Atopic Dermatitis: Emerging therapies

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Speaker Disclosures

- AbbVie\textsuperscript{A,C,RI,S}
- Actelion\textsuperscript{S}
- Amgen\textsuperscript{A,C,RI,S}
- Celgene \textsuperscript{A,C,RI,S}
- Coherus\textsuperscript{RI}
- Dermira\textsuperscript{RI}
- Eli Lilly \textsuperscript{A,C,RI,S}
- Galderma\textsuperscript{A,RI,S}
- GSK\textsuperscript{RI}
- Janssen\textsuperscript{A, C, RI,S}

- Kyowa Kirin Pharma\textsuperscript{C,RI}
- Leo Pharma Inc.\textsuperscript{A,C,RI,S}
- Medimmune\textsuperscript{RI}
- Merck\textsuperscript{RI}
- Novartis\textsuperscript{RI,S}
- Pfizer\textsuperscript{A,RI}
- Regeneron\textsuperscript{RI}
- Roche\textsuperscript{RI}
- Sanofi Genzyme\textsuperscript{A,RI,S}
- UCB\textsuperscript{RI}
- Valeant\textsuperscript{A,S}

\textsuperscript{A} Advisory Board, \textsuperscript{C} Consultant, \textsuperscript{RI} Research Investigator, \textsuperscript{S} Speaker
Objectives

• Review *current biologic therapies* for atopic dermatitis (AD)

• Explore our understanding of AD pathophysiology

• Recognize *newly identified targets for AD* therapy that are under development to provide safe and effective treatment for this chronic condition
Atopic Dermatitis

Escalating Treatment Approaches to Meet Patient Needs

- Systemic Therapy (10%)
- Topical Treatment
- Nonpharmacologic Therapy

### Off-Label biologics investigated for AD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study, N</th>
<th>Benefits</th>
<th>Drawback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (anti-TNF)</td>
<td>Open label, N=9</td>
<td>2/9 experienced long term benefit</td>
<td>Initial clinical response was not maintained over time</td>
</tr>
<tr>
<td>Ustekinumab (anti-IL 12/23)</td>
<td>Case series and RCT N=37 (USA) RCT N=79 (Japan)</td>
<td>RCT – benefit did not reach statistical significance</td>
<td>Safe drug, further study is needed</td>
</tr>
<tr>
<td>Rituximab (anti-CD20)</td>
<td>OL, N=6</td>
<td>Results were inconclusive</td>
<td>Lack of data</td>
</tr>
<tr>
<td>Omalizumab (anti-IgE)</td>
<td>OL, RCT, case series N = 103</td>
<td>Conflicting data on efficacy</td>
<td>Safe drug; cost may outweigh clinical benefit</td>
</tr>
<tr>
<td>Mepolizumab (anti-IL5)</td>
<td>RCT, N=43</td>
<td>No clinical improvement at d14</td>
<td>No significant safety concerns</td>
</tr>
</tbody>
</table>
# Targeted biologics currently under investigation

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Details</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-5</td>
<td>Mepolizumab</td>
<td>RCT N=43 Phase 2 trial ongoing</td>
<td>GSK</td>
</tr>
<tr>
<td>IL-31RA</td>
<td>Nemolizumab</td>
<td>Phase 2, N=264 Published NEJM</td>
<td>Galderma /Chugai</td>
</tr>
<tr>
<td>IL-13</td>
<td>Tralokinumab</td>
<td>Phase 2 RCT, N=204 +TCS</td>
<td>MedImmune/ LEO</td>
</tr>
<tr>
<td></td>
<td>Lebrikizumab</td>
<td>Phase 2 RCT, N=209 +TCS (TREBLE)</td>
<td>Genentech/ Roche</td>
</tr>
<tr>
<td>IL-4RA (IL-4, -13)</td>
<td>Dupilumab (Dupixent®)</td>
<td>Phase 3, N &gt; 2000 approved US, EMA Published Lancet, NEJM</td>
<td>Regeneron/ Sanofi Genzyme</td>
</tr>
</tbody>
</table>

## Small molecules: JAK Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>AD studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK 1</td>
<td>PF-04698542</td>
<td>Phase 2 completed</td>
</tr>
<tr>
<td>JAK 1</td>
<td>Upadacinib (ABT-494)</td>
<td>Phase 2 completed</td>
</tr>
<tr>
<td>JAK 1/2</td>
<td>Baricitinib</td>
<td>Phase 2 completed (+ TCS)</td>
</tr>
</tbody>
</table>

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Gooderham M et al. PF-04965842, a JAK1 inhibitor, for treatment of atopic dermatitis: a 12-week, randomised, double-blind, placebo-controlled phase 2 clinical trial. Presented at EADV 2017, Geneva, Switzerland

