Positioning New Treatments for Atopic Dermatitis in Our Practice Parameter

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Disclosures

- Research Grants: NIH/NIAID, Anacor, Regeneron
- Consultant/Advisory Board: Regeneron, Sanofi-Genzyme, Pfizer
- Content will include discussion of off-label uses of medications for atopic dermatitis
Objectives

At the end of this session, participants will be able to:

1. Describe the burden of illness in patients with AD and barriers to treatment
2. Manage patients with AD in accordance with the latest treatment guidelines and expert recommendations
3. Apply knowledge of the pathophysiology and assessment of AD to the selection of treatment options
4. Summarize research on the safety, efficacy, and mechanisms of action of newly approved and emerging therapies for the treatment of AD
Practice Parameter Update: Flow chart of the diagnosis and management of AD

1. Patient presents with skin manifestations consistent with AD, e.g., an eczematous pruritic dermatitis

2. Evaluation based on history and exam to diagnose AD dermatitis

   - Atopic dermatitis severe?
     - YES
     - Management successful?
       - YES
       - Consideration of other conditions
       
       - NO
       - Follow-up: Consider proactive treatment for patients with relapsing disease

   - NO
     - Reasons: Is diagnosis of atopic dermatitis correct?
       - YES
       - Consultation with an AD specialist for consideration of other conditions
       - NO
       - Consultation with an AD specialist: intensification of management and treatment (Box 5)
         - Wet dressings
         - Hospitalization
         - Phototherapy
         - Systemic immunologic or anti-inflammatory therapies

3. Consideration of other conditions

5. Management of AD
   - Skin hydration/moisturizers
   - Topical corticosteroids
   - Tar preparations
   - Topical calcineurin inhibitors
   - Diflucan baths
   - Antihistamines

   Evaluation and treatment of:
   - Skin infection
   - Infections and food allergy
   - Non-specific triggers

J Allergy Clin Immunol
2013;131:295

Non-recommended & non-approved systemic therapies
Keystone 2017 talk

- Recognition of AD as not just a disease of children, non-atopic co-morbidities & systemic aspects
- Review of systemic treatment for severe AD
  - Systemic steroids approved but not recommended
  - CsA, methotrexate, mycofenolate, azathioprine not indicated for AD for any age in the US
  - Systematic review supports only short term use of CsA
- Review of pivotal phase 3 dupilumab studies for moderate-to-severe AD (Solo 1 & Solo 2)
  - dupilumab improved signs and symptoms of AD including pruritus, symptoms of anxiety and depression and quality of life as compared with placebo
  - Injection-site reactions and conjunctivitis were more frequent in dupilumab groups than in placebo groups
Persistence of mild to moderate AD

- Cross-sectional & cohort study of a long-term registry of children with AD enrolled in PEER*
- 7157 pts enrolled in PEER with at least 2 yrs of f/u for 4248 and at least 5 yrs of f/u for 2416
- At every age (2-26 yrs), >80% of PEER participants had symptoms of AD and/or were using medication to treat their AD
- It was not until age 20 yrs that 50% of pts had at least 1 lifetime 6-mo symptom- and treatment-free period

*Pediatric Eczema Elective Registry; ~ 16% of PEER subset with FLG mutations

Margolis JS, et al. JAMA Dermatol 2014;150:593
US prevalence: adults

- 2010 and 2012 National Health Interview Survey data of US adults 18–85 y
  - Nationally representative cohort from all 50 states (n=27,157 and 34,613)
  - 1-year prevalence was 10.2% (less specific question) and 7.2% (more specific question)
  - 1-year prevalence of eczema with asthma or hay fever 3.2%

Children: 12.0% (11.3-12.7%)
Adults: 7.2% (6.9-7.6%)

Silverberg JI. Dermatol Clin 2017;35;283-9
Adult onset/recurrence of AD

TNS household panel (n=60,000)


54% with onset of AD after the age of 18 years

16.8% with onset of AD after age 18 years
Clinical relevance

- Adult onset / recurrent AD is more common than previously recognized
- Important to rule out the differential diagnosis
Fig 1. Flow chart of the diagnosis and management of AD

Differential diagnosis

J Allergy Clin Immunol 2013;131:295
Differential diagnosis of AD

Congenital disorders
• Netherton's syndrome

Chronic dermatoses
• Seborrheic dermatitis
• Contact dermatitis (allergic or irritant)
• Nummular eczema
• Lichen simplex chronicus

