Atopic Dermatitis – 2016: Looking forward towards a New Treatment Paradigm

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Disclosures

- **Speakers Bureau** - SunPharma/Ranbaxy, Merz, LEO Abggvie, Janssen, Celgene, Galderma

- **Advisory Board** - Lilly

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I HATE IT
WHEN THIS HAPPENS
itch, itch, itch... scratch, scratch... itch...
Objectives

- Review and characterize the clinical features of atopic dermatitis (AD)
- Discuss the current immunopathophysiology of AD
- Identify strategies for comprehensive treatment of atopic dermatitis in pediatric and adult populations
- Update and position emerging topical therapies as well as targeted biologic agent as a new treatment category for AD
Overview of Atopic Dermatitis (AD)
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.
Atopic Dermatitis – Multiple Pathogenic Factors
Factors Contributing to the Pathogenesis of Atopic Dermatitis

Epidermal Barrier Dysfunction

Factors Contributing to the Pathogenesis of Atopic Dermatitis

Genetics

Atopic

Skin

Environmental

Atopic Dermatitis

Immunology

Epidermal Barrier Dysfunction

Atopic Dermatitis

- Chronic, recurrent inflammation of the skin.
  - Patients suffer exacerbations / relapses
- Common!
  - 10% infants (as high as 20% in childhood, 1% adults)
  - 3% general population
- Characterized by **pruritus and xerosis**
- 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**
AD is the most common chronic skin disease of children (onset < 1 yr 60% / > 5 yrs 85%)

Persists into adulthood 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 with increasing prevalence of asthma)
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
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 Comorbidities in AD

- Obesity
- Osteoporosis, Fractures
- More accident prone
- Vitiligo
- Alopecia areata
- Visual Problems
- Dental issues


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

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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

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

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

- 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)
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
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
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
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
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)
The understanding of the pathogenesis of AD has evolved and improved in recent years. Historically, immunoglobulin E (IgE) was viewed as the key mediator of AD. AD is understood to have a complex pathogenesis involving genetic, immunologic, and environmental factors. This multifaceted pathophysiology leads to a poorly functioning skin barrier and dysregulation of the immune system.
A primary immune model was suggested based on the clinical resolution of AD with topical and systemic immunosuppressants.2

Trials with broad, nonselective T-cell–targeted therapeutics (eg, cyclosporine, phototherapy, alefacept, and efalizumab) also showed benefit in patients with moderate-to-severe AD and led to the further exploration of specific T-cell mechanisms in AD onset and persistence.2
In the last decade, Th2 and Th22 cytokines were reported to modulate the epidermal barrier, including suppression of keratinocyte differentiation, hyperplasia, keratinocyte apoptosis, and antimicrobial peptide production.1

Analyses of cytokine expression in AD lesions revealed that Th2 cells of early lesions produced the cytokines IL-4, IL-5, and IL-13.23

Increased amounts of the Th2 cytokines IL-25 and IL-33 were also detected in AD skin, as were soluble factors such as thymic stromal lymphopoietin, which promotes Th2 responses.22
Gittler et al described genomic, molecular, and cellular characteristics in the skin of patients with AD that were observed through 3 stages of AD progression: nonlesional skin, acute lesions, and chronic lesions.24

The complex interactions between the epidermal barrier and immune activation in these 3 stages are illustrated in Figure 1 and summarized in the next slide.
WHAT HAPPENS AT VARIOUS STAGES OF AD?
Nonlesional AD skin contains a variety of immune infiltrates that play a role in mediating the inflammation that may contribute to defects in the epidermal barrier.

Epidermal barrier defects allow penetration by epicutaneous allergens.

These allergens encounter Langerhans cells in the epidermis and dermal dendritic cells (DCs) in the dermis; this process activates and recruits the inflammatory cells (e.g., Th2, Th22, and Th17) involved in acute disease onset.

Significant pathology already occurs in nonlesional skin, perhaps explaining why suboptimal responses are seen when only the skin lesions are treated with topical therapy.
Acute AD lesions show an increased activation of Th2 and Th22, with smaller increases in Th1 and Th17 (in Figure 1, the level of activation of each T-cell subset is represented by its size relative to other T-cell subsets [eg, Th2 and Th22 are larger to represent greater inductions]).

- The T cells and DCs produce cytokines (eg, IL-4, IL-13) and chemokines (eg, CCL17, CCL18, CCL19, CXCL9, CXCL10, CXCL11), which induce the recruitment of additional immune cells and cause even more immune activation.

- IL-31, the itch-associated Th2 cytokine, is released and abruptly upregulated.
Acute-Stage Atopic Dermatitis

- IL-22, released by Th22 cells, induces epidermal hyperplasia and works in synergy with IL-17 (the Th17 cytokine) to increase a subset of epidermal differentiation complex genes (e.g., S100A7, S100A8, and S100A9 proteins); these proteins have important functions in inflammation and may contribute to the chemotaxis of immune cells, particularly T cells, which are markedly increased in acute AD.