## Small molecules: JAK Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>AD studies</th>
<th>Results to date</th>
</tr>
</thead>
</table>
| JAK 1   | PF-04698542           | Phase 2 completed | • IGA 0/1 (200 mg) 44.5% at 12 wks vs. 6.3% (PBO) (p<0.003)  
• 82% reduction (200 mg) in EASI score vs. 35% (PBO) |
| JAK 1   | Upatacitinib (ABT-494) | Phase 2 completed | • IGA 0/1 (30 mg) 50% vs. 2% (PBO) at 16 wks  
• 74% reduction (30mg) in EASI score vs. 23% (PBO) |
| JAK 1/2 | Baricitinib           | Phase 2 completed (+ TCS) | • EASI 50 (4mg) 61% vs. 37% with TCS alone (p<0.05) at 16 wks             |

Gooderham M et al. PF-04965842, a JAK1 inhibitor, for treatment of atopic dermatitis: a 12-week, randomised, double-blind, placebo-controlled phase 2 clinical trial. Presented at EADV 2017, Geneva, Switzerland  
Targeting IL-5

Mepolizumab
- Blocks IL-5
- Phase 2 trials in AD underway
- Approved in asthma (high eos)

AD, atopic dermatitis; AMPs, antimicrobial proteins; IgE, immunoglobulin E; IL, interleukin; DC, dendritic cell; IDEC, Inflammatory dendritic epidermal cells; dDC, dermal dendritic cell; TSLP, thymic stromal lymphopoietin; IFN, interferon

Nemolizumab
- Blocks IL-31RA
- Completed phase 2
- Phase 3 trials ongoing
- Effective for control of itch

AD, atopic dermatitis; AMPs, antimicrobial proteins; IgE, immunoglobulin E; IL, interleukin; DC, dendritic cell; IDEC, Inflammatoty dendritic epidermal cells; dDC, dermal dendritic cell; TSLP, thymic stromal lymphopoietin; IFN, interferon

Anti–Interleukin-31 Receptor A Antibody for Atopic Dermatitis

A Percentage Change from Baseline in Pruritus Score at 12 Wk

B Weekly Percentage Change in Pruritus Score

Anti–Interleukin-31 Receptor A Antibody for Atopic Dermatitis

Secondary Outcome Measures Wk 16

% change EASI  
% change SCORAD  
% change BSA

Improvement IGA

Results Up to Week 64:

EASI-50

EASI-75

Absolute DLQI

Pruritus VAS: % Change from Baseline

Ruzicka T, et al. Presented at EADV 2017; Presentation #FC03.08.
Tralokinumab, Lebrikizumab
- Blocks IL-13
- Currently in Phase 3
Tralokinumab Phase 2: Primary/Secondary Endpoints at Wk 12 + TCS

- At wk 12, tralokinumab 150 mg/300 mg, reduced total EASI from baseline: –4.4 (p=0.027) and –4.9 (p=0.011), respectively, compared with PBO.

- Secondary endpoints showed significant reduction in SCORAD, DLQI in the tralokinumab arm (150mg/300 mg) compared with PBO.

- Reduction in pruritus NRS in the tralokinumab 300 mg group was greater than PBO.

Tralokinumab Phase 2b Primary Efficacy Data

Change in EASI score at week 12

EASI, Eczema Area and Severity Index; SE, standard error; TCS, topical corticosteroids. *P≤0.05 vs. placebo (intent-to-treat population). Wollenberg et al. AAD 2017
Lebrikizumab Phase 2 (TREBLE): Primary/Secondary endpoints at wk 12 + TCS

• EASI 50 and EASI 75 was only significant with monthly dosing of 125 mg lebrikizumab
• SCORAD 50 was significant at monthly 125 mg and 250 mg x 1 dose
• Adverse events – more herpes infections and conjunctivitis in the treatment group

http://www.mdedge.com/edermatologynews/article/115736
Targeting IL-4, -13

Dupilumab (Dupixent)
- Blocks IL-4R
- Approved for use in US, EU and awaiting approval in Canada (2017 Q4)

AD, atopic dermatitis; AMPs, antimicrobial proteins; IgE, immunoglobulin E; IL, interleukin; DC, dendritic cell; IDEC, Inflammatory dendritic epidermal cells; dDC, dermal dendritic cell; TSLP, thymic stromal lymphopoietin; IFN, interferon