Infections and infestations
• Scabies
• HIV-associated dermatitis

Malignancy
• Cutaneous T cell lymphoma (mycosis fungoides/Sézary syndrome)

Immunodeficiencies
• Wiskott-Aldrich syndrome
• SCID
• Hyper-IgE syndrome
• DOCK8 mutations
• IPEX

Metabolic disorders
• Zinc deficiency
• Pyridoxine (vitamin B6) and niacin deficiency
• Multiple carboxylase deficiency
• Phenylketonuria

Proliferative disorder
• Letterer-Siwe disease

Boguniewicz M, Leung DY. Middleton’s Allergy 2014
A pragmatic approach to patch testing atopic dermatitis patients: Clinical recommendations based on expert consensus opinion

*e.g. head/neck predominance, hand or foot, eyelid, perioral

Differential diagnosis of AD

Congenital disorders
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Boguniewicz M, Leung DY. Middleton’s Allergy 2014
Mycosis fungoides happens...

- The most common form of CTCL
- Epidermotropic neoplasm of CD4+ T cells

Moving beyond the Practice Parameter and Guidelines

J Allergy Clin Immunol 2013;131:295

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Topical PDE4 inhibitor

MoAb vs IL-4 receptor alpha

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1. Patient presents with skin manifestations consistent with AD, e.g., an eczematous pruritic dermatitis

2. Evaluation based on history and exam diagnostic for AD dermatitis

   - Atopic dermatitis severe?

   - YES

   - NO

   - Consideration of other conditions

3. Topical PDE4 inhibitor

4. Management of AD
   - Skin hydration/moisturizers
   - Topical corticosteroids
   - Tar preparations
   - Topical calcineurin inhibitors
   - Dithiothreitol baths
   - Antihistamines
   - Evaluation and treatment of:
     - Skin infection
     - Inflamed and food allergy
     - Nonspecific triggers

5. Follow-up
   - Consider proactive treatment for patients with relapsing disease

6. Management successful?

   - YES
   - NO

7. Reason(s):
   - diagnosis of atopic dermatitis correct?

   - YES
   - NO

8. Consultation with an AD specialist

9. Consultation with an AD specialist for consideration of other conditions

10. Consultation with an AD specialist and consideration of management and treatment (Box 5)

    - Wet dressings
    - Hospitalization
    - Phototherapy
    - Systemic immunologic or anti-inflammatory therapies
You are asked to consult on a 6 year old male who has severe atopic dermatitis (AD), complicated by MRSA skin infections, animal allergies and serum IgE 1100 IU/ml. In discussing therapeutic options with his parents, the correct answer to their queries about a new treatment for AD would be:

A. Crisaborole is an oral JAK inhibitor approved for severe AD
B. Crisaborole is a new topical steroid approved for patients as young as 3 months of age
C. Crisaborole is a PDE4 inhibitor approved for mild-to-moderate AD in patients 2 years or older
D. Patients on crisaborole should have blood pressure and renal function monitored monthly
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D. Patients on crisaborole should have blood pressure and renal function monitored monthly
The role of phosphodiesterase 4 inhibition in the pathophysiology of atopic dermatitis

Crisaborole
$M_r = 251$ D

E6005/RVT-501
$M_r = 472$ D

LEO 29102
$M_r = 441$ D

Apremilast
$M_r = 461$ D

Crisaborole: targeting PDE4

Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis in children and adults

- To assess the efficacy and safety of crisaborole ointment, a PDE4 inhibitor in 2 phase III AD studies
- 2 identical VC, DB studies randomly assigned (2:1, crisaborole:vehicle) pts aged 2 yrs or older with an Investigator’s Static Global Assessment (ISGA) score of mild or moderate for 2x/d application for 28 days
- Primary end point was ISGA score at day 29 of clear (0)/almost clear (1) with 2-grade or greater improvement from baseline

• More crisaborole- than vehicle-treated patients achieved ISGA score success (clear/almost clear with ≥2-grade improvement; AD-301: 32.8% vs 25.4%, P = .038; AD-302: 31.4% vs 18.0%, P < .001), with a greater percentage with clear/almost clear (51.7% vs 40.6%, P = .005; 48.5% vs 29.7%, P < .001)

