NEW APPROACHES TO ATOPIC DERMATITIS

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Pathogenesis: Immune Dysregulation

Barrier Defect

Interplay Between Barrier, Allergy/Immunology, Pruritus

ATOPIC DERMATITIS

• BARRIER ABNORMALITY IS NOT JUST AN EPIPHENOMENON
• INITIATOR OF THE PATHOGENESIS OF THE DISEASE STATE
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Author, 3/21/2016
Common Loss-of-function Variants of Filaggrin are a Predisposing Factor for AD

• Filaggrin - key protein that facilitates terminal differentiation of the epidermis and formation of the skin barrier
• 2 loss-of-function genetic variants (R510X and 2282del4) in the gene encoding filaggrin (FLG) are very strong predisposing factors for AD
• These variants also show highly significant association with asthma occurring in context of AD
• These data suggest a key role for impaired skin barrier function in development of atopic disease


ONE OF THE MOST CHALLENGING ASPECTS OF DISEASE MANAGEMENT
ONE ASPECT THAT BOTHERS PARENTS THE MOST
PARENTS OF CHILDREN WITH ATOPIC DERMATITIS LOSE ONE TO ONE AND ONE HALF HOURS OF SLEEP EVERY NIGHT

• DECREASE OF SKIN HYDRATION BY 10% = CRUCIAL FOR THE INDUCTION OF ITCH
• IMPAIRED SKIN BARRIER FACILITATES THE ENTRY OF IRRITANTS AND ITCH CAUSING AGENTS

LEE C-H
BRIT J DERMATOL 2006;154(6);p 1100-1107

GOOD SKIN LUBRICATION HELPS REDUCE ITCHING
• CHILLED NOXZEMA HELPS CONTROL ITCHING:
  - MAY BE APPLIED AS OFTEN AS NEEDED
  - "REPLACES" SENSATION OF ITCHING WITH COOLING, TINGLING SENSATION
  - BRAND MEDICALLY NECESSARY
  - DOES NOT NEED TO BE WASHED OFF
  - COST EFFECTIVE

NIGHTTIME LOSS OF SLEEP DUE TO ITCHING AND SCRATCHING:
• CHILDREN MAY WAKE UP ON AVERAGE: 36 TIMES
• LOSS OF DEEP SLEEP MEANS LESS GROWTH HORMONE IS SECRETED WITH POTENTIAL FOR IMPAIRMENT OF LINEAR GROWTH
• LACK OF SLEEP MEANS:
  - POOR COPING STRATEGIES THE NEXT DAY
  - IMPAIRED SCHOOL PERFORMANCE
  - BEHAVIORAL ISSUES (ATTENTION DEFICIT DISORDERS)

ANTIHISTAMINES DO NOT ADEQUATELY CONTROL THE ITCHING ASSOCIATED WITH ATOPIC DERMATITIS
SEDATIVE EFFECTS OF ANTIHISTAMINES:
  - HELP CHILDREN SLEEP
  - HELP THE FAMILY GET THE REST THEY NEED
PATHOPHYSIOLOGY OF ATOPIC DERMATITIS

Targeted Agents for AD

- Targeted immunotherapies
  - Phase 2 and 3 trials in patients with moderate to severe AD

- Crisaborole
  - Inhibitor of PDE4
  - Topical agent
  - Phase 3 trials in patients with mild to moderate AD

FUTURE THERAPIES FOR ATOPIC DERMATITIS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Decrease in VAS, %</th>
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<tbody>
<tr>
<td>Nemolizumab 0.1 mg/kg</td>
<td>-41.5*</td>
</tr>
<tr>
<td>Nemolizumab 0.5 mg/kg</td>
<td>-61.2*</td>
</tr>
<tr>
<td>Nemolizumab 2.0 mg/kg</td>
<td>-60.5*</td>
</tr>
<tr>
<td>Placebo</td>
<td>-20.1</td>
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</tbody>
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Other Targeting Agents Under Investigation for Moderate to Severe AD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Mechanism of Action</th>
<th>Study Phase</th>
</tr>
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<tbody>
<tr>
<td>Lebrikizumab</td>
<td>IL-13</td>
<td>IL-13 mAb</td>
<td>2</td>
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<tr>
<td>Tralokinumab</td>
<td>IL-13</td>
<td>IL-13 mAb</td>
<td>2</td>
</tr>
<tr>
<td>Bencitinib</td>
<td>JAK 1/2</td>
<td>Oral JAK 3s Inhibitor</td>
<td>2</td>
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<tr>
<td>Tofacitinib</td>
<td>JAK</td>
<td>Oral/Topical JAK inhibitor</td>
<td>Approved for RA</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>IL-12/23</td>
<td>IL-12/23 p40 mAb</td>
<td>Approved for PsO and PsA</td>
</tr>
</tbody>
</table>

*P < .001

Rates of SAEs (12% to 31%) were comparable between groups.
AEIs that were higher in the dupilumab groups were injection site reactions and conjunctivitis.