An Update on Atopic Dermatitis

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Disclosures for Mark Boguniewicz, MD

For the 12 months preceding this CME activity, I or my spouse/partner disclose the following types of financial relationships:

- Grant/Research Support from: Anacor, Merck, NIH
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- Speaker’s Bureau for: None
- Major Stock Shareholder for: None
- Other Financial or Material Support from: None
- Other: Celgene (Advisory Board)

I will be discussing products that are investigational or not labeled for use under discussion.
Objectives

Upon completion of this session, participants should be able to:

1. Evaluate patients with eczematous rashes for diseases in the differential of atopic dermatitis
2. Discuss new insights into pathogenesis of atopic dermatitis and therapeutic options
Atopic dermatitis 2014 literature review*

• Differential diagnosis/co-morbidities
• Epidemiology/natural history
• Pathophysiology
• Treatment
• Prevention

* PubMed review of 2014 citations for AD:
- 1054 citations reviewed
- 141 abstracts selected
- 28 articles presented
Fig 1. Flow chart of the diagnosis and management of AD

1. Patient presents with skin manifestations consistent with AD, e.g., an eczematous pruritic dermatitis
2. Evaluation based on history and exam diagnostic for AD dermatitis
3. Consideration of other conditions
4. Atopic dermatitis severe?
   - YES
     - Management of AD
       - Skin hydrations/moisturizers
       - Topical corticosteroids
       - Tar preparations
       - Topical calcineurin inhibitors
       - Dilute bleach baths
       - Antihistamines
       - Evaluation and treatment of:
         - Skin infection
         - Inhalant and food allergy
         - Nonspecific triggers
     - NO
   - NO
5. Management successful?
   - YES
     - Follow-up
       - Consider proactive treatment for patients with relapsing disease
   - NO
6. Reassess: Is diagnosis of atopic dermatitis correct?
   - YES
     - Consultation with an AD specialist
     - Consultation with an AD specialist
     - Consultation with an AD specialist
     - Consultation with an AD specialist
   - NO
7. Consultation with atopic dermatitis specialist for consideration of other conditions