• Crisaborole-treated patients achieved success in ISGA score and improvement in pruritus earlier than those treated with vehicle (both P ≤ .001)

• Treatment-related adverse events were infrequent and mild to moderate in severity

# Crisaborole Improves ISGA at Day 29

## Phase 3 Primary Outcome

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Age groups (%)</th>
<th>AD-301</th>
<th>AD-302</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crisaborole (n = 503)</td>
<td>Vehicle (n = 256)</td>
</tr>
<tr>
<td>2–6 yrs</td>
<td>32.2</td>
<td>30.5</td>
</tr>
<tr>
<td>7–11 yrs</td>
<td>30.8</td>
<td>28.5</td>
</tr>
<tr>
<td>12–17 yrs</td>
<td>24.1</td>
<td>26.2</td>
</tr>
<tr>
<td>≥ 18 yrs</td>
<td>12.9</td>
<td>14.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline ISGA (%)</th>
<th>AD-301</th>
<th>AD-302</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (2)</td>
<td>39.0</td>
<td>36.3</td>
</tr>
<tr>
<td>Moderate (3)</td>
<td>61.0</td>
<td>63.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% BSA</th>
<th>AD-301</th>
<th>AD-302</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>18.8</td>
<td>18.6</td>
</tr>
<tr>
<td>Range</td>
<td>5–95</td>
<td>5–90</td>
</tr>
</tbody>
</table>

* ISGA of 0 [clear] or 1 [almost clear] with ≥ 2 grade improvement from baseline.

Crisaborole Improves Pruritus in Mild-to-Moderate AD

Phase 3 Predefined Outcome

A greater proportion of crisaborole-treated patients achieved improvement in pruritus across all study visits

Median time to improvement = 1.37 days active vs 1.73 days control ($P = 0.001$)

* Score of 0 or 1 with $\geq 1$ grade reduction from baseline.

More crisaborole- than vehicle-treated patients achieved ISGA score success (clear/almost clear with ≥2-grade improvement; AD-301: 32.8% vs 25.4%, P = .038; AD-302: 31.4% vs 18.0%, P<.001), with a greater percentage with clear/almost clear (51.7% vs 40.6%, P = .005; 48.5% vs 29.7%, P < .001)

Crisaborole-treated patients achieved success in ISGA score and improvement in pruritus earlier than those treated with vehicle (both P ≤.001)

Treatment-related adverse events were infrequent and mild to moderate in severity

Crisaborole ointment 2% approved by FDA in Dec 2016 for treatment of mild-moderate AD in patients 2 years and older

Which statement about dupilumab is correct?
A. It is a biologic targeting interleukin 31 (IL-31)
B. It is currently approved in patients 12 years or older
C. It is available in 2 strengths (300 mg for moderate AD and 600 mg for severe AD)
D. All patients receive a 600 mg loading dose when starting dupilumab therapy
Which statement about dupilumab is correct?
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D. All patients receive a 600 mg loading dose when starting dupilumab therapy
Dupilumab, a fully human monoclonal Ab against IL-4 receptor alpha inhibits signaling of IL-4 & IL-13

Type I Receptor
- B cells, T cells, Monocytes, Eosinophils, Fibroblasts

Type II Receptor
- Epithelial cells, Smooth muscle cells, Fibroblasts, Monocytes, Activated B cells
Two phase 3 trials of dupilumab vs placebo in atopic dermatitis

Dupilumab approved by FDA on Mar 28, 2017 for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable

*FDA approved dosing regimen: 600 mg loading dose, then 300 mg q 2 weeks by subcutaneous injection

Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial

Andrew Blauvelt, Marjolein de Bruin-Weller, Melinda Gooderham, Jennifer C Cather, Jamie Weisman, David Pariser, Eric L Simpson, Kim A Papp, H Chih-Ho Hong, Diana Rubel, Peter Foley, Erral Prens, Christopher E M Griffiths, Takafumi Etoh, Pedro Herranz Pinto, Ramon M Pujol, Jacek C Szepietowski, Karel Ettler, Lajos Kemény, Xiaoping Zhu, Bolanle Akinlade, Thomas Hultsch, Vera Mastey, Abhijit Gadkari, Laurent Eckert, Nikhil Amin, Neil M H Graham, Gianluca Pirozzi, Neil Stahl, George D Yancopoulos, Brad Shumel
Dupilumab + TCS efficacy at week 16 and week 52: CHRONOS Phase 3 results

