An Update on Topical Therapy for Atopic Dermatitis

Amy S. Paller, M.D.
Professor and Chair of Dermatology
Professor of Pediatrics
Northwestern University
Feinberg School of Medicine
Chicago, Illinois

Disclosures
Consultant: Eli Lilly, Galderma, Genentech, GSK-Stiefel, Novartis, Pfizer, Sanofi-Regeneron, Valeant
Investigator: Galderma, Incyte, Leo, Pfizer, Regeneron
Evidence-based guidelines

Guidelines of care for the management of atopic dermatitis

Section 2. Management and treatment of atopic dermatitis with topical therapies

Work Group: Lawrence F. Eichenfield, MD (Co-chair),
Wynnis L. Tom, MD, Timothy G. Berger, MD,
Alfons Krol, MD, Amy S. Paller, MS, MD, Kathryn Schwarzenberger, MD,
James N. Bergman, MD,
Sarah L. Chamlin, MD, MSCI, David E. Cohen, MD,
Kevin D. Cooper, MD, Kelly M. Cordoro, MD,
Dawn M. Davis, MD, Steven R. Feldman, MD, PhD,
Jon M. Hanifin, MD, David J. Margolis, MD, PhD,
Robert A. Silverman, MD, Eric L. Simpson, MD,
Hywel C. Williams, DSc, Craig A. Elmets, MD,
Julie Block, BA, Christopher G. Harrod, MS,
Wendy Smith Begolka, MBS, and Robert Sidbury, MD (Co-chair)
San Diego, San Francisco, and San Rafael, California; Portland, Oregon; Chicago and Schaumburg, Illinois; Memphis, Tennessee; Vancouver, British Columbia, Canada; New York, New York; Cleveland, Ohio; Rochester, Minnesota; Winston-Salem, North Carolina; Philadelphia, Pennsylvania; Fairfax, Virginia; Nottingham, United Kingdom; Birmingham, Alabama; and Seattle, Washington

Correlation between an impaired barrier and risk of AD

- 2 day/old TEWL in upper quartile = 7.1x more AD at 12 months
  - Regardless of FLG mutation status (no effect on neonatal TEWL)
  - Lowest quartile protective

Barrier abnormality increases risk of AD and may drive relationship between AD and food allergy

Ova to tape-stripped skin $\rightarrow$ AD

- 2 day/old TEWL in upper quartile = 18.7x more likely to have food allergy at 2 yrs than lower quartile if AD and 3.5x if no AD

Kelleher et al. JACI 2015; 135: 930

Spergel et al. JCI 1998;101:1614

Kelleher et al. JACI 2016; 137: 1111
If we reverse the early barrier impairment, can we reduce the risk of AD and the later development of allergies?

Simpson et al. JACI 2014;134:818
Early moisturization to prevent AD

- Randomized controlled trials in first weeks of life of high risk infants
  - At least daily application of full-body emollient therapy vs. controls

- At 6 months, emollient reduced cumulative incidence of AD
  - Relative risk reduction of 50% (95% CI, 0.28-0.9; p=0.017)
    US and UK: Simpson et al. JACI 2014;134:818

- At 32 wks, 32% fewer infants with emollient had AD (p = 0.012)
  Japan: Horimukai et al. JACI 2014;134:824

Larger prospective studies in progress:
What is impact on AD and later allergy/ asthma development?
Beyond emollient: Can we replace specific deficiencies?

- Skin biopsies from lesional and nonlesional skin of children <5 y/o with AD onset in previous 6 months (TEWL: 32 & 16 g/m²/h)

- Filaggrin deficiency is not an issue in early pediatric AD (unless mutation)
  - In adults, may reflect chronic exposure to cytokines and *S. aureus*

How is barrier defective?

- **Microarray study:** Deficient expression for genes encoding **tight junction proteins** and **lipid synthesizing enzymes**, not proteins of differentiation

- **Lipids** markedly reduced in Nile red-stained stratum corneum

Brunner et al, 2017
What about topical anti-inflammatory therapy?