- Th2 and Th22 inhibit terminal differentiation gene products (e.g., filaggrin, loricrin, corneodesmosin)1,24

- The increased expression of Th2 cytokines also results in downregulation of antimicrobial peptides1.
Chronic AD lesions are characterized by a progressive intensification of Th2, Th22, Th1, and Th17. IL-4 may also play a role in the transition from early AD to chronic self-perpetuating 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.
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 – STAPH – STAPH (Schachner))
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 with 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 (eg, eczema-like morphology, distribution, and duration of lesions) as well as pertinent features of past medical and family history

Who Gets Atopic Dermatitis?
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

Scaling
Signs and Symptoms

Lichenification
Natural Course of Atopic Dermatitis

- Variable and difficult to predict
- “The itch that rashes”

**NO REALLY EFFECTIVE TXs**

- Often chronic symptoms
  - Seasonal flares - worse in winter
  - Other triggers
Contact irritants (detergents, nickel, harsh soap)
- Rough fabrics (wool, nylon)
- Sweating
- Dust mites
- Food allergies (eggs, milk, nuts)
- Aeroallergens (animal dander, weeds, molds)
- Infections (staph superantigens)
- Climate (humidity, temperature)
- Emotions-stress, anxiety ("S A D")
Localized Atopic Dermatitis

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

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

Signs and Symptoms

Hyperlinearity of palms
Signs and Symptoms

Morgan-Dennie Folds
“Allergic Shiners”
Complications and Secondary Factors Associated with Atopic Dermatitis
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

Controversial; clinical significance unclear

Increased risk of IgE-mediated food allergy in patients with AD

Common offenders: cow’s milk, soy, eggs, peanut, wheat, tree nuts, fish, shellfish

Co-management vital

3. Tom, W Pediatric Annals January 2012 - Volume 41 - Issue 1: e1-e5
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/o 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)

NOTE – ALLERGY TESTING INDEPENDENT OF Hx NOT RECOMMENDED
Management of Eczema
Management of Atopic Dermatitis

- Multifactorial
- Education vital
2014 AAD Guidelines of Care (AD)

- **Key recommendations**

- Based on a comprehensive review of available data for diagnosing and managing atopic dermatitis, the first section of the Academy’s guidelines include key recommendations:

  - Monitoring of patients’ immunoglobulin E levels is not recommended because they do not correlate with disease severity.

  - Physicians should ask their patients general questions about itch, sleep, impact on daily activity, and persistence of the disease.
Patient and Caregiver Education Is Vital to Treatment Success

- Multidisciplinary educational programs (or "eczema schools," decreased the SCORAD index relative to a control group in 1 study)a
  - Nurse-led educational clinics demonstrated increased patient satisfaction, an 89% decrease in disease severity, and an 800% increase in emollient use.b
- Practitioners and caregivers should take advantage of educational and support group resources offered by groups such as the National Eczema Association.c

Eczema (AD) Action Plans

- Written plans help patients understand what to use and where.
- Reduces patient callbacks.
- Safeguards against medication errors and overusing potent steroids.
- Improved adherence.

Credit: UCSF School of Medicine

Allergic contact dermatitis (ddx or excacerbant)
Nutritional, metabolic and immunologic ds in children
CTCL in adults
Degree of itch, impact on ADLs, disease persistency – be on look out for other disorders concomitant to AD or a known co-morbid factor s – food allergies, asthma, AR(eg., sleep disturbances, depression)
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
Eczema: A Chronic, Recurring Condition

The Eczema Cycle

Flare

First Signs Or Symptoms

Clear Skin
Goal of 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\(^1\-^3\)
  - Baths, bathing rituals
  - Emollients
  - Herbal preparations
  - Alternative medicine
  - Dietary intervention
  - Environmental intervention
  - Wet wrap therapy

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

Moisturizers or Emollients\textsuperscript{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

Emollients (OTC)

- CeraVe
- Cetaphil
- Cetaphil Restoraderm
- Aveeno
- Eucerin
- Aquaphor
- VaniCream
Barrier Restoration and Repair (Rx)

- Mimyx
- Atopiclair
- EpiCeram
- Hyaltopic
- Neosalus
- Eletone
Key lipids and proteins essential to stratum corneum integrity are deficient in AD skin, including:

- Filaggrin
- Ceramides
- Cholesterol
- Free fatty acids

Skin barrier function is impaired, leading to:

- ↑ transepidermal water loss (TEWL)
- ↑ environmental allergen and irritant exposure
- ↑ infectious microbe exposure


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}
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
An 82% resolution of target lesions as measured by percent of target lesions that achieved an IGA value of “clear” or “almost clear” at Week 4.