Patients achieving IGA of 0 or 1 and ≥ 2 points Improvement from BL (Primary End Point)

- Wk 16
  - Placebo qwk + TCS: 12%
  - Dupilumab 300 mg q2wks + TCS: 39%
  - Dupilumab 300 mg qwk + TCS: 36%

- Wk 52
  - Placebo qwk + TCS: 13%
  - Dupilumab 300 mg q2wks + TCS: 40%

EASI-75 (Key Secondary End Point)†

- Wk 16
  - Placebo qwk + TCS: 23%
  - Dupilumab 300 mg q2wks + TCS: 69%
  - Dupilumab 300 mg qwk + TCS: 64%

- Wk 52
  - Placebo qwk + TCS: 22%
  - Dupilumab 300 mg q2wks + TCS: 65%
  - Dupilumab 300 mg qwk + TCS: 64%

* P < 0.0001 vs placebo + TCS

Significant improvement in pruritus as early as Week 2 and sustained to Week 52

† Co-primary end point in the EU and Japan
Chronos: EASI 50 & 75 over 52 weeks

## Dupilumab: Safety at 52 Weeks

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo qwk + TCS (n = 315)</th>
<th>Dupilumab 300 mg q2wks + TCS (n = 110)</th>
<th>Dupilumab 300 mg qwk + TCS (n = 315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 AE</td>
<td>226 (84)</td>
<td>97 (88)</td>
<td>261 (83)</td>
</tr>
<tr>
<td>≥ 1 SAE</td>
<td>16 (5)</td>
<td>4 (4)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>1* (&lt; 1)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>24 (8)</td>
<td>2 (2)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>AEs occurring in ≥ 5% of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>61 (19)</td>
<td>25 (23)</td>
<td>60 (19)</td>
</tr>
<tr>
<td>URTI</td>
<td>32 (10)</td>
<td>11 (10)</td>
<td>43 (14)</td>
</tr>
<tr>
<td>AD</td>
<td>144 (46)</td>
<td>20 (18)</td>
<td>52 (17)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>24 (8)</td>
<td>16 (15)</td>
<td>60 (19)</td>
</tr>
<tr>
<td>Asthma</td>
<td>19 (6)</td>
<td>5 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Herpes infections</td>
<td>25 (8)</td>
<td>8 (7)</td>
<td>22 (7)</td>
</tr>
<tr>
<td>Non-herpetic skin infections</td>
<td>56 (18)</td>
<td>12 (11)</td>
<td>26 (8)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>25 (8)</td>
<td>15 (14)</td>
<td>61 (19)</td>
</tr>
</tbody>
</table>

* Motor vehicle accident not considered related to study drug.
Dupilumab with concomitant topical corticosteroids in adult patients with atopic dermatitis who are not adequately controlled with or are intolerant to ciclosporin A, or when this treatment is medically inadvisable: a placebo-controlled, randomized phase 3 clinical trial (LIBERTY AD CAFÉ)

CAFÉ study design

• To evaluate efficacy and safety of dupilumab with concomitant TCS in adults with AD with inadequate response to/intolerance of CsA or for whom CsA was medically inadvisable
• 16 wk, double-blind, randomized, placebo-controlled phase 3 trial with pts randomized 1:1:1 to subq dupilumab 300 mg qw:q2w:placebo All received concomitant medium-potency TCS from wk 2 through wk 16; dosage could be tapered if lesions cleared or stopped for adverse reactions to TCS

CAFÉ results

- 325 pts randomized and 318 completed trial
- Significantly more pts on dupilumab qw+TCS/q2w+TCS achieved ≥75% improvement from baseline in EASI at wk 16 vs placebo+TCS (1° endpoint) (59.1%/62.6% vs 29.6%; P<0.0001 vs placebo+TCS, both doses)
- Dupilumab qw+TCS/q2w+TCS significantly improved pruritus, pain, sleep disturbance, symptoms of anxiety and depression, and QOL
- Treatment groups had ~ overall rates of adverse events (69.1%/72.0%/69.4%; qw+TCS/q2w+TCS/placebo+TCS) and serious adverse events (1.8%/1.9%/1.9%)
- Conjunctivitis more frequent with dupilumab+TCS; skin infections more frequent with placebo+TCS

CAFÉ Conclusions

• Dupilumab+TCS significantly improved signs and symptoms of AD and QOL in adults with history of inadequate response to/intolerance of CsA, or for whom CsA treatment was medically inadvisable
• No new safety signals were identified

Dupilumab trials in adolescents & children with AD...

