Clinical Update: Novel Agents for the Long-Term Management of Moderate-to-Severe Atopic Dermatitis

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Atopic Dermatitis Overview

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Disclosure of Relevant Relationships with Industry

AbbVie (I, A)
Altus Labs (A, Stock)
Amyris, Inc (A)
AOBiome (A, I)
Arbonne (A)
Burt’s Bees (A)
Bodewell (A)
Dermavant (A)
Dermira (A)
Eli Lilly (A, S)
Exeltis (A)
Gpower, Inc (A)
Galderma (A, S)
IntraDerm (A)
Johnson & Johnson (A)
Kiniksa (A)
La Fondation pour la Dermatite Atopique (R)
La Roche-Posay/L’Oreal (A)
LearnSkin/DermVeda (A, S)
LEO Laboratories (A)
Menlo Therapeutics (A)
Micreos (A, Stock)
National Eczema Association (A, R)
Pfizer Inc (A, S)
Pierre-Fabre (A, S)
Realm Therapeutics (A)
Regeneron/Sanofi Genzyme (A, I, S)
Sincere Skin (A, Stock)
Theraplex (A, Royalties)
TopMD (A, S)
Unilever (A)
Verrica (A)
YoBee (A, Stock)

Advisor (A), Investigator (I), Speaker (S), Research funding (R), Stock option (Stock)

Progress?


Filaggrin

*filament-aggregating protein*


IL-4 and IL-13

Keratinocytes differentiated in the presence of IL-4 and IL-13 exhibited significantly reduced filaggrin gene expression

Topical Steroids and Barrier

![Graph showing comparison between BMVc and TACo treatments.]


Either Way...

The Barrier Problem is here to stay
Psyche

Stress and Sleep...

- Stress can worsen AD and directly slows healing skin barrier (Muizzuddin, 2003)
- Psychosocial stress and sleep deprivation disrupt skin barrier function in healthy patients (Altemus, 2001)


Staphylococcus δ-toxin induces allergic skin disease by activating mast cells

Table 1. *Staphylococcus aureus* Proteins That Contribute to Atopic Dermatitis

<table>
<thead>
<tr>
<th><strong>S. aureus proteins</strong></th>
<th><strong>Possible role in AD</strong></th>
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<tbody>
<tr>
<td>Clumping factor B</td>
<td>Adhesion to corneocytes in stratum corneum via loricrin or other ligands</td>
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<tr>
<td>Fibronectin-binding proteins</td>
<td>Adhesion to fibronecrtin that is present at high levels in the upper strata of epidermis and stratum corneum of AD skin</td>
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<tr>
<td>Protein A</td>
<td>Proinflammatory. Binds to TNFR-1 on keratinocytes</td>
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<tr>
<td>Lipoproteins</td>
<td>Proinflammatory. Activate TLR-2 on keratinocytes</td>
</tr>
<tr>
<td>α-Toxin</td>
<td>Membrane damage/lysis of keratinocytes</td>
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<tr>
<td>δ-Toxin</td>
<td>Mast cell degranulation. Synergy with IgE. Allergic skin inflammation</td>
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<tr>
<td>Phenol-soluble modulins</td>
<td>Trigger proinflammatory responses associated with AD in keratinocytes at sublytic concentrations</td>
</tr>
<tr>
<td>Enterotoxins and TSST-1</td>
<td>Excessive T cell cytokine production and toxicity. Allergens. Enterotoxins might trigger mast cell degranulation directly</td>
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<tr>
<td>Staphopain</td>
<td>Inactivation of antimicrobial peptides</td>
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<td>Aureolysin</td>
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<td>V8 serine protease</td>
<td>Epidermal barrier dysfunction in hairless mice</td>
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<tr>
<td>Serine protease-like proteins</td>
<td>Potent allergens in idiopathic asthma following <em>S. aureus</em> colonization. Similar role in AD?</td>
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*HEIDI H. KONG ET AL. GENOME RES. 2012;22:850-859*
Nerves...

Unmet Needs in ITCH

- This is a wide-open area
- Almost nothing really works here
- Pipeline has promise, but a powerful topical anti-itch could literally change the field overnight

Conclusions

- We are learning more about the underpinnings of AD and the pathogenesis than ever before
- Barrier, Psyche, Microbiome, Inflammation, and Itch represent 5 important pillars of this disease
- A deep understanding of the pathophysiology should engender and enhance our therapeutic approach