, the rate of discontinuations due to AEs were the same (1.2%, crisaborole; 1.2%, vehicle).

No clinically meaningful differences were observed between crisaborole- and vehicle-treated patients in vital signs, ECGs, and clinical laboratory parameters.

### Treatment-Emergent Adverse Events (≥2% of Patients)

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<tr>
<th>Adverse Event</th>
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<th>AD-302</th>
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<tr>
<td></td>
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<td>Vehicle</td>
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<td>Application site pain</td>
<td>6.2%</td>
<td>1.2%</td>
<td>2.7%</td>
<td>1.2%</td>
<td>4.4%</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>2.8%</td>
<td>4.0%</td>
<td>3.1%</td>
<td>2.0%</td>
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AE, adverse event; ECG, electrocardiogram
Conclusions: Supportive Endpoints

- **Crisaborole Topical Ointment, 2%:**
  - Demonstrated greater improvement than vehicle in all measured clinical signs of AD (erythema, induration/papulation, exudation, excoriation, and lichenification)
  - Demonstrated greater Improvement in Pruritus than vehicle across all study visits
  - 50% of treated patients achieved Improvement in Pruritus by 1.37 days
  - May represent an effective treatment for reducing the signs and symptoms of AD in patients with mild to moderate AD 2 years of age and older
Emerging Topical Therapies for AD

- Roflumilast (PDE4 inhibitor) in Phase II (others)

- Janus Kinase inhibitors (JAK) – Topical Tofacitinib 2% ointment also in Phase II RCT

- Calcineurin inhibitors in the pipeline – Some proof of concept studies (Phase II – NCT02079688)
Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial  (Bissonette et. Al. Nov. 2016)

Results
The mean percentage CFB at week 4 in EASI score was significantly greater (P < 0·001) for tofacitinib (−81·7%) vs. vehicle (−29·9%). Patients treated with tofacitinib showed significant (P < 0·001) improvements vs. vehicle across all prespecified efficacy end points and for pruritus at week 4. Significant improvements in EASI, PGA and BSA were observed by week 1 and improvements in pruritus were observed by day 2. Safety/local tolerability were generally similar for both treatments, although more adverse events were observed for vehicle vs. tofacitinib.

Conclusions
Tofacitinib ointment showed significantly greater efficacy vs. vehicle across end points, with early onset of effect and comparable safety/local tolerability to vehicle. JAK inhibition through topical delivery is potentially a promising therapeutic target for AD.
Systemic Therapies (Treating severe AD)

- AAD recommendations for Systemic Immunomodulatory therapy should be considered

- Indicated for subset of pts who do not respond to aggressive local care and topical therapies and/or phototherapy or if pts severe disease has significant impact on ADLs

- When responses to systemic tx are obtained, adjust to minimal effective dosing regimens (yet optimal data not available for exacting dose regimens)

- Individualize therapeutic regimens
Systemic AD Treatment Approach

- Severe refractory disease: (Cys A 5mg/kg/day)
- Moderate to severe / Maintenance (NBUVB)
- MTX, Azathiaprine, MPM
- Biologics
- Photopheresis
Oral Cyclosporine: Long Term Safety and Efficacy

- Duration of Therapy (Plan for 3-4 mo course of therapy)
- Transition to NBUVB or safer option
- FDA guidance – 1 year – possibly 2 (no info on when advisable, if at all to restart)
- Side effects (HTN, renal insuff, elevated lipids, tremors, hypomagnesemia, peripheral neuropathy, GI, neuro)
- DO NOT use if preexisting uncontrolled HTN, systemic infections, or Ca
What About the STEROIDS???