- Study to determine safety and tolerability of dupilumab in patients aged ≥6 to <18 years with atopic dermatitis - Canada, Europe (NCT02407756) - completed
- Study to assess long-term safety of dupilumab administered in patients 6 to <18 years of age with atopic dermatitis – Canada, Europe (NCT02612454) - ongoing
- FDA approval for pediatric dupilumab trials in US: Efficacy and safety of dupilumab in patients ≥12 to <18 years of age with moderate-to-severe atopic dermatitis (NCT03054428) – enrollment complete
- Study to determine safety and tolerability of dupilumab in patients aged 6 to 11 years with atopic dermatitis

Fitzpatrick’s Dermatology in Gen Med 2012;170
Theme Editorial

Are Biotherapeutics Revolutionizing Treatment of “Allergic” Diseases?

William W. Busse, MD  Madison, Wis
Clinical Commentary Review

Biologic Therapy for Atopic Dermatitis: Moving Beyond the Practice Parameter and Guidelines

Mark Boguniewicz, MD  Denver, Colo

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic diseases to those who research, teach, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation Provider/Statement and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for 1.50 AMA PRA Category 1 CME Credit(s)™. Physicians who enter only the posttest will receive only the credit commensurate with the extent of their participation in the activity.

List of Disclosure Committee/Authors: Mark Boguniewicz, MD

Learning objectives:
1. To describe new insights into our understanding of atopic dermatitis (AD).
2. To review limitations of currently available treatment for AD.
3. To discuss efforts to move current clinical trials of new biologics in adults with moderate to severe AD.

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Atopic dermatitis (AD), a common chronic parasitic inflammatory skin disease, impacts the quality of life of patients and caregivers and has become a global health problem, which is increasingly recognized as a disease not only of children but also of adults who may have a persistent or relapsing condition from childhood to adolescence to adult disease. Besides well-established atopic dermatitis, associations with a number of non-atopic comorbidities have been reported. AD is characterized by both increased immunoglobulin and episodic barrel wall thickening. The findings that atopic dermatitis is in both humans and animals have also contributed to different definitions and immune abnormalities as well as multiple markers of immune and inflammatory activity in the circulation to the systemic names of the disease and have important translational implications. Although AD is predominantly associated with type 2 immune response, activation of other cytokines pathways, including Th2, Th3, Th22, and Th7/IFN-gamma, suggests that potential therapeutic targets and provide a hypothesis for treatment with novel biologics. Dupilumab, a fully human monoclonal anti-IL-4 and IL-13 receptor, block signals of both IL-4 and IL-13 and is the first biologic to be approved for the treatment of moderate-to-severe AD in adult patients. Other biologics in current trials for AD are targeting the IL-51 receptor, IL-13, and the common p70 subunit of IL-12/23. © 2017 American Academy of Allergy, Asthma & Immunology

J Allergy Clin Immunol Pract 2017;5:1477

Special Article

Expert Perspectives on Management of Moderate-to-Severe Atopic Dermatitis: A Multidisciplinary Consensus Addressing Current and Emerging Therapies

Mark Boguniewicz, MD; Andrew F. Alexis, MD, MPH; Lisa A. Beck, MD, MS; Julie Black, BA, BS; Lawrence F. Eichenfield, MD1,2; Luz Fonacier, MD; Emma Gutmann-Yassky, MD, PhD; Amy S. Paller, MD; David Parmelee, MD; Jennifer A. Zlotnik, MD, PhD, MPH; and Mark Litonjua, MD1,3; 4; 5

Atopic dermatitis (AD) is a common, chronic, relapsing, inflammatory skin disease that affects children and adults. Used recently, the only Food and Drug Administration-approved systemic treatment options for patients with moderate-to-severe AD was systemic steroids, which are not recommended by current guidelines and are commonly associated with disease.

