The Therapeutic Landscape in Atopic Dermatitis

International Eczema Council 2019

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Disclosures

- Consultant and investigator for:
  - Regeneron/Sanofi
  - Genentech
  - Medimmune
  - GSK
  - Leo
  - Celgene
  - Pfizer
  - Chugai

- I will be talking about off-label use

- Dermira
- Lilly
- Tioga
- Incyte
- Abbvie
- Kiniksa
- Menlo
- Ortho Dermatologica
- Forte Biotech
Outline

- Topicals
- Biologics
- Oral therapy
Current Guideline-recommended or Approved Therapies

- Corticosteroids
- Tacrolimus
- Pimecrolimus
- Crisaborole
- Phototherapy
- Dupilumab
- Cyclosporine
- Methotrexate
- Mycophenolate
- Azathioprine
Current Therapeutic Gaps

Topical
• Non-steroidal topical therapy with high efficacy AND without significant burning or safety concerns
• Topical therapy that is infrequently dosed and easily applied

Systemic
• Systemic therapy with improved EASI 90s and lacks conjunctivitis
• Less frequent dosing
• Oral therapy option that is safe and effective
TARGETS IN ATOPIC DERMATITIS

**Barrier Defects**
- Barrier proteins, lipids, AMPs

**Keratinocyte Cytokines**
- IL-25, IL-33, TSLP, IL-17C

**Dysbiosis**
- *S. aureus*

**Costimulatory Molecules**

**Type 2 Cytokines**
- IL-4, IL-5, IL-13, IL-31

**Dysbiosis**

**Hyperplasia**

**Barrier structure proteins**

**Lichenification**

**Th1**

**Th2**

**Th22**

**Th17**

**IFN-γ**
Microbiome as a Target
Commensal bacteria- BACTERiAD I/II Trial

- Gram neg present in flexures
- G neg bacteria reduced in AD
- *Roseomonas mucosa* from healthy volunteers improved dermatitis in mice
- Strain-level differences in AD compared to NL
  - Mono-methyl glutarate, histidinal
  - Phosphatidylcholine (PC 37:2)
  - Phosphatidylethanol and PE-ceramides

• 10 adults-
  - 6 weeks
  - Antecubitals

• 5 children
  - 16 weeks
  - All areas

• Decrease n S. aureus colonization

Microbiome as a Target

Commensal bacteria

- Coag- Staph make AMPs
- Reduced number in AD patients
- Screened for bacteria with anti-S. aureus activity
  - S. epidermidis and S. hominis
- Lantibiotics synergize with AMPs
- Clones identified and cultured and applied to AD skin

😊 Nonsteroidal, no burning, less frequent dosing

S. Epidermidis
S. hominis
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- Th22
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- Barrier structure proteins

**Th1**
- Not for Distribution
Phase 2 study of topical delgocitinib (JTE-052) in adult AD

- 327 Japanese 16-65 years
- Mod-severe AD
- 4 weeks of treatment
- 5g of treatment allowed-20%BSA
- Scalp excluded from treatment
- LOCF for rescued pts

- Sign reduction in itch
- No increase in AEs
- 1 case of burning
- 3 cases of EH (1.1%)

Ruxolitinib (JAK 1/2) - Phase 2 in Adult AD

Key inclusion criteria:
- 18–70 years with active AD
- AD duration >2 years
- IGA 2/3
- BSA 3–20%

Key exclusion criteria:
- Active infections
- Use of other topical treatments within 2 weeks of baseline
- Systemic drug use within 4 weeks of baseline

**Primary endpoint:** Mean % change from baseline in EASI score at Week 4 in ruxolitinib 1.5% bid group vs vehicle

**Secondary and exploratory endpoints:** IGA and EASI responder rates, itch NRS score and safety

Kim B, et al. EADV 2018, FC03.01. Sponsored by Incyte
Ruxolitinib (JAK 1/2) - Phase 2 in Adult AD

- No increase in AEs in treatment groups
- Rapid reduction in itch
- Highest doses similar to triamcinolone 0.1

😊 No significant burning, high efficacy

*P<0.05; †P<0.01; ‡P<0.001 vs vehicle; Error bars represent 95% confidence intervals; TAC, triamcinolone
Kim B, et al. EADV 2018, FC03.01. Sponsored by Incyte
Tapinarof (GSK2894512), a novel non-steroidal anti-inflammatory agent, is a therapeutic AhR modulating agent cream