Stewise Therapy in AD

- **Step 1**: Basic treatment: Skin hydration, emollients, avoidance of irritants, identification and addressing of specific trigger factors.
- **Step 2**: Low-mid potency TCS and/or TCI*
- **Step 3**: Mid-high potency TCS and/or TCI*
- **Step 4**: Systemic therapy (e.g., CyA) or UV therapy

TCS = Topical corticosteroids, TCI = Topical calcineurin inhibitors, CyA = Cyclosporine A

* Over the age of 2 years
Treatment Options – (cont’d)

- OTC/Rx topical corticosteroids
- Topical calcineurin inhibitors (pimecrolimus and tacrolimus)
- Oral/topical anti-infectives
- Antihistamines
- Systemic immunosuppressants, including oral corticosteroids
- Phototherapy
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
- Tachyphylaxis (loss of efficacy with use)
- Ocular toxicity

LIMIT IRRATIONAL STEROID a PHOBIA (Eichenfeld)

HPA = hypothalamic-pituitary-adrenal.
Treatment – Topical Corticosteroids

- Topical Corticosteroids
  - Anti-inflammatory
  - Antimitotic
  - Immunosuppressant
  - Vasoconstrictive
Severe or Refractory Disease

- Systemic steroids - rarely, in severe cases, as a “jump start”
- Systemic immunosuppressants - recalcitrant therapy
Systemic Agents for AD Management

- **Mycophenolate mofetil** (1-1.5g bid)
- **Methotrexate** (7.5-25mg/week)
- **Azathiaprine** [check TPMT levels – 1-3mg/kg/d]
- **Cyclosporine A** (100-300mg/d)
- **More aggressive systemics:**
  - IVIG
  - IFN-gamma
  - Omalizumab
  - Other biologics (TNF inhibitors?)
  - Dupilumab
Steroid Side Effects

Striae
Steroid Side Effects

Acne
Steroid Side Effects

Atrophy
Steroid Side Effects

- **Systemic effects:**
  - Cataracts, glaucoma
  - Loss of bone density - osteoporosis
  - Adrenal (Hypothalamic-Pituitary-Adrenal axis) suppression
  - Growth retardation
  - Cushing’s syndrome
  - Hypertension
Other Steroid Usage Concerns

- Tachyphylaxis
- Rebound flare
Treatment

- **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/NB UVB/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
  - 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
Nonsteroidal topical immunomodulator

Tacrolimus acts by specifically inhibiting the early cell cycle stages of T-cell activation

Binds to unique immunophilin, FK506 binding protein (FKBP-12)

Inhibits calcineurin, thereby blocking migration of nuclear factor of activated T-cells into nucleus

Inhibits production of cytokines associated with atopic dermatitis
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 Improves Extent and Severity of Eczema

Mean % Improvement in Overall EASI Scores

ELIDEL (n=267)
Placebo Cream (n=136)

Data on file, Novartis Pharmaceuticals Corporation.
Based on ANCOVA models of EASI scores.
Pimecrolimus Effectively Relieves Pruritus

% Subjects With Mild/No Pruritus

ELIDEL (n=267) vs Placebo Cream (n=136)

*P<.001.

ELIDEL® Patients Spent Fewer Days on Corticosteroids

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

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

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

Data on file, Novartis Pharmaceuticals Corporation.
TCIs may be used on all skin surfaces, including the face, around the eyes, neck, hands, and other sensitive skin areas.
Caucasian Male With Eczema on Elbow Flexures

Baseline

Day 6

Data on file, Novartis Pharmaceuticals Corporation. Results described here may not be representative of entire patient population; individual results may vary.
Individual results may vary.

Reprinted from J Am Acad Dermatol 2001;44(Suppl1) with permission from Mosby, Inc.
0.1% Tacrolimus ointment reduced *S. aureus* colonization of atopic dermatitis lesions

- significant reduction from baseline by first week of treatment (*p* = .012; *n*=19)
- reduction remained significant throughout 6 month (*p* < 0.001; *n*=19) and 12 month period (*p* = 0.008; *n*=9)

Authors attributed reduction of colonization to healing of lesions

Current articles confirming the safety of TCIs

- Topical Calcineurin Inhibitors and Lymphoma risk: Evidence Update with Implications for Daily Practice
  14:163-178

TCIs available since 2001 – Approved for chronic tx of AD
- Black box warning concerns – never proven and primarily theoretical....
- Post marketing registry analyses – rates of lymphoma comparable to SEER data and lower in the AERS of the FDA compared to the general population
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
Need for New and Emerging therapies:

- Topical phosphodiesterase (PDE) inhibitors
- Janus Kinase (JAK) Inhibitors
- Calcineurin inhibitor (new)
Emerging Topical Therapies
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

Paller AS, Tom WL, Lebwohl MG, et al. 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 Presented at the 34th Fall Clinical Dermatology Conference. October 1-4, 2015. Las Vegas, NV
Objective

- Herein, we report results from 2 Phase 3 studies that were conducted to evaluate the efficacy and safety of Crisaborole Topical Ointment, 2%, in patients ≥2 years with mild to moderate atopic dermatitis
Two Multicenter, Double-Blind, Vehicle-Controlled Phase 3 Studies of Identical Design

- Study drug was applied twice daily to all treatable areas of the body except the scalp.