J Allergy Clin Immunol 2013;131:295
Immunodeficiency with *DOCK8* mutations

Herpes simplex virus, Human papilloma virus, Molluscum contagiosum

Table 1 -- DOCK8-deficient patient cohort

<table>
<thead>
<tr>
<th>Mutation</th>
<th>DOCK8-1</th>
<th>DOCK8-2</th>
<th>DOCK8-3</th>
<th>DOCK8-4</th>
<th>DOCK8-5</th>
<th>DOCK8-6</th>
<th>DOCK8-7</th>
<th>DOCK8-8</th>
<th>DOCK8-9</th>
<th>DOCK8-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at evaluation</td>
<td>13 y</td>
<td>12 y</td>
<td>6 y</td>
<td>17 y</td>
<td>18 y</td>
<td>3 y</td>
<td>8 y</td>
<td>26 y</td>
<td>17 mo</td>
<td>12 y</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Mutation</td>
<td>Homozygous deletion upstream of</td>
<td>Homozygous deletion (2 bp) in</td>
<td>Homozygous splice donor site</td>
<td>Homozygous splice donor site</td>
<td>Homozygous deletion (2 bp) in</td>
<td>Homozygous deletion</td>
<td>Heterozygous deletion g(371,</td>
<td>Heterozygous deletion</td>
<td>Homozygous deletion</td>
<td>Homozygous deletion</td>
</tr>
<tr>
<td></td>
<td>exon 1 including exon 2</td>
<td>exon 8: c850_861 delCT, pL234fsX293</td>
<td>mutation: c3120+1 g&gt;t (exon 25+1</td>
<td>mutation: c3120+1 g&gt;t (exon 25+1</td>
<td>exon 8: 9p24.3</td>
<td>g(371, 489_380, 404)_ (462,145_468,814) del plus 1266delC</td>
<td>g(371, 489_380, 404)_ (462,145_468,814) del plus 1266delC</td>
<td>del 22-25; heterozygous deletion of exon 22-25; heterozygous deletion of exon 3-21 and 26-32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE levels (IU/mL)</td>
<td>10,970</td>
<td>35,720</td>
<td>2,303</td>
<td>25,987</td>
<td>62,429</td>
<td>38,908</td>
<td>1,162</td>
<td>1,143</td>
<td>6,270</td>
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<tr>
<td>Eosinophils (cells/µL)</td>
<td>8,968</td>
<td>4,365</td>
<td>2,835</td>
<td>11,033</td>
<td>693</td>
<td>12,096</td>
<td>NA</td>
<td>260</td>
<td>430</td>
<td>1,100</td>
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<tr>
<td>Eczema</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Viral infections</td>
<td>HSV, MCV</td>
<td>HSV</td>
<td>HSV, MCV</td>
<td>VZV, HSV</td>
<td>none</td>
<td>MCV</td>
<td>CMV, BKV</td>
<td>HSV, HPV</td>
<td>HSV, VZV, MCV</td>
<td>HPV, MCV</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>Recurrent pneumonia, skin abscesses</td>
<td>Pneumonia, skin abscesses</td>
<td>Recurrent pneumonia, skin abscesses</td>
<td>Pneumonia, skin abscesses</td>
<td>Pneumonia, skin abscesses</td>
<td>Chronic salmonella and recurrent sinopulmonary infections, skin abscesses</td>
<td>Recurrent sinopulmonary infections</td>
<td>Recurrent sinopulmonary infections</td>
<td>Meningitis, bacteremia</td>
<td>Meningitis, bacteremia</td>
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<tr>
<td>Fungal infections</td>
<td>No</td>
<td>Skin</td>
<td>CMC</td>
<td>CMC</td>
<td>Skin</td>
<td>Skin</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Skin</td>
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<tr>
<td>Autoimmunity</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Hemolytic anemia</td>
<td>No</td>
<td>No</td>
<td>Sclerosing cholangitis</td>
<td>No</td>
<td>No</td>
<td>Vasculopathy</td>
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<tr>
<td>Asthma</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Food allergies</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Malignancy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SCC</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Previously published</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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</table>
Vaccine strain varicella-zoster virus–induced central nervous system vasculopathy as the presenting feature of DOCK8 deficiency

AD, STAT3- and DOCK8-hyper-IgE syndromes differ in IgE-based sensitization pattern

- Total serum IgE levels similarly increased in STAT3-HIES, DOCK8-HIES & AD pts
- Aeroallergen-specific IgE: total IgE highest in AD, DOCK8-HIES patients showed highest specific serum IgE against food allergens
- SIgE, SPTs, & T-cell subsets of STAT3-HIES patients comparable with those of healthy individuals except decreased Th17-cell counts

Boos AC, et al. Allergy 2014;69:943
STAT3-HIES, DOCK8-HIES, and AD patients differ in specificity of their increased serum IgE.

Boos AC, et al. Allergy 2014;69:943
Flow cytometry biomarkers distinguish DOCK8 deficiency from severe atopic dermatitis

• Lymphocyte profile on whole blood of CD3^+ and CD4^+ T cell lymphopenia and decreased naive CD8^+ T cells, along with a preserved total B cell percentage in conjunction with a decrease in memory B cells is strongly suggestive of DOCK8 deficiency rather than AD in a patient with severe eczema