- Topical steroids continue to be the mainstay

- **Reactive therapy** of aggressive intervention to suppress inflammation

- **Proactive therapy**: then dial down to continue topical steroid or calcineurin inhibitor 2-3 times weekly to maintain clear/ almost clear

Focus on adherence to regimen

- Personalize to patient and family

- Educate to combat phobia against topical steroids and calcineurin inhibitors (no red flags for malignancy, despite black box warning)
PDE4 Inhibitor: Crisaborole

- Increased phosphodiesterase (PDE) activity associated with AD (and asthma and AR)
- PDE inhibitors prevent degradation of cAMP to AMP
- Increased intracellular cAMP levels activate protein kinase A and suppress transcription of pro-inflammatory cytokines

- **Crisaborole**: First commercially available PDE4 inhibitor
  - Boron-based structure improves penetration and increases binding affinity to PDE4 site

Primary endpoint: Success in ISGA* at 4 wks

Success in ISGA at all visits

*ISGA = Investigator’s Static Global Assessment
Improvement in Pruritus

• Frew TEAEs in >1% in long-term 48-week open-label safety trial
  - Atopic dermatitis flares (3.1%)
  - Application site burning or stinging in 2.3%
  - Application site infection 1.2%

Minimal or no blood levels after topical application in children and adolescents
  - No clinically important safety signals

Tom et al. Pediatr Derm 2016;33:150;

Eichenfield et al. JAAD 2017;77:641

Paller et al. JAAD 2016;75:494
Other topical PDE4 inhibitors in trials and coming

- OPA-15405
- E6005/RVT-501
- DRM02
- GW842470X
- Leo-29102

See clinicaltrials.gov for information on studies related to these PDE4 inhibitors
JAK inhibitors to prevent cytokine receptor signaling

Topical tofacitinib for AD

- JAK1/3 and STAT6 are involved in Th2/IL-4 signalling
- 4-wk, phase IIa, randomized, double-blind, vehicle-controlled trial
- 69 adults with mild-to-moderate AD (2-20% BSA)
- 2% tofacitinib (n=35) vs. vehicle (n=34) twice daily

Topical tofacitinib for AD

BSA

Itch (0-10)

45%

p<.001

p<.001

Topical tofacitinib for AD

- Detectable systemic absorption but >6-fold lower than systemic administration
- Infrequent treatment-emergent adverse events (TEAEs) in both groups
- No patient discontinued because of TEAE; good tolerability
- No serious AEs

JTE-052 (pan-JAK inhibitor) for AD

- 4 wk 2x/d study in 327 AD adults (Japan)

23% treated with 3% JTE-052 achieved IGA 0/1 and ≥2 point improvement vs 3% with vehicle (p=.04)

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Vehicle Group</td>
<td>30</td>
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<tr>
<td>JTE-052 0.25% Group</td>
<td>60</td>
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<tr>
<td>JTE-052 0.5% Group</td>
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<tr>
<td>JTE-052 1% Group</td>
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<tr>
<td>JTE-052 3% Group</td>
<td>60</td>
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<tr>
<td>Tacrolimus Group</td>
<td>30</td>
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Baseline: 90% moderate; mean baseline EASI of 17
mEASI reduction -42 (0.025%) to -73 (3%) (all p<0.001) vs vehicle (-12) and TCL (-62)
Both daytime and nighttime pruritus reduction $p<0.001$ at all concentrations. Pruritus with greater reduction by day 1.

Dose-dependent levels detectable in blood (52% with 3%) but far below when given orally (max dose per application 5g).

Reduction in Itch NRS
• Directly activates aryl hydrocarbon receptor (AhR)
  - Abundant in keratinocytes
  - Increased barrier protein expression when activated
  - Coal tar prevents the Th2-cytokine-induced reduction in barrier proteins

van den Bogaard et al. JCI 2013;123:917
In vivo Screening for Drug Assessment

- Test products applied bid to distinct sites on areas of equal AD severity for 2 wks
- Vehicle vs pimecrolimus vs betamethasone dipropionate vs clobetasol creams

Guttman-Yassky et al. JACI 2017;140:1032
In vivo Screening for Drug Assessment

- Quick screening assessment of comparative efficacy and local adverse effects

Guttman-Yassky et al. JACI 2017;140:1032
Development of Draft Guidance for Industry on New Therapeutic Agents for Atopic Dermatitis (AD) in Children and Adolescents

• Literature-based, consensus recommendations for the conduct of clinical trials of systemic and topical agents
• Comprehensive, including: endpoints, duration, patient population, ethics, safety, drug product, randomization, monitoring, statistical and regulatory considerations
• Focusing on pediatric and patient-centered principles

Siegfried et al. Pediatric Dermatol 2017 (submitted for publication)
Summary

- Topical therapy is an important component of AD care for barrier repair and delivery of anti-inflammatory compounds.
- Daily application with emollients in at-risk babies, beginning as neonates, is showing promise in decreasing the risk of developing AD and possibly other atopic disorders.
- Newer topical nonsteroidal medications, such as PDE4 inhibitors, JAK inhibitors and tapinarof/AhR inhibitor, show promise as steroid-sparing agents and may be particularly important for sensitive sites, maintenance, and proactive intervention.