**Screening Criteria**

**Key Inclusion Criteria:**
- ≥ 2 years of age or older
- Clinical diagnosis of mild (ISGA 2) or moderate AD (ISGA 3)
- AD involvement ≥5% BSA

**Key Exclusion Criteria:**
- Use of TCS or TCI within 14 days
- Significant active infection
- Any previous use of biologic therapy

**Physician Evaluation at Days 1 (baseline), 8, 15, 22, 29, 36**

- **Primary Efficacy Endpoint:** Proportion of patients achieving Success in ISGA (clear [0] or almost clear [1] with ≥2-grade improvement from baseline at Day 29)
- **Secondary Efficacy Endpoints:**
  - Proportion of patients with ISGA score of clear (0) or almost clear (1) at Day 29
  - Time to Success in ISGA
- **Primary Safety Endpoints:** AEs, vital signs, ECGs, and clinical laboratory parameters

AD, atopic dermatitis; AE, adverse event; BID, twice daily; BSA, body surface area; ECG, electrocardiogram; ISGA, Investigator’s Static Global Assessment; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid.

*Proprietary vehicle developed by Anacor*
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)

**Graph:**

- **AD-301**
  - 503 patients
  - 32.8% Success
  - Crisaborole: 25.4%
  - Vehicle: 18.0%
  - $P = 0.038$

- **AD-302**
  - 513 patients
  - 31.4% Success
  - Crisaborole: 18.0%
  - Vehicle: 31.4%
  - $P < 0.001$

ISGA, Investigator’s Static Global Assessment
Proportion of Patients Achieving Success in ISGA (Clear [0] or Almost Clear [1] With ≥2-Grade Improvement From Baseline at Days 1, 8, 22, and 29)

- More patients achieved Success in ISGA with crisaborole versus vehicle across all study visits
Secondary Efficacy Endpoint: Proportion of Patients With ISGA Score of Clear (0) or Almost Clear (1) at Day 29

- Significantly more patients achieved clear (0) or almost clear (1) ISGA scores with crisaborole at Day 29.
Photographs of Primary Efficacy Endpoint Successes in Patients Treated With Crisaborole

Baseline, ISGA = 3

Day 29, ISGA = 1

Baseline, ISGA = 3

Day 29, ISGA = 0

2-year-old patient

7-year-old patient

ISGA, Investigator’s Static Global Assessment
Safety Summary of Crisaborole Topical Ointment, 2%

- 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)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>AD-301 Crisaborole (n = 502)</th>
<th>AD-301 Vehicle (n = 252)</th>
<th>AD-302 Crisaborole (n = 510)</th>
<th>AD-302 Vehicle (n = 247)</th>
<th>Pooled Crisaborole (n = 1012)</th>
<th>Pooled Vehicle (n = 499)</th>
</tr>
</thead>
<tbody>
<tr>
<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>
<td>1.2%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2.8%</td>
<td>4.0%</td>
<td>3.1%</td>
<td>2.0%</td>
<td>3.0%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

AE, adverse event; ECG, electrocardiogram
Conclusions

- Crisaborole Topical Ointment, 2%, is a novel, investigational, nonsteroidal, anti-inflammatory, PDE4 inhibitor
- Crisaborole Topical Ointment, 2%, demonstrated statistically significant improvements compared with vehicle across all primary and secondary efficacy endpoints in two Phase 3, multicenter, double-blind, vehicle-controlled studies
- Crisaborole Topical Ointment, 2%, demonstrated a favorable safety profile in patients as young as 2 years of age
- Crisaborole Topical Ointment, 2%, may represent a new safe and efficacious treatment for patients 2 years of age and older with mild to moderate atopic dermatitis
Supportive Endpoints: Pruritus and Signs of Atopic Dermatitis With Crisaborole Topical Ointment, 2%, a Novel, Investigational, Nonsteroidal, Topical, Anti-inflammatory Phosphodiesterase 4 Inhibitor, in Two Phase 3 Studies in Children and Adults With Mild to Moderate Atopic Dermatitis

More patients treated with crisaborole achieved improvements in all clinical signs of AD than vehicle at Day 29.
A greater proportion of crisaborole-treated patients achieved Improvement in Pruritus across all study visits.
Conclusions: Supportive Endpoints

- Crisaborole Topical Ointment, 2%:
  - Is a novel, investigational, nonsteroidal, anti-inflammatory PDE4 inhibitor
  - 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 Tx for AD

- 2% Ointment version (AN 2728) in Phase III RCT
- Roflumilast (PDE4 inhibitor) in Phase II (others)
- Janus Kinase inhibitors (JAK) – Topical Tofacitinib 2% ointment also in Phase II RCT
- Calicineurin inhibitors in the pipeline – Some proof of concept studies (Phase II – NCT02079688)
Targeting Moderate-to-Severe Atopic Dermatitis: Evolving Treatment Strategies to Address a Key Unmet Medical Need
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
- Avoid systemic steroids where possible
Severe refractory disease (Cys A 5mg/kg/day)

Moderate to severe / Maintenance (NBUVB)
MTX, Azathiaprine, MPM

Biologics
Photopheresis
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 ISN’T ANTHING ELSE!!!!)
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, reanal insuff, elevated lipds, tremors, peripheral neuropathy, GI, neuro)
DO NOT use if preexisting uncontrolled HTN, systemic infections, or Ca
Alternative Systemics-Maintenance Meds