<table>
<thead>
<tr>
<th>Lymphocyte Subsets</th>
<th>Percentage of Patients</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T cells (CD3⁺)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4⁺</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naïve (CD45RA⁺CCR7⁺)</td>
<td>Low: 0.22</td>
<td></td>
</tr>
<tr>
<td>Effector memory (CD45RA⁻CCR7⁻)</td>
<td>Normal: 0.56</td>
<td></td>
</tr>
<tr>
<td>Central memory (CD45RA⁺CCR7⁺)</td>
<td>Low: 0.22</td>
<td></td>
</tr>
<tr>
<td>Exhausted effector memory (CD45RA⁺CCR7⁻)</td>
<td>Low: 0.47</td>
<td></td>
</tr>
<tr>
<td>CD8⁺</td>
<td></td>
<td></td>
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<tr>
<td>Naïve (CD45RA⁺CCR7⁺)</td>
<td>Low: 0.02</td>
<td></td>
</tr>
<tr>
<td>Effector memory (CD45RA⁺CCR7⁺)</td>
<td>Normal: 0.22</td>
<td></td>
</tr>
<tr>
<td>Central memory (CD45RA⁺CCR7⁺)</td>
<td>Low: 0.56</td>
<td></td>
</tr>
<tr>
<td>Exhausted effector memory (CD45RA⁺CCR7⁻)</td>
<td>Low: 0.52</td>
<td></td>
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<tr>
<td><strong>B cells (CD19⁺)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naïve (CD19⁺ CD27⁻)</td>
<td>Low: 0.04</td>
<td></td>
</tr>
<tr>
<td>Unswitched memory B cells (CD27⁺IgD⁺)</td>
<td>Low: 0.00002</td>
<td></td>
</tr>
<tr>
<td>Switched memory B cells (CD27⁺IgD⁻)</td>
<td>Low: 0.02</td>
<td></td>
</tr>
<tr>
<td>Transitional B cells (CD19⁺ CD24⁺CD38⁺)</td>
<td>Low: 0.05</td>
<td></td>
</tr>
<tr>
<td>Plasmablasts (CD24⁺CD38⁻)</td>
<td>Low: 0.42</td>
<td></td>
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</table>
Allergic contact dermatitis in children: review of the past decade

- Prevalence of (+) patch tests in referred children with suspected ACD ranges from 27 - 95.6 %
- Most common allergens in children in N America are nickel, neomycin, cobalt, fragrance, Myroxylon pereirae (Balsam of Peru), gold, formaldehyde, lanolin/wool alcohols, thimerosal & potassium dichromate
- Relationship between ACD and AD is complicated with conflicting reports of prevalence in the literature; however, in a patient with dermatitis not responding to traditional therapies or with new areas of involvement, ACD should be considered as part of the work-up

Children with atopic dermatitis should always be patch-tested if they have hand or foot dermatitis

- Contact allergy found in 22/82 children (26.8%)
- Most common contact allergens were Amerchol L101 [type of lanolin] (11.0%), potassium dichromate (7.3%) and nickel sulphate (4.9%)
- Statistically significant difference in contact allergy frequency demonstrated for those with hand and/or foot eczema compared to those without

Siblings, asthma, rhinoconjunctivitis and eczema: A worldwide perspective from the International Study Of Asthma And Allergies In Childhood (ISAAC)

• Questionnaire data for 210,200 children 6-7 yrs from 31 countries and 337,226 children 13-14 yrs from 52 countries (phase 3)

• In both age groups, inverse trends (P<0.0001) were observed for reported "hay fever ever" and "eczema ever" with increasing numbers of total siblings and more specifically older siblings (inverse associations significantly (P<0.005) stronger in more affluent countries)

In contrast, symptoms of severe asthma and severe eczema were positively associated (P<0.0001) with total sibship size in both age groups. These associations with disease severity were largely independent of position within the sibship and national GNI per capita.

2 distinct trends:
- Inverse associations with older siblings ("hygiene hypothesis") mainly phenomenon of more affluent countries, whereas greater severity of symptoms in larger families is globally more widespread.

Persistence of mild to moderate AD

• A cross-sectional and cohort study of a nation-wide long-term registry of children with AD enrolled in the Pediatric Eczema Elective Registry (PEER)

• Total of 7157 patients enrolled in PEER study with at least 2 yrs of f/u for 4248 and at least 5 yrs of f/u for 2416

• At every age (2-26 yrs), >80% of PEER participants had symptoms of AD and/or were using medication to treat their AD

• It was not until age 20 yrs that 50% of patients had at least 1 lifetime 6-month symptom- and treatment-free period

Margolis JS, et al. JAMA Dermatol 2014;150:593

*~ 16% of PEER subset with FLG mutations
Atopic dermatitis: a [complex] disease of altered skin barrier and immune dysregulation
Genetic and immunologic influences on filaggrin expression

Role of filaggrin in the skin and structural and biophysical consequences of filaggrin deficiency