- Generally advisable to avoid – Long/short term consequences
- Unfavorable Risk/Benefit profile (A RCT was held because of significant rebound) – (J Schmidt) – MP vs Cys A trial
- Reserve for ONLY severe ACUTE exacerbations
- Short courses have been shown to increase atopic flares
- Still used frequently in children (…. BECAUSE THERE HASN’T BEEN ANYTHING ELSE!!!!!)
Phototherapy Narrow Band UVB (NB-UVB)

- First line maintenance therapy
- Favorable SE profile
- Inconvenient – costly (co-pays each O/V)
- DO NOT commence during flares
- Risk of Skin Ca
Targeted Biologic Therapy for the Treatment of Moderate to Severe AD
Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis in adults: a pooled analysis of two phase 2 randomized clinical trials

Kim Papp¹, Eric Simpson², Lisa Beck³, Diamant Thaçi⁴, Thomas Bieber⁵, Andrew Blauvelt⁶, Howard Sofen⁷, Melinda Gooderham⁸, Richard Wu⁹, Neil Graham⁹, Gianluca Pirozzi¹⁰, E. Rand Sutherland¹¹, Marius Ardeleanu⁹

¹Clinical Research and Probity Medical Research, Waterloo, ON, Canada; ²Oregon Health & Science University, Portland, OR, USA; ³Department of Dermatology, University of Rochester Medical Center, Rochester, NY, USA; ⁴Comprehensive Center for Inflammation Medicine, University Medical School Schleswig-Holstein Campus, Lübeck, Germany; ⁵Department of Dermatology and Allergy, University of Bonn, Bonn, Germany; ⁶Oregon Medical Research Center, Portland, OR, USA; ⁷Department of Medicine/Dermatology, UCLA School of Medicine, Los Angeles, CA, USA; ⁸SKiN Centre for Dermatology, Peterborough, ON, Canada; ⁹Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; ¹⁰Sanofi, Bridgewater, NJ, USA; ¹¹Sanofi, Cambridge, MA, USA
Dupilumab

*IL-4 R mAb*

- Inhibits IL-4 and IL-13 pathway
- Phase 3 studies in adults (N = 1379) with moderate-to-severe AD
- Preliminary data recently published
  - Dupilumab demonstrated efficacy vs placebo
  - No unexpected safety issues

Significant improvement in SCORAD and IGA with dupilumab vs placebo at Week 12 in pooled studies

**SCORAD**

*Mean score (± SEM)*

- Placebo
- Dupilumab 300 mg qw

**Percent of patients achieving IGA 0 (clear) or 1 (almost clear) at Week 12**

- Placebo
- Dupilumab 300 mg qw

*P < 0.0001 vs placebo
Significant improvement in EASI-50 and EASI-75 with dupilumab vs placebo at Week 12 in pooled studies

*P < 0.0001 vs placebo

*P < 0.0001 vs placebo
Significant improvement in pruritus NRS with dupilumab vs placebo at Week 12 in pooled studies

*P < 0.0001 vs placebo

LS, least squares.
### Pooled adverse events

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NEW THERAPIES ON THE HORIZON
Emerging Systemic Therapies

• Apremilast - small molecule PDE4 inhibitor
• Indicated for PsO / PsA in adults
• Investigations underway in a variety of systemic inflammatory immune mediated diseases RA, Behcets, and AS)
• Open label study underway for AD in adults:
  • 50% improvement on EASIs (GI intolerance)
  • Recruiting for more full scale efficacy and safety RCTs in adult patients with AD
Emerging Systemic Therapies

• Ustekinumab

• Retrospective descriptive study of 4 male pts (23-29) with severe refractory AD

• 4-6 injections – 26 mo tx period
• Skin lesion improvements, reduction in pruritus, and improved QOL parameters after just 2 injections in 2 pts, and after 3, in the remaining 2
• No relevant AEs or infections reported