- NB-UVB
- MTX
- Azathiaprine
- Mycophenolate Mofetil

Others:
- Biologics, Photopheresis
Narrow Band UVB (NB-UVB)

- First line maintenance therapy
- Favorable SE profile
- Inconvenient – costly (co-pays each O/V)
- DO NOT commence during flares
Alternative Systemics- Maintenance Meds – Methotrexate (MTX)

- Safe, underutilized and understudied (start up or transitional from Cys A)

- 2 controlled trials (Adults 42% decrease SCORAD – Children 49% decrease SCORAD)
  - Schram ME J Allergy Clin Immunol 2011
  - El-Khalawany, MA Eur J Ped 2013

- Dosing in children 0.2-0.6 mg/kg weekly
Azathioprine (AZA)

- Variable responses to tx – 25-39% improvement in 3 trials
- Better on cost
- Use in children
- Check TPMT level before commencing therapy
- Regular labs (CBC w diff, CMP – monitor LFTs)
- One systemic review detailed a case lymphoma in a treatment follow-up period (Schram, ME. *Arch Dermatol* 2011)
Mycophenolate Mofetil

- Trials not abundant – mostly anecdotal case reports and some open label studies
- Efficacy variable - 40% SCORAD improvement
  - 5 pts – no improvement
  - RCT – comparable to Cys A
    ( Haeck IM JAAD 2011 )

Disadvantages ( Primarily with long term use )
- Congenital malformations (Category E Pregnancy)
- 17 cases of PML ( SLE pts and those on combined immunosuppressants )
IFN Gamma (Hanifin JM JAAD 1993) recent unpublished trial – negative findings
Mepolizumab, Omalizumab (neg findings)
TNF inhibitors: much data – not + results
Rituximab – some case series – variable findings
Alefacept – also variable results – data conflict ( off the market )
Cyclosporine – 1st line therapy – “cool down” not for long term use

Maintenance therapies – NB-UVB, MTX, AZA MMF

Overall, all oral systemics somewhat limited by SE profiles

Still NO SAFE, WELL TOLERATED & EFFECTIVE systemic therapies for AD
Targeted Biologic Therapy for the Treatment of Moderate to Severe AD
EFFICACY AND SAFETY OF DUPILUMAB IN ADULTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS (AD) INADEQUATELY CONTROLLED BY TOPICAL THERAPIES: FINAL RESULTS OF A PHASE 2B STUDY

Diamant Thaçi¹, Eric Simpson², Thomas Bieber³, Lisa Beck⁴, Andrew Blauvelt⁵, Kim Papp⁶, Weily Soong⁷, Margitta Worm⁸, Jacek C. Szepietowski⁹, Richard Wu¹⁰, Steven Weinstein¹⁰, Neil Graham¹⁰, Gianluca Pirozzi¹¹, Ariel Teper¹¹, E. Rand Sutherland¹², Marius Ardeleanu¹⁰

¹Comprehensive Center for Inflammation Medicine, University Medical School Schleswig-Holstein Campus, Lübeck, Germany; ²Department of Dermatology, Oregon Health & Science University, Portland, OR, USA; ³Department of Dermatology and Allergy, University of Bonn, Bonn, Germany; ⁴Department of Dermatology, University of Rochester Medical Center, Rochester, NY, USA; ⁵Oregon Medical Research Center, Portland, OR, USA; ⁶K. Papp Clinical Research and Probity Medical Research, Waterloo, ON, Canada; ⁷Alabama Allergy & Asthma Center, Birmingham, AL, USA; ⁸Department of Dermatology and Allergy, Charité University, Berlin, Germany; ⁹Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland; ¹⁰Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA; ¹¹Sanofi, Bridgewater, NJ, USA; ¹²Sanofi, Cambridge, MA, USA
• **Atopic dermatitis (AD)** is a disease of immune dysregulation and altered skin barrier function.

• **Interleukin (IL)-4 and IL-13** are T-helper cell type 2 (Th2) cytokines and are thought to mediate many features of AD.

• **Dupilumab** is a fully human mAb directed against a component (i.e., IL-4Rα) of the IL-4 and IL-13 receptors.

• **Dupilumab** blocks intracellular signaling of both IL-4 and IL-13.