National Science Foundation supports funding from various corporate sponsors, which are guided by our Corporate Relations Policy and disclosed in the public (L. F. Eichenfield has received consultancy fees and travel support from Altimmune, Amgen, AstraZeneca, Biogen, BI-0525, BI-0535, BIAL, Blueskyn Health, Celgene, Genentech, Glaxosmithkline, Heat Biologics, Janssen, Janssen Biotech, LEO Pharmacuticals, Merck, Novartis, Regeneron, and Roche and has received research support from Altimmune, Amgen, AstraZeneca, Biogen, BI-0525, BI-0535, BIAL, Blueskyn Health, Celgene, Genentech, Glaxosmithkline, Heat Biologics, Janssen, Janssen Biotech, LEO Pharmacuticals, Merck, Novartis, Regeneron, and Roche). LEO Pharmacuticals, Merck, Novartis, Regeneron, and Roche have also contributed to the following: LEO Pharmacuticals, Merck, Novartis, Regeneron, and Roche.

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J Allergy Clin Immunol Pract 2017;5:1519

Key words: Atopic dermatitis; Eczema; Comorbidities; Immune dysregulation; Biologic therapy

Biologic therapy for atopic dermatitis (AD) recognizes an existing advance in the treatment of this common chronic parasitic inflammatory skin disease. Evaluating how biologics fit into the treatment armamentarium for AD supports an understanding of the prevalence and burden of the disease, nor to just individual patients but also to society-associated comorbidities, to complex pathophysiology, as well as limitations of current treatments, as we do to biomarkers specific for the disease and

Boguniewicz M. J Allergy Clin Immunol Pract 2017;5:1477

Complex pathophysiology of atopic dermatitis and selected targets of biologics
Targeting IL-31 in atopic dermatitis: Anti–Interleukin-31 receptor A antibody for atopic dermatitis

• Randomized, double-blind, placebo-controlled, multi-center, multi-dose phase 2 study of 264 adult patients with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy treated with subcutaneous nemolizumab (CIM331) 0.1 mg, 0.5 mg or 2.0 mg/kg vs placebo q 4 wks or 2 mg/kg q 8 wks

• 1° end point - percentage improvement from baseline in score on pruritus VAS (negative change indicates improvement) at week 12

• 216 (82%) pts completed the study

Percentage change from baseline in pruritus scores

Changes on EASI were −23.0%, −42.3% and −40.9%, respectively, in nemolizumab groups versus −26.6% in placebo group

JAK-STAT signaling as a therapeutic target

Phase 2b results for oral upadacitinib (ABT-494)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mean percentage change in EASI score****</th>
<th>EASI 75****</th>
<th>EASI 90****</th>
<th>Investigator Global Assessment (IGA) of &quot;0&quot; or &quot;1&quot;*****</th>
<th>Percent change in pruritus/itch numerical rating scale******</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg (n=42)</td>
<td>74%***</td>
<td>69%***</td>
<td>50%***</td>
<td>50%***</td>
<td>69%*** (N=42)</td>
</tr>
<tr>
<td>15 mg (n=42)</td>
<td>62%***</td>
<td>52%***</td>
<td>26%****</td>
<td>31%***</td>
<td>48%*** (N=37)</td>
</tr>
<tr>
<td>7.5 mg (n=42)</td>
<td>39%*</td>
<td>29%*</td>
<td>14%*</td>
<td>14%*</td>
<td>40%** (N=40)</td>
</tr>
<tr>
<td>Placebo (n=41)</td>
<td>23% (N=39)</td>
<td>10%</td>
<td>2%</td>
<td>2%</td>
<td>10% (N=37)</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.001

Targeting pruritus

H4R antagonist
• ZPL-3893787 (oral) Phase 2a

NK1R antagonists (oral)
• VLY-686/tradipitant
• Serlopitant

TPRV1 Channel Antagonist
• PAC-14028 (cream)

Atopic Dermatitis Yardstick: Practical recommendations for an evolving therapeutic landscape