Nemolizumab

- In patients with AD, CIM331 reduced pruritus visual analogue scale score to about -50% at week 4 with CIM331 compared with -20% with placebo.
- CIM331 increased sleep efficiency and decreased the use of hydrocortisone butyrate.
- No deaths, serious adverse events (AEs) or discontinuations due to AEs were reported in any part of the study.
- No dose-dependent increase in the incidence of AEs occurred in any part of the study.
- In healthy volunteers, all AEs occurred once in the placebo groups, and increased creatine phosphokinase was more common in the CIM331 groups.
Anti–Interleukin-31 Receptor A Antibody for Atopic Dermatitis

Thomas Ruzicka, M.D., Jon M. Hanifin, M.D., Masutaka Furue, M.D., Ph.D., Grazyna Pulka, M.D., Izabela Mlynarczyk, M.D., Andreas Wollenberg, M.D., Ryszard Galus, M.D., Ph.D., Takafumi Etoh, M.D., Ryosuke Mihara, M.S., Hiroki Yoshida, M.S., Jonathan Stewart, M.B., Ch.B., and Kenji Kabashima, M.D., Ph.D., for the XCIMA Study Group*

DOI: 10.1056/NEJMoa1606490
Conclusions

In this phase 2 trial, nemolizumab at all monthly doses significantly improved pruritus in patients with moderate-to-severe atopic dermatitis, which showed the efficacy of targeting interleukin-31 receptor A. The limited size and length of the trial preclude conclusions regarding adverse events.
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### Targeted Agents for Moderate-to-Severe AD

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<th>Target</th>
<th>Mechanism of Action</th>
<th>Clinical Trial</th>
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<td>Apremilast</td>
<td>PDE4</td>
<td>Oral PDE4 inhibitor</td>
<td>NCT02087943</td>
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<tr>
<td>Dupilumab</td>
<td>IL-4/IL-13</td>
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<td>NCT02277743, NCT02277769</td>
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<td>IL-31</td>
<td>IL-31 Receptor mAb</td>
<td>NCT01986933</td>
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<td>Lebrikizumab</td>
<td>IL-13</td>
<td>IL-13 mAb</td>
<td>NCT02340234</td>
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<td>Tralokinumab</td>
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<td>IL-13 mAb</td>
<td>NCT02347176</td>
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<td>Baricitinib</td>
<td>JAK 1/2</td>
<td>Oral JAK 1/2 inhibitor</td>
<td>NCT02576938</td>
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<tr>
<td>MEDI9929</td>
<td>TSLP</td>
<td>TSLP mAb</td>
<td>NCT02525094</td>
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While the exact cause of AD and its pathophysiology are unknown – clearer evidenced based study has provided a more detailed understanding of this largely Th2 immune mediated disease

Attributed to a combination of factors: hereditary, dysfunctional stratum corneum, immunologic, environmental, neurogenic

Hypotheses regarding the immune pathophysiology (Inside-Out & Outside-In) offer further and intriguing understanding of the mechanism of diseases in AD patients
Summary

Treatment Goals:

- Treat active inflammation
  - Adopt good skin care routines
  - Identify and avoid triggers
  - Treat skin infection
- Manage the disease long-term

Topical Treatment Options

- Topical corticosteroids (TCS)
- Calcineurin inhibitors & soon Topical PDE4 inhibitors to achieve long term control of disease – decrease use of TCS
Summary

- **Systemic Therapy:**
- Cys A for severe and/or recalcitrant disease
- Transitional or maintenance therapies = NBUVB, MTX, AZA, MMF
- Oral systemics may be by toxicity and variable efficacy
- New systemic therapies such as dupilumab be useful for refractory AD
QUESTIONS
Till You Fall Asleep

Every night
I hold your hands
Every night
Sweet dreams I send
Every night
I’ll sing to you
Every night
I’ll pray for you
For you to sleep

But you can’t, you don’t
You hardly fall asleep
You scratch, you cry
You barely can sleep

Till you fall asleep
I will say the same prayer
Till you fall asleep
I will sing the same songs
Till you fall asleep
I will hold your hands
Till I fall asleep
I will do all that I can