**IL-4Rα**, IL-4 receptor-alpha; **IL-13Rα1**, IL-13 receptor-alpha; **JAK**, Janus kinase; **STAT**, signal transducer and activator of transcription; **TYK2**, tyrosine kinase type 2; **γc**, common cytokine receptor gamma chain.
Study design and objective

Objective: to evaluate clinical efficacy and safety of multiple dosing regimens of SC dupilumab × 16 weeks in adult patients with moderate-to-severe AD inadequately controlled by topical medications

- Multicenter, international, randomized, double-blind, placebo-controlled, dose-ranging, phase 2b study
- ClinicalTrials.gov identifier: NCT01859988

*Loading doses:
- 600 mg for 300 mg dose regimens
- 400 mg for the 200 mg and 100 mg dose regimens

- Dupilumab 100 mg q4w (n = 65)
- Dupilumab 300 mg q4w (n = 65)
- Dupilumab 200 mg q2w (n = 62)
- Dupilumab 300 mg q2w (n = 64)
- Dupilumab 300 mg weekly (n = 63)
- Placebo (n = 61)

q4w, every 4 weeks; q2w, every 2 weeks; SC, subcutaneous.
Key inclusion/exclusion criteria

**Inclusion**
- Male or female aged ≥ 18 years
- Chronic AD ≥ 3 years
- EASI score ≥ 16
- IGA score ≥ 3
- ≥ 10% BSA with AD involvement
- History of inadequate response to topical corticosteroids or calcineurin inhibitors within 6 months prior to screening visit

**Exclusion**
- Prior treatment with dupilumab
- Active acute or chronic infections
- Topical medications for AD within 1 week of baseline
- Systemic immunosuppressive/immunomodulating drugs within 4 weeks of baseline
- Significant comorbidities or laboratory abnormalities

**BSA**, body surface area; **EASI**, Eczema Area and Severity Index; **IGA**, Investigator’s Global Assessment.
**Mean percentage change in EASI score**

**EASI: mean percentage change at Week 16 (LOCF; primary endpoint)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>100 mg q4w</th>
<th>300 mg q4w</th>
<th>200 mg q2w</th>
<th>300 mg q2w</th>
<th>300 mg weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % change from baseline</td>
<td>0</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

**EASI: mean percentage change over 16 Weeks (LOCF)**

- *P < 0.0001 vs placebo, Week 16, and *P < 0.05 for each dupilumab dose vs placebo, Week 1 and onwards

**LOCF**, last observation carried forward.
Proportion of patients achieving EASI-50/75/90 over 16 weeks

**EASI-50**, 50% improvement in EASI score; **EASI-75**, 75% improvement in EASI score; **EASI-90**, 90% improvement in EASI score

*P < 0.0001, †P < 0.001, and ‡P < 0.05 (vs placebo, Week 16)
Proportion of patients achieving IGA score ≤1, and mean percentage change in SCORAD

IGA: proportion achieving score ≤ 1 at Week 16

SCORAD: mean % change over 16 weeks (LOCF)

*P < 0.05, †P < 0.001, and ‡P < 0.0001 vs placebo

*P < 0.05 and †P < 0.0001 vs placebo, Week 16, and
P < 0.01 for each dupilumab dose vs placebo, Week 1 and onwards
Mean % change in percentage BSA and peak weekly pruritus NRS

Percentage BSA affected: mean % change over 16 Weeks (LOCF) vs placebo, Week 16, and P < 0.05 for each dupilumab dose vs placebo Week 2 and onwards (BSA), or Week 1 and onwards (pruritus NRS).

Peak weekly pruritus NRS: mean % change over 16 Weeks (LOCF)

*P < 0.05 and †P < 0.0001 vs placebo, Week 16,
### TEAEs over 32 weeks (16 weeks treatment + 16 weeks follow up)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dupilumab</th>
<th>All dupilumab doses combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 61</td>
<td>n = 65</td>
<td>n = 65</td>
</tr>
<tr>
<td>Total number of TEAEs</td>
<td>184</td>
<td>249</td>
<td>212</td>
</tr>
<tr>
<td>Total number of serious TEAEs</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Any TEAE, %*</td>
<td>80.3</td>
<td>81.5</td>
<td>86.2</td>
</tr>
<tr>
<td>Any serious TEAE, %*</td>
<td>6.6</td>
<td>7.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Discontinuation due to TEAE, %*</td>
<td>4.9</td>
<td>15.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Any infection, %*</td>
<td>59.0</td>
<td>63.1</td>
<td>63.1</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>41.0</td>
<td>38.5</td>
<td>43.1</td>
</tr>
<tr>
<td>Bacterial infections (NEC)</td>
<td>11.5</td>
<td>9.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Herpes viral infections</td>
<td>1.6</td>
<td>12.3</td>
<td>6.2</td>
</tr>
<tr>
<td>Skin structures &amp; soft tissue infections</td>
<td>8.2</td>
<td>7.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>6.6</td>
<td>7.7</td>
<td>6.2</td>
</tr>
<tr>
<td>Viral infections (NEC)</td>
<td>9.8</td>
<td>4.6</td>
<td>4.6</td>
</tr>
<tr>
<td>AD or eczema exacerbation, %*</td>
<td>19.7</td>
<td>24.6</td>
<td>18.5</td>
</tr>
<tr>
<td>Headache, %*</td>
<td>3.3</td>
<td>10.8</td>
<td>7.7</td>
</tr>
<tr>
<td>Nausea &amp; vomiting symptoms, %*</td>
<td>6.6</td>
<td>3.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Injection site reactions, %*</td>
<td>3.3</td>
<td>4.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Musculoskeletal &amp; connective tissue pain, %*</td>
<td>8.2</td>
<td>6.2</td>
<td>4.6</td>
</tr>
<tr>
<td>Conjunctival infections, irritations, &amp; inflammations, %*</td>
<td>3.3</td>
<td>1.5</td>
<td>6.2</td>
</tr>
</tbody>
</table>