- Bacterial-derived
- Polyphenol
- Binds AhR
- Anti-oxidant

**Inclusion criteria:**
- Age 12–65 years
- Diagnosis of AD with active inflammation
- BSA ≥5–≤35% (excl scalp)
- IGA ≥3

**Primary efficacy analysis**
- Patients with IGA 0/1 and ≥2 grade improvement in IGA from baseline at Week 12

AhR, aryl hydrocarbon receptor

Peppers J, et al. EADV 2017, OP03.04 Sponsored by GlaxoSmithKline
Dose-finding study of tapinarof (GSK2894512) cream for the treatment of adults with moderate to severe AD

IGA 0/1 and ≥2-point improvement

- Vehicle qd
- 0.5% qd tapinarof
- 1% qd tapinarof
- Vehicle bid
- 0.5% bid tapinarof
- 1% bid tapinarof

Safety

- More AEs in treatment groups
- 10% with HA in highest dose
- Some LFT increases (not AEs)
- Some systemic effect at high doses?

Outline

• Topicals
• Biologics
• Oral therapy
Warning! Lack of standardization ahead!

Endpoints:
- EASI 50
- EASI %Δ
- EASI 75
- SCORAD

TCS Use:
- None
- As needed
- Run-in
- Mandatory

Not for Distribution
Standardization of Clinical Research in AD

Harmonizing Outcome Measures for Eczema

Core Outcome Sets for Trials and Practice\(^1\)

Guidance Document for Industry\(^2\)

Endpoint Training and Standardization

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Dysbiosis
Staphylococcus aureus

Hyperplasia

Th1

Th2

IFN-γ

Th17

IL-17

IL-22

Th22

ILC2

Costimulatory Molecules

Barrier structure proteins

Lichenification

Not for Distribution
Rationale for Targeting IL-33 in AD

- Epidermal “alarmin”
- IL-1 cytokine family
- Receptors on keratinocytes, Th2 cells, mast cells
- Activates NfKb
- Promotes type 2 inflammation (Th2 and ILC2)

Etokimab (anti-IL-33)

- Open-label phase 2a
- 12 adult patients
- Mod-severe AD
- Placebo at -7d
- 1X 300mg infusion
- Unclear TCS use

😊 High efficacy, infrequent dosing
Rationale for Targeting IL-17C

- Produced by keratinocytes
- Upregulated in psoriasis and AD
- Initiates inflammatory cascade

MOR106, an anti-IL-17C mAb, a potential new approach for treatment of moderate-to-severe atopic dermatitis: Phase 1 study, AAD February 2018
MOR106 (anti-IL-17c mAB) Phase I Study

- N=25
- 4 weekly infusions
- Adults with mod-severe AD

*Primary endpoint was safety; secondary endpoint was pharmacokinetics.

Rationale for Targeting TSLP

• Produced by epithelium- lung and skin
• Promotes Th2 responses via dendritic cell binding
• Upregulated in skin in AD and lung in asthma
• Tezepelumab works in asthma
Tezepelumab (Anti-TSLP)- Phase 2a Alleviad

- 113 adult pts with AD
- 26 centers
- 2 weeks of TCS run-in
- Class 3 daily
- 12 weeks of dosing
- 280mg SQ q2 weeks

Tezepelumab (Anti-TSLP)- Phase 2a Alleviadi

- Some enhanced effects seen with biomarker subgroups:
  - DPP4-high
  - Periostin-low
  - TARC-low
  - IgE high
- No significant AE signal
- Positive signal in asthma Phase 2 with breakthrough status
- Another Phase 2 planned!

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- IL-4, IL-5, IL-13

Th22 Cells
- IL-22

Costimulatory Molecules

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- S. aureus

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IFN-γ

Barrier structure proteins

Not for Distribution
Current Opinion in Virology
Rationale for Targeting OX40

• OX40L is a co-stimulatory molecule that promotes Th2 polarization of naïve OX40-bearing T cells

• OX40 antagonism:
  • Suppresses activated T cells (particularly atopic Th2 inflammation)
  • Potentially increases T regulatory cells, which may achieve immunologic tolerance → disease modification?

Anti-OX40 (KHK 4083)

- KHK4083 is a fully human, non-fucosylated antagonistic anti-OX40 antibody

**Study design**
- A phase 1, single-center, open-label, three-dose study
- KHK4083 10 mg/kg iv administered every other week (Weeks 0, 2, 4)
- TCS/TCI, oral immunosuppressants and phototherapy were prohibited (Week –1 to Week 22)
- Rescue treatment for AD was permitted at investigator’s discretion
- 22 patients received the 3 doses of treatment; 20 were evaluated
- 4 patients received rescue (documented as missing)

**Percent Reduction in EASI**

Nakagawa H, et al. EADV 2018, P0252. Sponsored by Kyowa Hakko Kirin
Phase 2a study of GBR 830 (anti-OX40 mAb) in adults with moderate to severe AD