If your patient has early-onset, severe, persistent atopic dermatitis with asthma and allergic sensitization...
Filaggrin haplo-insufficiency and increased risk of several complex traits

Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations

- Exposure to peanut antigen in dust within the first year of life was measured in a population-based birth cohort
- Peanut sensitization and peanut allergy (defined by oral food challenges or component-resolved diagnostics) assessed at 8 & 11 years
- Genotyping was performed for 6 FLG mutations

Among children with FLG mutations, for each ln unit increase in house dust peanut protein level, there was a >6-fold increased odds of peanut SPT sensitization, CRD sensitization or both in children at ages 8 yrs, 11 yrs, or both and >3-fold increased odds of peanut allergy compared with odds seen in children with wild-type FLG mutations.

No significant effect of exposure in children without FLG mutations.

In children carrying FLG mutation, threshold level for peanut SPT sensitization was 0.92 μg of peanut protein/g (95% CI, 0.70-1.22 μg/g), that for CRD sensitization was 1.03 μg/g (95% CI, 0.90-1.82 μg/g), and that for peanut allergy was 1.17 μg/g (95% CI, 0.01-163.83 μg/g).

Data support hypothesis that peanut allergy develops through transcutaneous sensitization in children with an impaired skin barrier.

Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence

- Longitudinal relationship between 3 FLG-LOF mutations and FA using the Isle of Wight birth cohort [FLG mutations genotyped in 1150 (79%) of 1456 children]
- No direct effect of FLG-LOF mutations on FA at any age; however, indirect effect found on FA at all ages through eczema and FAS in earlier years

Analytic path model exploring direct effects of FLG-LOF mutation and eczema at ages 1 and 2 yrs and 4 yrs on FA and FAS at 4, 10, & 18 yrs

Skin exposure promotes a Th2-dependent sensitization to peanut allergens

• In mice, epicutaneous peanut exposure induced sensitization to Ara h 1 and Ara h 2, which is also observed in human peanut allergy

• Both crude peanut extract and Ara h 2 alone served as adjuvants, as both induced a bystander sensitization similar to that induced by AD-associated SEB

• In cultured human keratinocytes and in murine skin, peanut extract directly induced cytokine expression

• Moreover, topical peanut extract application induced an alteration dependent on the IL-33 receptor ST2 in skin-draining DCs, resulting in Th2 cytokine production from T cells

• Data support hypothesis that peanuts are allergenic due to inherent adjuvant activity and suggest that skin exposure to food allergens contributes to sensitization to foods in early life

Filaggrin-stratified transcriptomic analysis of pediatric skin identifies mechanistic pathways in patients with atopic dermatitis

- 2430 differentially expressed genes (false discovery rate, \( P < 0.05 \)) identified with 211 significantly upregulated and 490 downregulated by >2-fold
  - Gene ontology terms for "extracellular space" and "defense response" enriched, whereas "lipid metabolic processes" downregulated
- Subset of FLG wild-type cases showed dysregulation of genes involved with lipid metabolism, whereas filaggrin haploinsufficiency affected global gene expression and was characterized by a type 1 interferon-mediated stress response
- Importance of extracellular space and lipid metabolism independent of FLG genotype, whereas aberrant defense response seen in subjects with FLG mutations

FLG wild-type subjects show dysregulation of genes involved with lipid metabolism

Tight junctions and claudin-1: A second barrier defect in atopic dermatitis?

- Reduced expression of TJ protein claudin-1 in AD pts validated at mRNA & protein levels
- Claudin-1 expression inversely correlated with Th2 biomarkers
- Functional relevance associated with impairment of bioelectric barrier function in AD
- CLDN1 SNPs associated with AD

Distinct behavior of human Langerhans cells and inflammatory dendritic epidermal cells at tight junctions in patients with atopic dermatitis

- Activated LCs penetrate TJs in human skin increased ~ 5-fold in lesional AD skin but not in nonlesional skin or lesions of patients with ichthyosis vulgaris or psoriasis
- IDECs localized in lower epidermis and dendrites extended horizontally without penetration through TJs
- Although langerin accumulated on the tips of dendrites of activated LCs, FcεRI was expressed diffusely on the cell surfaces on LCs and IDECs in lesional skin from patients with AD

TJ penetration of a Langerhans cell dendrite

TJ penetration of HLA-DR\textsuperscript{high} activated LCs (yellow arrows) and habitation below the TJs of HLA-DR\textsuperscript{perinuclear} steady-state LCs (open arrowheads) and langerin\textsuperscript{−} IDECs (yellow arrowheads) in a 90°-rotated 3D image of AD skin.