*%, percent of patients. NEC, not otherwise classified; TEAE, treatment-emergent adverse event.
Conclusions

• In adults with moderate-to-severe AD inadequately controlled by topical therapy, all dupilumab doses improved:
  – signs of AD as measured by EASI, SCORAD, BSA, EASI-50/70/90, and IGA response
  – symptoms of AD as measured by reductions in pruritus NRS

• There was an apparent dose response trend for efficacy:
  – Dupilumab 300 mg weekly consistently outperformed the other dose regimens, but not by a large margin
  – Dupilumab 100 mg q4w, although significantly better than placebo for most efficacy outcomes, underperformed

• No dose-related or dose-limiting toxicities. In this study, compared with placebo, dupilumab-treated patients had:
  – numerically slightly greater rates of headache, injection site reactions, and conjunctival infection/irritation/inflammation
  – numerically similar overall rate of infections, greater rate of herpes viral infections, and lower rate of other viral infections
Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis in adults: a pooled analysis of two phase 2 randomized clinical trials

Kim Papp\textsuperscript{1}, Eric Simpson\textsuperscript{2}, Lisa Beck\textsuperscript{3}, Diamant Thaçi\textsuperscript{4}, Thomas Bieber\textsuperscript{5}, Andrew Blauvelt\textsuperscript{6}, Howard Sofen\textsuperscript{7}, Melinda Gooderham\textsuperscript{8}, Richard Wu\textsuperscript{9}, Neil Graham\textsuperscript{9}, Gianluca Pirozzi\textsuperscript{10}, E. Rand Sutherland\textsuperscript{11}, Marius Ardeleanu\textsuperscript{9}

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

**Screening**

(Dupilumab 300 mg qw SC or placebo for 12 weeks [phase 2a] or 16 weeks [phase 2b], loading dose\(^a\) on Day 1)

**Study treatment**

- Placebo (n = 115)
- Dupilumab 300 mg qw (n = 118)

**Safety follow-up**

(16 weeks)

- **Objective:** safety and efficacy of a high-dose regimen of dupilumab vs placebo
- **Data were pooled for patients treated with dupilumab 300 mg qw or placebo in two similarly-designed randomized, double-blind, placebo-controlled phase 2 studies:**
  - Phase 2a\(^b\): European 12-week study (placebo, n = 54; dupilumab 300 mg qw, n = 55)
  - Phase 2b\(^c\): International 16-week dose-ranging study (placebo, n = 61; dupilumab 300 mg qw, n = 63)

  *Note: The phase 2b study had four other dupilumab treatment groups with lower-dose regimens; not included in this analysis*

- **Efficacy outcomes were analyzed at Week 12:**
  - Absolute and least square means percent change in SCORAD, EASI, and pruritus NRS
  - Proportion of patients achieving IGA of 0 (“clear”) or 1 (“almost clear”), EASI-50, or EASI-75

\(^a\)Loading dose for dupilumab 300 mg qw regimen: phase 2a, 300 mg; and phase 2b: 600 mg.

\(^b\)ClinicalTrials.gov identifier: NCT01548404

\(^c\)ClinicalTrials.gov identifier: NCT01859988

EASI, Eczema Area Severity Index; EASI-50 and -75, proportion of patients who achieved improvement in EASI score of ≥ 50% and ≥ 75%, respectively; IGA, Investigator’s Global Assessment; NRS, numeric rating score; qw, weekly; SC, subcutaneous injection; SCORAD, SCORing AD.
# Pooled adverse events

<table>
<thead>
<tr>
<th>Patients with TEAE, % of patients</th>
<th>Placebo (n = 115)</th>
<th>Dupilumab 300 mg qw (n = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 TEAE</td>
<td>80.9</td>
<td>81.4</td>
</tr>
<tr>
<td>Patients with any serious TEAE</td>
<td>9.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Patients who discontinued due to TEAE</td>
<td>8.7</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**TEAEs reported in ≥ 5% of patients**

<table>
<thead>
<tr>
<th>TEAE</th>
<th>Placebo</th>
<th>Dupilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infections</td>
<td>33.9</td>
<td>42.4</td>
</tr>
<tr>
<td>Skin infection (adjudicated)</td>
<td>29.7</td>
<td>16.4</td>
</tr>
<tr>
<td>Conjunctival infections, irritations, and inflammations</td>
<td>3.5</td>
<td>15.3</td>
</tr>
<tr>
<td>Headaches NEC</td>
<td>7.8</td>
<td>14.4</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>6.1</td>
<td>13.6</td>
</tr>
<tr>
<td>Dermatitis and eczema</td>
<td>14.8</td>
<td>11.0</td>
</tr>
<tr>
<td>Asthenic conditions</td>
<td>6.1</td>
<td>5.9</td>
</tr>
<tr>
<td>Coughing and associated symptoms</td>
<td>0.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Upper respiratory tract signs and symptoms</td>
<td>1.7</td>
<td>5.1</td>
</tr>
</tbody>
</table>