<table>
<thead>
<tr>
<th>Maintenance Treatment</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASIC MANAGEMENT</strong></td>
<td><strong>BASIC MANAGEMENT + REFFERAL to AD Specialist</strong></td>
</tr>
<tr>
<td><strong>Non-lesional</strong></td>
<td>Phototherapy</td>
</tr>
<tr>
<td><strong>Mild</strong></td>
<td>Dupilumab⁴</td>
</tr>
<tr>
<td><strong>Basic Management</strong></td>
<td>Systemic Immunosuppressants</td>
</tr>
<tr>
<td><strong>Skin Care</strong></td>
<td>Cyclosporine A³</td>
</tr>
<tr>
<td>1. Skin Care</td>
<td>Methotrexate⁵</td>
</tr>
<tr>
<td>• Moisturizer, liberal and frequent (choice per patient preference)</td>
<td>Mycophenolate mofetil³</td>
</tr>
<tr>
<td>• Warm baths or showers using non-soap cleansers, usually once daily and followed by moisturizer (even on clear areas)</td>
<td>Azathioprine³</td>
</tr>
<tr>
<td>2. Trigger Avoidance</td>
<td>Corticosteroids⁴</td>
</tr>
<tr>
<td>• Proven allergens and common irritants (e.g., soaps, wool, temperature extremes)</td>
<td>Consider acute tx for some patients to help gain control:</td>
</tr>
<tr>
<td>3. Trigger Avoidance</td>
<td>• Wet wrap therapy</td>
</tr>
<tr>
<td>• Consider comorbidities</td>
<td>• Short-term hospitalization</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASIC MANAGEMENT + TOPICAL ANTI-INFLAMMATORY MEDICATION</strong></td>
</tr>
<tr>
<td><strong>Apply TCS to Inflamed Skin</strong></td>
</tr>
<tr>
<td>Low to medium potency TCS 2x daily for 3-7 days beyond clearance</td>
</tr>
<tr>
<td>[Consider TCI, crisaborole]</td>
</tr>
<tr>
<td><strong>Apply TCS to Inflamed Skin</strong></td>
</tr>
<tr>
<td>Medium to high potency TCS 2x daily for 3-7 days beyond clearance</td>
</tr>
<tr>
<td>[Consider TCI, crisaborole]</td>
</tr>
<tr>
<td>If not Resolved in 7 Days, Consider</td>
</tr>
</tbody>
</table>

⁴Indicated for patients with mild-to-moderate AD, ages 2 years and older; ⁵Indicated for patients with moderate-to-severe AD, ages 18 years and older; ⁶Not FDA-approved to treat AD; ⁷FDA approved to treat AD, but not recommended for long-term maintenance.
# Atopic Dermatitis Yardstick: Practical recommendations for an evolving therapeutic landscape

**Table 2**

Scoring Systems for Clinician Assessment Used in Clinical Research of Atopic Dermatitis