TJ penetration of a LC dendrite

Recent insights into atopic dermatitis and implications for management of infectious complications

Increased susceptibility to infections or colonization with microbial organisms: Staphylococcus aureus, Herpes simplex

The presence and impact of biofilm-producing staphylococci in atopic dermatitis

- AD-affected samples contained multidrug-resistant staphylococci, with S aureus (42.0%) and Staphylococcus epidermidis (20.0%) as the predominant species
- All isolates were positive for extracellular polysaccharide and biofilm (85.0% strong biofilm producers and 15.0% moderately to weakly positive)
- Polymerase chain reaction revealed the biofilm-mediating icaD (93.0%) and aap (12.5%) genes in the isolates

Allen HB, et al. JAMA Dermatol 2014;150:260
• Also examined tissues for microbial identification, extracellular biomass formation, biofilm formation, and staphylococcal biofilm in skin tissues
• Occlusion of sweat ducts with periodic acid-Schiff-positive and Congo red-positive material was noted on microscopic tissue examination
• Toll-like receptor 2 was shown to be activated in AD lesional skin (immediately proximal to the sweat ducts), which likely led to the initiation of proteinase-activated receptor 2-mediated pruritus and MyD88-mediated spongiosis

Allen HB, et al. JAMA Dermatol 2014;150:260
Effect of tacrolimus compared with betamethasone valerate on skin barrier in volunteers with quiescent atopic dermatitis

- Twenty volunteers with quiescent AD (no active signs for 6 months) participated in a randomized observer-blind study, wherein BMVc was applied to one forearm and TACo to the other, twice daily for 4 weeks
- BMVc significantly reduced skin barrier function, integrity and cohesion, and levels of pyrrolidone carboxylic acid (PCA) and urocanic acid (UCA) towards the subclinical barrier defect observed in patients with AD (nonlesional sites)

TACo preserved skin barrier function, integrity, cohesion and PCA and UCA levels, while significantly increasing skin hydration to levels comparable with healthy skin.

Both treatments reduced skin surface pH and trypsin-like protease activity with TACo doing so to a significantly greater degree.

Understanding the influence of social media in medicine: lesson learned from Facebook


negative posts about topical steroids (61%)
Patient-centered, direct-access online care for management of atopic dermatitis: A randomized clinical trial

• 1-year randomized controlled equivalency trial in medically underserved areas, outpt clinics & general community

• Participants included 156 children and adults with AD with access to Internet, computers and digital cameras

• After initial in-person visit, pts randomized 1:1 to direct-access online or usual in-person care for follow-up management of AD
  – Direct-access online group captured & transmitted clinical images and history asynchronously to dermatologists online; derms evaluated clinical information, provided rec & ed and prescribed meds online asynchronously
  – In-person group visited derms in their offices for follow-up care

Between baseline & 12 mos, mean (SD) within-group difference in POEM score in pts in direct-access online group was −5.1 (5.48) (95% CI, −6.32 to −3.88); in in-person group, within-group difference was −4.86 (4.87) (95% CI, −6.27 to −3.46)

Difference in change in POEM scores between 2 groups was 0.24 (6.59) (90% CI, −1.70 to 1.23) which was contained within predetermined 2.5 equivalence margin

% of pts achieving clearance or near-clearance of their disease (IGA 0 or 1) was 38.4% (95% CI, 27.7% to 49.3%) in direct-access online group and 43.6% (95% CI, 32.6%-54.6%) in in-person group

Difference in % pts achieving clearance or near-clearance between 2 groups was 5.1% (90% CI, 1.7%-8.6%), which was contained within the predetermined 10% equivalence margin

Direct-access online model results in equivalent improvements in AD clinical outcomes as in-person care