# Dupilumab AD Clinical Development Program

## Adult patients

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-week monotherapy (×2)(^1)</td>
<td>4-week concomitant TCS(^1)</td>
<td>SOLO 1 &amp; 2: 16-week monotherapy(^7)</td>
</tr>
<tr>
<td>Drug-drug interactions(^2)</td>
<td>12-week monotherapy(^1)</td>
<td>CHRONOS: 52-week concomitant TCS(^8)</td>
</tr>
<tr>
<td>16-week monotherapy dose-ranging(^3)</td>
<td>16-week monotherapy(^1)</td>
<td>SOLO-CONTINUE: 36-week monotherapy(^9)</td>
</tr>
<tr>
<td>EXPLORE: 16-week monotherapy biopsy/biomarkers(^4) (serum CCL17, CCL18, periostin, and IgE; \textit{S. aureus} abundance)</td>
<td>EVALUATE: 16-week vaccine interaction(^5,6) (Tdap and MPSV4)</td>
<td>CAFÉ: 16-week concomitant TCS in cyclosporine-experienced patients(^6,10)</td>
</tr>
</tbody>
</table>

### The Canadian Regulatory Submission includes data from a total of 2526 patients with AD treated with dupilumab in clinical trials\(^6\)

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SOLO -1, 2: Efficacy of Dupilumab for Moderate-to-Severe AD

Patients Achieving Primary Endpoint Based on IGA Score, %

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dupilumab Q2W</th>
<th>Dupilumab QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLO 1</td>
<td>10</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>SOLO 2</td>
<td>8</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>n=224</td>
<td>n=224</td>
<td>n=223</td>
<td>n=233</td>
</tr>
</tbody>
</table>

Patients With EASI-75, %

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dupilumab Q2W</th>
<th>Dupilumab QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLO 1</td>
<td>15</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>SOLO 2</td>
<td>12</td>
<td>44</td>
<td>48</td>
</tr>
<tr>
<td>n=224</td>
<td>n=224</td>
<td>n=223</td>
<td>n=233</td>
</tr>
</tbody>
</table>

\(^aP<0.001\) for all comparisons of dupilumab vs placebo.

EASI-75, improvement from baseline of ≥75% on the EASI; IL-4R\(\alpha\), IL-4 receptor \(\alpha\); QW, every week.

Patients ≥18 years of age with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy were randomized to dupilumab 300 mg QW, dupilumab 300 mg Q2W, or placebo for 16 weeks (dupilumab-treated patients received a 600-mg loading dose on day 1).

# Dupilumab Safety

## Adverse Event

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>SOLO 1, % of patients</th>
<th>SOLO 2, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=222)</td>
<td>Dupilumab Q2W (n=229)</td>
</tr>
<tr>
<td>At least 1 adverse event</td>
<td>65</td>
<td>73</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Noninfectious Adverse Eventa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Injection-site reaction</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>• Headache</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>• Allergic conjunctivitis</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Infectious Adverse Eventa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Infections and infestations</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>— Nasopharyngitis</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>— Upper respiratory tract infection</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>— Conjunctivitis</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>• Any herpes viral infection</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>• Nonskin infection</td>
<td>22</td>
<td>30</td>
</tr>
</tbody>
</table>

*Adverse events occurring in ≥5% of patients in at least 1 dupilumab arm and more frequently than in the corresponding placebo arm.

One death occurred in each dupilumab treatment group in SOLO 2 (one from an asthma attack and one from suicide).

**CHRONOS:** Both Primary Endpoints Met at wk 16

**IGA (0,1) and ≥2-Point Improvement From Baseline at Week 16**

- Placebo + TCS (n=315)
- Dupilumab 300 mg q2w + TCS (n=106)
- Dupilumab 300 mg qw + TCS (n=319)

*P<0.0001

**EASI-75 at Week 16**

- Placebo + TCS (n=315)
- Dupilumab 300 mg q2w + TCS (n=106)
- Dupilumab 300 mg qw + TCS (n=319)

*P<0.0001

Fewer patients experienced disease flares in DUP QW (12.7%) and DUP Q2W (13.6%) compared to PBO (41.3%)

Conjunctivitis and injection-site reactions were more common in DUP-treated patients

\(^a\)P<0.0001 for all comparisons of dupilumab vs placebo; TCS, topical corticosteroids.
N=623 patients treated with dupilumab 300 mg QW, dupilumab 300 mg Q2W, or placebo for 52 weeks weeks (dupilumab-treated patients received a 600-mg loading dose on day 1). Blauvelt A, Lancet 2017
Conclusions

• Increased understanding of the pathophysiology of AD has led to **new targets** in development for treatment
• **JAK 1 inhibitors, IL-5, IL-31RA, IL-13 mAb** are in **development** and are promising targets for AD therapy
• **IL-4RA mAb** (IL-4, IL-13) is the furthest in development and has **proven safety and efficacy** based on Phase 3 data
Thank you!