- Clinical improvement was associated with a reduction in mRNA biomarkers for disease activity, indicating an effect on acute and chronic stages of AD
- In the GBR 830 cohort, 17 of 23 patients (74%) achieved EASI 50 scores at Day 57 vs baseline, a key secondary endpoint of the study¹

¹ Glenmark Pharmaceuticals SA. GBR 830 AD Phase 2a press release
Guttman-Yassky E, et al. AAD 2018, P7931 Sponsored by Glenmark Pharmaceuticals SA
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**Not for Distribution**
Dupilumab
 IL-4/13 Blockade

- IGA 0/1: ~38%
- EASI reduction of ~80%
- Itch reduction of ~50%
- Improved QOL
- Reduced anxiety and depression symptoms
- Similar in ages 12-17

↓ Th2 cyto/chemokines
↓ Th17 and 22
↓ Proliferation
↓ Serum Th2 inflammation
↑ Epidermal differentiation
A higher proportion of patients achieved EASI-50 or NRS ≥ 3-point improvement or DLQI ≥ 4-point improvement with dupilumab monotherapy (SOLO pooled).

**SOLO pooled**

*P < 0.0001 vs placebo

**Week 16**

- **Placebo**
  - EASI-50: 1.9%
  - NRS ≥ 3: 28.6%
  - DLQI ≥ 4: 8.1%

- **Dupilumab q2w**
  - EASI-50: 16.1%
  - NRS ≥ 3: 22.4%
  - DLQI ≥ 4: 3.1%

- **Dupilumab qw**
  - EASI-50: 19.9%
  - NRS ≥ 3: 50.6%
  - DLQI ≥ 4: 5.4%
Example of a patient (48 years old; 8 years with AD) achieving EASI-50, NRS ≥ 3-point improvement and DLQI ≥ 4-point improvement (monotherapy)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Week 16</th>
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<tbody>
<tr>
<td>4</td>
<td>IGA</td>
</tr>
<tr>
<td>58%</td>
<td>BSA</td>
</tr>
<tr>
<td>48</td>
<td>EASI</td>
</tr>
<tr>
<td>10</td>
<td>NRS pruritus</td>
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<tr>
<td>21</td>
<td>DLQI</td>
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</table>

<table>
<thead>
<tr>
<th>Point improvement</th>
<th>% improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>EASI</td>
<td>34.7</td>
</tr>
<tr>
<td>NRS pruritus</td>
<td>6.1</td>
</tr>
<tr>
<td>DLQI</td>
<td>19</td>
</tr>
</tbody>
</table>
Conjunctivitis at q2week dosing through Week 16:
SOLO Pooled data: 10% vs 2%
CHRONOS: 9% vs 5% (11.8 vs 6% at Week 52)
CAFÉ: 28% vs 11%
Phase 2b Study of Tralokinumab (IL-13)

A randomized, double-blind, placebo-controlled, multicenter, multidose study

- Concomitant Class 3 once daily TCS were administered throughout the study and run-in

- Exploratory analyses: high serum DPP-4 levels and high periostin levels may be predictive of response

- Safety: acceptable safety and tolerability profile

- Did not meet asthma endpoints

Phase 2 Study of Lebrikizumab in Moderate-to-Severe AD
TREBLE: a randomized controlled study

• Concomitant bid class 3 TCS were administered throughout the study \cite{1,2}
• PRO endpoints: improvements in sleep loss VAS (125 mg, q4w and SD) and ADIQ (125 mg q4w)\cite{2}
• Safety: rates of AEs were generally similar between treatment groups, and AEs were mostly mild or moderate in severity\cite{2}

Primary Endpoint: Patients Achieving IGA 0/1

- Placebo: EASI: 53.1%
- Lebrikizumab 125 mg SD: EASI: 58.5%
- Lebrikizumab 250 mg SD: EASI: 57.7%
- Lebrikizumab 125 mg q4w: EASI: 70.5%
Rationale for Biologics Targeting IL-31

- The itch cytokine
- Receptors on neurons
- Increased expression in AD lesions\textsuperscript{1,2}
- Correlations with disease severity\textsuperscript{3}

Phase 2a Study of Nemolizumab in Moderate-to-Severe AD

"no imputation was performed for missing data. Data measured during or after rescue therapy were included in the analyses."
Anti-OSM receptor β mAb (KPL-716)

- Phase 1b, dose-escalation study (AD patients): n=32
- Single IV infusion
- KPL-716 simultaneously inhibits IL-31 and oncostatin M (OSM) signaling

The Great Wave off Kanagawa (1833) - Katsushika Hokusai
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Costimulatory Molecules

