Therapeutics on the Horizon

Linda Stein Gold, MD
Director of Clinical Research
Department of Dermatology
Henry Ford Hospital
Detroit, MI

Disclosures

• Investigator, Speaker, and/or Advisor:
  • Pfizer
  • Regeneron-Sanofi
  • Dermira, Leo
  • AbbVie
  • Incyte
  • Dermavant
  • Ortho Derm
Pipeline: Selected Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
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<tbody>
<tr>
<td><strong>TOPICAL</strong></td>
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<tr>
<td>Delgocitinib</td>
<td>JAK1, JAK2, JAK3, TYK2</td>
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<tr>
<td>E8005</td>
<td>PDE4</td>
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<tr>
<td>OPA-15406</td>
<td>PDE4</td>
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<tr>
<td>Ruxolitinib</td>
<td>JAK1 and JAK2</td>
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<td>Tapinarof</td>
<td>AHR receptor ligand</td>
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<td><strong>ORAL</strong></td>
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<tr>
<td>Abrocitinib</td>
<td>JAK1</td>
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<tr>
<td>ASN002</td>
<td>JAK</td>
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<tr>
<td>Baricitinib</td>
<td>JAK1 and JAK2</td>
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<tr>
<td>Upadacitinib</td>
<td>JAK1</td>
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<td><strong>SYSTEMIC INJECTION</strong></td>
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<tr>
<td>Lebrikizumab</td>
<td>IL-13</td>
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<tr>
<td>Nemolizumab</td>
<td>IL-31</td>
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<tr>
<td>Tralokinumab</td>
<td>IL-13</td>
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National Eczema Association.  

Topical Therapy

- PDE4 inhibitors
- Tapinarof
The Safety and Efficacy of Roflumilast Cream 0.15% and 0.05% in Atopic Dermatitis: Phase 2 Proof-of-Concept Study

- Roflumilast = PDE4 inhibitor with **50-300X more potent** than crisaborole and apremilast
- Oral formulation, roflumilast is FDA-approved for COPD, with well established safety

Figure 1. Study Design


Tapinarof Phase 2b Study in Atopic Dermatitis

- Tapinarof is a small molecule therapeutic AhR modulating agent (TAMA) that directly binds to and activates AhR transcription factor
  - Inhibits Th17 and Th2 cell differentiation
  - Upregulates skin barrier protein expression in keratinocytes including filaggrin
  - Tapinarof chemical structure also has direct anti-oxidant activity

Biologic Pipeline

IL-13 Inhibitors

- **Tralokinumab**: fully human immunoglobulin G4 monoclonal antibody that specifically binds to the IL-13 cytokine with high affinity, preventing interaction with the IL-13 receptor
- **Lebrikizumab**: monoclonal antibody that selectively targets IL-13 and prevents formation of the IL-13Rα1/IL-4Rα heterodimer receptor signaling complex while not binding to the IL-13Rα2 decoy receptor, which is thought to be involved in endogenous regulation of IL-13

IL-31 Inhibitor

- **Nemolizumab**: humanized monoclonal antibody against interleukin-31 receptor A

Not Identical

- **Dupilumab**: binds IL-4Rα, blocking IL-13 and IL-4 signaling
- **Lebrikizumab**: binds IL-13, specifically preventing formation of IL-13Rα1/IL-4Rα complex, thus blocking downstream signaling
- **Tralokinumab**: binds IL-13, preventing IL-13 binding to IL-13Rα1 and IL-13Rα2 decoy receptor, thus blocking both IL-13 signaling and endogenous IL-13 regulation

Lebrikizumab does not prevent binding to Ra2 → no increased levels of IL-13
Tralokinumab prevents the binding to Ra2 → thus increased total IL-13 levels
What does this mean?
We don’t know!

Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicenter, placebo-controlled phase III trials- Adults

- SQ 300 mg q 2 weeks or placebo.
- Primary endpoints: IGA score of 0/1 at week 16 and ≥ 75% improvement in EASI 75 at week 16.
- Patients achieving an IGA 0/1 and/or EASI 75 at week 16 were rerandomized to tralokinumab Q2W or every 4 weeks or placebo, for 36 weeks.


Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial

Trial of Nemolizumab and Topical Agents for Atopic Dermatitis with Pruritus

- In a 16-week, double-blind, phase 3 trial, Japanese patients with AD and moderate-to-severe pruritus 2:1 ratio to receive subcutaneous nemolizumab (60 mg) or placebo q 4 weeks X 16 weeks, with concomitant topical agents.
- Primary end point was the mean % change in the visual-analogue scale (VAS) score for pruritus (range, 0 to 100)