Direct-access online care may represent an innovative model of delivering dermatological services to patients with chronic skin diseases

Safety and efficacy of topical E6005, a phosphodiesterase 4 inhibitor, in Japanese adult patients with atopic dermatitis: Results of a randomized, vehicle-controlled, multicenter clinical trial

- topical E6005, a novel phosphodiesterase 4 inhibitor, in Japanese adults with atopic dermatitis evaluated in 78 patients randomized to 0.2% E6005 ointment or vehicle control. The randomization phase of 4 weeks was followed by an extension phase of 8 weeks. In the extension phase, all 67 subjects who completed the randomization phase were treated with 0.2% E6005 ointment. The 4-week application of topical E6005 twice daily was safe and well tolerated. The safety profile for up to 12 weeks was similar to that for the first 4 weeks.
- Group receiving topical E6005 for 12 weeks showed significant score reductions from baselines for EASI (P = 0.030), SCORAD-objective (P < 0.001) and SCORAD-C (P = 0.038). These results further support the development of topical E6005 for the treatment of atopic dermatitis.

Two subjects treated with E6005 ointment showing symptomatic improvement

(a,c) Baseline  (b,d) week 4

Day Hospital Program/Wet wrap therapy

Wet wrap therapy in children with moderate to severe atopic dermatitis in a multidisciplinary treatment program

Paired SCORAD for 72 pts, sorted by admission SCORAD high-low

Wet wrap therapy in children with moderate to severe atopic dermatitis in a multidisciplinary treatment program

Mean ADQ (black) vs SCORAD (red)

*off WWT!

Proactive wet-wrap method with diluted corticosteroids vs emollients in children with AD: prospective, randomized, double-blind, placebo-controlled trial

- Randomized, DBPC study in children 6 mos - 10 yrs with severe AD (objective SCORAD at least 40 ± 5), comparing WWT with diluted steroids (1:3 mometasone 0.1% ointment, face 1:19 mometasone 0.1% ointment under a mask) with emollient x 4 wks
- Primary outcome: improvement of objective SCORAD; secondary outcomes included Patient-Oriented Eczema Measure and QOL index
- WWT with diluted steroids acted faster and was more efficacious than WWT with emollients
- WWT for severe AD is an effective therapy option for at least a period of 4 wks

Fitted average longitudinal profiles for objective SCORAD

Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review

• RCTs evaluating systemic immunomodulating treatments for moderate-to-severe AD were included using Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach
  – Efficacy outcomes were clinical signs, symptoms, quality of life, and course of AD
  – Safety data were compared by calculating weekly incidence rates for adverse events
• 34 RCTs with 12 different systemic treatments totaling 1653 patients were included
  – 14 trials consistently indicate that CsA efficaciously improves clinical signs of AD
• CsA is recommended as first-line treatment for short-term use

Retrospective review of relapse after systemic cyclosporine in children with atopic dermatitis

• 15 pts with mean age at initiation of CsA 11.2 ± 3.4 years, mean duration of CsA 10.9 ± 2.7 months (range 7-15 months), starting dose of 2.8 ± 0.6 mg/kg/day

• 12 pts (80%) responded to CsA, 5 pts (42%) relapsed at a follow-up of 22.7 ± 15.0 mos

• Duration of therapy longer in patients who did not relapse (17.7 ± 10.7 months) than in those who did (10.2 ± 2.7 months) (p = 0.06)

• Results suggest longer duration of low-dose CsA may decrease risk of relapse in pts with severe AD resistant to topical therapies

Cyclosporine in patients with atopic dermatitis modulates activated inflammatory pathways and reverses epidermal pathology

Reversal of atopic dermatitis with narrow-band UVB phototherapy and biomarkers for therapeutic response

CsA vs narrow band-UVB

- CsA resulted in greater and more significant improvements in immune and epidermal phenotypes with highly significant decreases evident at week 2.
- Effects of CsA also extend to nonlesional skin, which shows similar but milder reversal of the inflammatory and epidermal components (improvement in nonlesional skin not seen in NB-UVB study in which inhibitory effects were mostly limited to lesional skin).