*TEAEs reported in ≥ 5% of patients in pooled placebo or dupilumab groups by Medical Dictionary for Regulatory Activities high-level term. NEC, not otherwise classified; TEAE, treatment emergent adverse event*
# Pooled adverse events

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<tr>
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**TEAEs reported in ≥ 5% of patients**

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<td>5.1</td>
</tr>
</tbody>
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*TEAEs reported in ≥ 5% of patients in pooled placebo or dupilumab groups by Medical Dictionary for Regulatory Activities high-level term. NEC, not otherwise classified; TEAE, treatment emergent adverse event.*
# Pooled adverse events

<table>
<thead>
<tr>
<th>Patients with TEAE, % of patients</th>
<th>Placebo (n = 115)</th>
<th>Dupilumab 300 mg qw (n = 118)</th>
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<td>Patients with ≥ 1 TEAE</td>
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<td>Patients with any serious TEAE</td>
<td>9.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Patients who discontinued due to TEAE</td>
<td>8.7</td>
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**TEAEs reported in ≥ 5% of patients**

- **Upper respiratory tract infections**: 33.9 vs. 42.4
- **Skin infection (adjudicated)**: 29.7 vs. 16.4
- **Conjunctival infections, irritations, and inflammations**: 3.5 vs. 15.3
- **Headaches NEC**: 7.8 vs. 14.4
- **Injection site reactions**: 6.1 vs. 13.6
- **Dermatitis and eczema**: 14.8 vs. 11.0
- **Asthenic conditions**: 6.1 vs. 5.9
- **Coughing and associated symptoms**: 0.9 vs. 5.9

*TEAEs reported in ≥ 5% of patients in pooled placebo or dupilumab groups by Medical Dictionary for Regulatory Activities high-level term. NEC, not otherwise classified; TEAE, treatment emergent adverse event.*
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*TEAEs reported in ≥ 5% of patients in pooled placebo or dupilumab groups by Medical Dictionary for Regulatory Activities high-level term.*

NEC, not otherwise classified; TEAE, treatment emergent adverse event
Significant improvement in SCORAD and IGA with dupilumab vs placebo at Week 12 in pooled studies

**SCORAD**

- **Placebo**
- **Dupilumab 300 mg qw**

*Mean score (± SEM)*

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*P < 0.0001 vs placebo*

**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 score with dupilumab vs placebo at Week 12 in pooled studies

**LS mean % change in EASI score (±SE)**

*P < 0.0001 vs placebo

*LS, least squares.*
Significant improvement in EASI-50 and EASI-75 with dupilumab vs placebo at Week 12 in pooled studies

*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.
In pooled studies, AD patients treated with high-dose dupilumab responded well

- Significant improvement of dupilumab 300 mg qw at Week 12 vs placebo:
  - SCORAD
  - IGA response
  - EASI score
  - Pruritus NRS
  - EASI-50 and EASI-75

- Dupilumab safety profile was favorable in these studies
  - Consistent with previous studies¹

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
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 dieases in AD patients.
Inflammatory component modulated by multiple host immune response mechanisms including:

- Immunoglobulin E (IgE) upregulation
- \( T_{H2} \) immune response
- Proinflammatory cytokines
- Bacterial superantigen triggers
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
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 may be useful for refractory AD
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
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
Disclosures

- **K Papp**: speaker, consultant, and/or investigator for AbbVie, Active Biotech, Akesis, Allergan, Amgen, Anacor, Astellas, AstraZeneca, Basilea, Bayer, Biogen-Idec, Boehringer-Ingelheim, Bristol Myers Squib, Cato, Cepheid, Celgene, CellScale Biomaterials, Centocor, Cipher, Coherus, Dow Pharma, Eli Lilly, Endocyte, Ferring Pharma, Forward Pharma, Galderma, Genentech, Gilead, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, Kythera, Leo Pharma, MedImmune, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mylan, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Rigel, Roche, Sanofi-Aventis, Sosei, Takeda, UBC, Vertex, Xoma

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- **A Blauvelt**: consultant for and has received research support from AbbVie, Amgen, Boehringer-Ingelheim, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Sandoz

- **H Sofen**: investigator and consultant for, and receives honoraria, advisory board, or consulting fees from Amgen, AstraZeneca, AbbVie, Celgene, Genentech, Janssen, Novartis, Regeneron Pharmaceuticals, Inc.

- **M Gooderham**: consultant, speaker, has received honoraria, and is an investigator for AbbVie, Amgen, Astellas, Boehringer-Ingelheim, Celgene, Galderma, Genentech, Janssen, Kyowa, Eli Lilly, Leo Pharma, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc.; and has been an investigator for Allergan, Kythera, Medimmune, Roche, Takeda, UBC

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- **G Pirozzi and ER Sutherland**: employees and shareholders of Sanofi

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THANK YOU
AOCD!!!