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Description</th>
<th>Severity rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Validated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCORing Atopic Dermatitis (SCORAD)55,43,45</td>
<td>3 components: (A) extent—sites affected are shaded on a body drawing and scored by percentage (head and neck 9%; upper and lower limbs 9% each; anterior trunk 18%; back 18%; maximum 100%); (B) intensity score (0 = little or none to 3 = severe) for redness, swelling, crusting or oozing, skin thickening (lichenification), dryness, scratch marks (maximum 18%); (C) Global score (VAS, 0 = none to 10 = worst imaginable) for sleeplessness and itch (maximum 20); SCORAD total score = A% + B% + C (maximum 163)</td>
<td>Mild ≤25, moderate &gt;25 to ≤50, severe &gt;50</td>
</tr>
<tr>
<td>**Eczema Area and Severity Index (EASI)**26,21,41</td>
<td>2 components: (1) area score (percentage of skin affected) recorded for 4 regions (head and neck, trunk and genitals, upper limbs, lower limbs and buttocks), 0 = none, 1 = 1–1.9%, 2 = 2–9.9%, 3 = 10–49%, 4 = 50–69%, 5 = 70–89%, 6 = 90–100%. (2) severity score for each region calculated based on intensity (0 = none to 3 = severe) of redness, crusting, or swelling, scaling, lichenification (maximum 12 for each region). Calculation of total regional scores: head and neck severity score = area score × 0.1 (in children 0.7–2 = 0.2); trunk severity score = area score × 0.3; upper limbs severity score = area score × 0.2; lower limbs severity score = area score × 0.4 (in children 0.3–1 = 0.2). EASI total score = sum of total regional scores (maximum 72)</td>
<td>Mild ≤1.5, moderate 1.5–7, severe &gt;7</td>
</tr>
<tr>
<td>**Patient-Oriented SCORAD (PO-SCORAD)**26,45</td>
<td>Adaptation of SCORAD for patients and available as an app online (to be shared with the clinician). Similar scoring to SCORAD except affected area severity of dry skin outside affected areas, symptom intensity of affected areas, severity of itching, and sleep disturbance; shown to be correlated with SCORAD</td>
<td>Mild ≤25, moderate &gt;25 to ≤50, severe &gt;50</td>
</tr>
<tr>
<td>**Patient-Oriented Eczema Measure (POEM)**34,41</td>
<td>7 symptoms scored over past week: 0 = no days, 1 = 1–2 d; 2 = 3–4 d; 3 = 5–6 d; 4 = every day (query: Over the last week, on how many days has your skin been itchy, red, bleeding, weeping or oozing clear fluid, cracking, fissuring, felt dry or rough because of your eczema?); maximum score 28</td>
<td>Clear or almost clear 0, mild 1–3, moderate 4–16, severe &gt;17–24, very severe ≥25–28</td>
</tr>
<tr>
<td>**Dermatology Life Quality Index (DLQI)**34,47</td>
<td>10-question validated questionnaire providing patient's perception of the impact of AD on quality of the last week, questions include effect of disease and treatment on physical, psychological, and social well-being</td>
<td>Each question is answered according to ratings: 0 = not at all, 1 = a little, 2 = a lot, 3 = very much; maximum 30</td>
</tr>
<tr>
<td><strong>Not validated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator Global Assessment (IGA) score, aka Investigator Global Assessment (IGA) score51</td>
<td>Intensity of severity of body surface area involved based on 6 signs (erythema, excoriation, dryness, cracking, lichenification) at each of 6 sites (arms, hands, legs, feet, head and neck, trunk)</td>
<td>0 = clear to 0 = severe</td>
</tr>
<tr>
<td>Six Signs Six Areas Atopic Dermatitis (SASSAD) scale51</td>
<td>Subjective evaluation of extent of body surface area involved based on 6 signs (erythema, excoriation, dryness, cracking, lichenification) at each of 6 sites (arms, hands, legs, feet, head and neck, trunk)</td>
<td>Each sign at each site is assessed using a scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe; maximum 108</td>
</tr>
<tr>
<td><strong>Three Item Severity (TIS) scale</strong>51</td>
<td>Subjective evaluation of a representative lesion based on erythema, edema or papulation, and excoriation</td>
<td>0 = none to 0 = severe</td>
</tr>
<tr>
<td>Patient's subjective of itch using a VAS similar to pain scales</td>
<td>Subjective evaluation of a representative lesion based on erythema, edema or papulation, and excoriation</td>
<td>Patient's subjective of itch using a VAS similar to pain scales</td>
</tr>
</tbody>
</table>

Abbreviations: AD, atopic dermatitis; FDA, Food and Drug Administration; VAS, visual analog scale.

Atopic Dermatitis Yardstick: Practical recommendations for an evolving therapeutic landscape

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<table>
<thead>
<tr>
<th>Table 5</th>
<th>Practical Pearls for Prescribing Dupilumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Document diagnosis of AD (not just eczema); see Table 1</td>
</tr>
<tr>
<td>2.</td>
<td>Qualify and document severity of AD as mild, moderate, or severe based on involved body surface area and/or other measures; see Table 2</td>
</tr>
<tr>
<td>3.</td>
<td>Provide supporting description in physical examination; see descriptions in EASI and SCORAD in Table 2</td>
</tr>
<tr>
<td>4.</td>
<td>Address prior therapies and/or therapeutic failures, including why the patient is not a candidate for other specific therapy</td>
</tr>
<tr>
<td>5.</td>
<td>Be specific when describing a therapeutic failure, which is defined as ≥1 of the following: Inadequate response to medium-to-high potency topical therapy Suboptimal clinical improvement Failure to achieve stable long-term control (eg, frequent exacerbations) Unacceptable adverse events</td>
</tr>
<tr>
<td>6.</td>
<td>Review the insurance requirements of the formulary because some insurers might require specific documentation and severity measurements (eg, use of EASI, positive determination that signs and symptoms are due to AD and not complicating factors such as parasitic infections, etc)</td>
</tr>
</tbody>
</table>

Atopic Dermatitis Program 1990-2018
A multidisciplinary team approach
NIAID Atopic Dermatitis Research Network