CsA vs narrow band-UVB con’t

- Compared with NB-UVB RDGP*, many barrier and immune genes already showed improvement at week 2 of CsA treatment, and RDGP at week 12 of CsA treatment was much smaller.

- Despite smaller CsA RDGP, AD lesions tend to reoccur faster after D/C’ing CsA treatment than after NB-UVB treatment (2-wk relapse vs 8-wk relapse).

*residual disease genomic profile

Histologic changes corresponding with CsA RDGP

NB-UVB increases stratum corneum thickness c/w CsA

Sublingual immunotherapy in mite-sensitized children with atopic dermatitis: a randomized, open, parallel-group study

Possible new therapeutic strategy to regulate AD through upregulating filaggrin expression

JTC801 promotes expression of filaggrin in human skin equivalent model

JTC801 attenuated atopic skin inflammation in NC/Nga mice

Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis

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Results

• In 4-week monotherapy studies, dupilumab resulted in rapid and dose-dependent improvements in clinical indexes, biomarker levels and disease transcriptome.

• In 12-week study, dupilumab monotherapy reproduced and extended the 4-week findings:
  – 85% of patients in dupilumab group vs 35% of placebo group had a 50% reduction in the EASI score (P<0.001)
  – 40% of patients in dupilumab group vs 7% in placebo group had a IGA of 0 to 1 (clear or almost clear) (P<0.001)
  – pruritus scores decreased by 55.7% in dupilumab group vs 15.1% in placebo group (P<0.001)

• In combination study, 100% of patients in dupilumab group vs 50% of placebo group had EASI-50 (P=0.002), despite fact that dupilumab + TCS group used < half amount of TCS used by placebo + TCS group (P=0.16)

Emollient enhancement of skin barrier from birth offers effective atopic dermatitis prevention

- Randomized controlled trial in US & UK of 124 neonates at high risk for AD
- Parents in intervention arm instructed to apply full-body emollient at least once/day starting within 3 weeks of birth; parents in the control arm asked to use no emollients
- Primary feasibility outcome was percentage of families willing to be randomized. Primary clinical outcome was cumulative incidence of AD at 6 mo, as assessed by a trained investigator

• 42% of eligible families agreed to be randomized into the trial. All participating families in the intervention arm found the intervention acceptable.

• A statistically significant protective effect was found with use of daily emollient on cumulative incidence of AD with a relative risk reduction of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; P = .017)

• No emollient-related adverse events and no differences in adverse events between groups

• Emollient therapy from birth represents a feasible, safe, and effective approach for AD prevention

Application of moisturizer to neonates prevents development of atopic dermatitis

- Prospective, randomized controlled trial to investigate whether protecting skin barrier with moisturizer during neonatal period prevents development of AD and allergic sensitization
- Moisturizer applied daily during first 32 wks of life to 59 of 118 neonates at high risk for AD (based on having a parent or sibling with AD)
- Onset of AD (eczematous symptoms lasting >4 weeks) and eczema (lasting >2 weeks) assessed by dermatology specialist on basis of modified Hanifin and Rajka criteria

MOC: The ABC’s of managing patients with severe atopic dermatitis

TABLE E1. ABC’s of atopic dermatitis

A = Avoidance of triggers (eg, irritants and proved allergens)
- Educate patients and caregivers about role of irritants
- Approach allergy evaluation in a critical manner, informing patient/caregiver before testing about predictive values of positive and negative test results, pros/cons of dietary eliminations, risks vs benefits of food challenges, and environmental control measures

B = Barrier repair and maintenance
- Emphasis on hydration and moisturizers
- Address itch-scratch cycle with medications but also behavioral modification
- Consider wet-wrap therapy for limited periods of time to areas of recalcitrant AD

C = Control of inflammation and infections
- Consider proactive (twice weekly) therapy in patients with relapsing course
- Use diagnostics effectively (eg, culture and sensitivity test, viral culture, or PCR)
- Use antimicrobial agents appropriately
- Use topical corticosteroids and TCIs appropriately (eg, prescribe appropriate potency, vehicle, and quantity)

Atopic Dermatitis Program 1990-2015
A multidisciplinary team approach