Barrier structure proteins

Hyperplasia

Lichenification

Dysbiosis Staphylococcus aureus

Th1

Th2

ILC2

Th22

Th17

IL-17

IL-23

Th2

Th1

IFN-γ
### JAK Inhibition - The Good and The Bad

**JAK1 Blockade**

<table>
<thead>
<tr>
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<th>Bad</th>
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<tr>
<td>IL-4</td>
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<td>IL-22</td>
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<tr>
<td>IL-2</td>
<td>?</td>
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<td>IL-6</td>
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<td>IFN a/g</td>
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<td>IL-15</td>
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**JAK1/2 Blockade**

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<td>IL-4</td>
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<td>IL-13</td>
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<td>IL-22</td>
<td>GM-CSF</td>
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**Disclaimer:** All JAK inhibitors inhibit all JAK signaling, just to greater or lesser extents. Dosing as important for efficacy and side effect profile as molecule.
Phase 2 study of baricitinib (JAK1/2) in adults with moderate to severe AD

- Steroid run-in X 4 weeks and TCS use during study
- Phase 3 studies underway
Phase 2b study of Abrocitinib (JAK1)

**IGA response of 0/1 and ≥2-point improvement**

- Placebo (n=55)
- PF-04965842 10 mg qd (n=49)
- PF-04965842 30 mg qd (n=51)
- PF-04965842 100 mg qd (n=56)
- PF-04965842 200 mg qd (n=55)

**Mean change from baseline in EASI score**

- Week 1: 27.8%
- Week 2: 44.5%
- Week 6: 6.3%

- No TCS use
- Phase 3 studies underway
**Phase 2b Trial Upadacitinib (JAK1) in Adult AD**

- Placebo (n=41)
- UPD 7.5 mg (n=42)
- UPD 15 mg (n=42)
- UPD 30 mg (n=42)

**Change from baseline in EASI score (LOCF)**

- UPD 30 mg (n=42)
- UPD 15 mg (n=42)
- UPD 7.5 mg (n=42)
- Placebo (n=39, 37 Week 2)

**IGA 0/1**

- 2
- 14
- 31
- 50

**Change from baseline in EASI score (LOCF)**

- 74.4
- 61.7
- 39.4
- 23.0

*P<0.05; †P<0.01; ‡P<0.001 UPD vs placebo

Guttman-Yassky E, et al. AAD 2018, Late-breaking Research: Clinical Trials
Phase 2b trial: Change from baseline in EASI score with upadacitinib through 32 weeks

**UPD 15 mg/placebo (n=19)**
- Entry: Week 0
- Week 2: 61.3%
- Week 20: 73.5%
- Week 24: 53.6%
- Week 32: 51.6%

**UPD 15 mg/UPD 15 mg (n=18)**
- Entry: Week 0
- Week 2: 14.3%
- Week 24: 12.7%
- Week 32: 11.8%

**UPD 30 mg/placebo (n=19)**
- Entry: Week 0
- Week 2: 72.9%
- Week 20: 74.6%
- Week 24: 70.8%
- Week 32: 69.3%

**UPD 30 mg/UPD 30 mg (n=19)**
- Entry: Week 0
- Week 2: 22.3%
- Week 24: 24.6%
- Week 32: 20.7%
- Week 32: 22.3%

*P<0.05; †P<0.01; ‡P<0.001; LOCF imputation for continuous variables

Guttmann-Yassky E, et al. EADV 2018, P0236
ASN002 (JAK/SYK inhibitor) in Adult AD

- Blocking Syk blocks IL-17 signaling
- 4 weeks study of 9 active, 2 placebo for each dose
- Blood and transcriptome improvements
- No TCS use

- Guttman-Yassky E, et al. EADV 2018, Late-breaking news D3T01.1H. Sponsored by Asana BioSciences
Summary of Adverse Events for JAKs

• Total AEs increase for all JAKs as doses increase
• Mainly driven by lab abnormalities
• Transient thrombocytopenia occurred with abrocitinib at highest dose
• Serious infections in AD populations are low and similar to placebo for all JAKs at all doses
• Black box warning for infection and malignancy for all JAKs likely, although AD data will likely be much safer than for RA
• If companies push doses for efficacy, will they get burned?
Summary and Conclusions

• Numerous targeted therapies being developed for AD with early studies showing a promising signal
• Blockade of IL-4/IL-13 very effective and safe strategy
• Blockade of other extracellular targets appear to have activity
• JAK inhibition promising, but efficacy will need careful balancing with side effect profile
• Exciting and hopeful time for patients suffering from AD!
Thank you for listening!

Wanderer above the Sea of Fog (1818) – Caspar David Friedrich