Moderate-to-Severe Atopic Dermatitis:

Targeting the Underlying Inflammatory Processes to Improve Patient Outcomes

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Moderate-to-Severe Atopic Dermatitis: Targeting the Underlying Inflammatory Processes to Improve Patient Outcomes

FACULTY

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PROGRAM OVERVIEW
This case-based activity will cover the underlying causes of atopic dermatitis along with current and emerging systemic agents as part of the overall treatment plan.

TARGET AUDIENCE
This activity is intended for allergists, immunologists, and other healthcare professionals involved in the management of patients with atopic dermatitis.

Learning Objectives

- Review the role of type 2 inflammation in the pathogenesis of atopic dermatitis
- Identify common atopic and non-atopic comorbid conditions in patients with moderate-to-severe AD
- Evaluate clinical trial evidence on the efficacy and safety of currently available treatments for moderate-to-severe AD in adult and pediatric patients
- Utilize shared decision-making to develop comprehensive treatment plans for atopic dermatitis and related comorbid conditions

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Peter Lio, MD has served on the advisory board for the National Eczema Association, Modernizing Medicine, Johnson & Johnson, DermTap Inc., IntraDerm Pharmaceuticals, Regeneron, Sanofi US Services, Realm Therapeutics, Menlo Therapeutics, Syncere Skin Systems, Dermveda, GPower Inc., UCB, Altus Labs, Dermavant Sciences, Micreos Human Health B.V., Verrica Pharmaceuticals Inc., Arbonne, Yobee Care Inc., and Bodewell. Dr. Lio is a stockholder in Modernizing Medicine, LearnHealth/LearnSkin, and Medable. He has been a speaker for Pierre Fabre Dermatologie, Regeneron, Pfizer, and La Roche-Posay. He has been an investigator for La Fondation pour la Dermatite Atopique (Foundation for Atopic Dermatitis), AOBiome LLC, Regeneron, AbbVie, and National Eczema Association. He has been a consultant for Exeltis, Theraplex, Odeza LLC, L'Oréal USA Inc., Franklin BioScience, AbbVie, Kiniksa Pharmaceuticals, Eli Lilly and Co., Unilever, Dermira, TopMD, Amyris Inc., Leo Pharma, and Burt's Bees.

Mark Boguniewicz, MD has been a consultant with Regeneron, Sanofi-Genzyme, Lilly, Leo, and Pfizer. He has contracted research with Regeneron and Incyte.

CME Content Review
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The reviewer of this activity has nothing to disclose.

CNE Content Review

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The reviewer of this activity has nothing to disclose.

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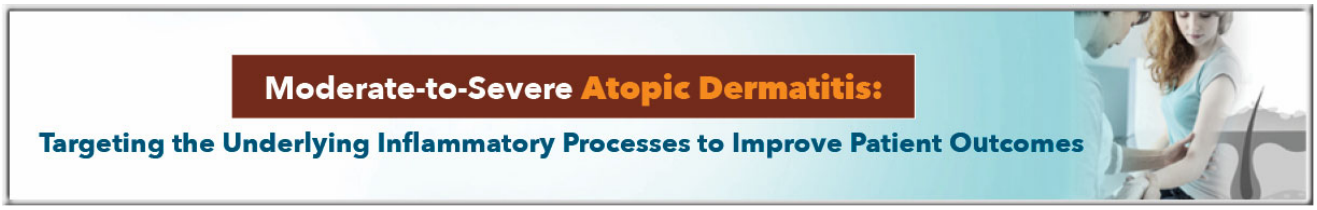
Please visit the **Atopic Dermatitis Thrive Initiative**, *which includes online CME offerings for clinicians and patients, toolkits, and a calendar of upcoming educational activities.*



AGENDA

I. Atopic Dermatitis (AD): Features and Mechanisms

- Features of AD
- The inflammatory loop
- Pathogenesis (video)

II. Evaluation and Diagnosis

- Diagnostic features and distribution
- Age and race-based differences
- Phenotypic mimics

III. Patient Impact

- The 5 I's and patient-centered treatment (video)
- Impact and associated morbidities

IV. Initial Management Considerations

- Assessing disease severity
- Guideline-based customized therapy
- Emollients/topicals
- Reactive/proactive treatment
- Shared decision-making

V. New and Targeted Therapy

- Conventional algorithm
- Dupilumab (mechanisms, clinical trials, safety)
- Targets beyond IGA
- Concepts in dose reduction
- Pipeline agents: JAK's and other systemics
- Case study

VI. Conclusions, Post-Test, and Q/A

February 27, 2021

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Disclosures

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- Identify common atopic and non-atopic comorbid conditions in patients with moderate-to-severe AD
- Evaluate clinical trial evidence on the efficacy and safety of currently available treatments for moderate-to-severe AD in adult and pediatric patients
- Utilize shared decision-making to develop comprehensive treatment plans for AD and related comorbid conditions

AD = atopic dermatitis.

Atopic Dermatitis: Features and Mechanisms

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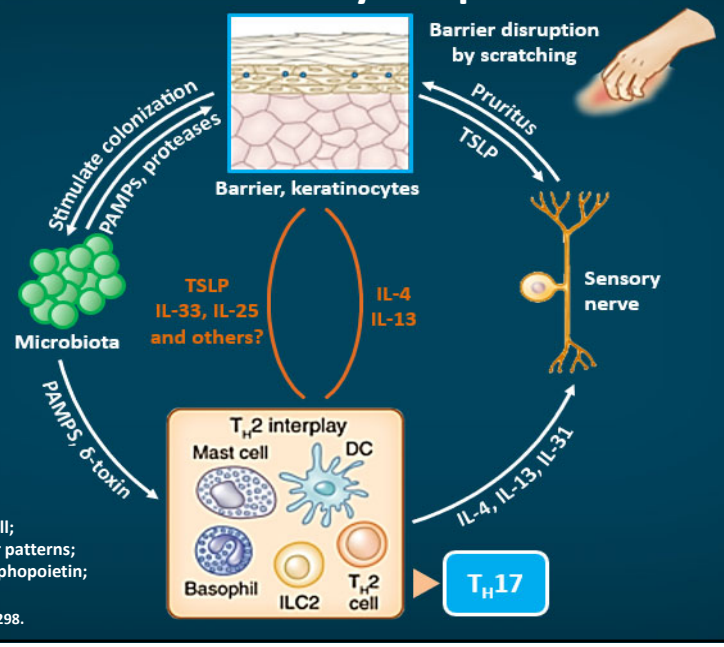
Features of Atopic Dermatitis (AD)

AD is a chronic, pruritic, inflammatory skin disease that typically involves:

- Childhood onset
- Familial occurrence
- Eczematous change
  - Erythema
  - Induration, papulation
  - Excoriation
  - Lichenification
- Characteristic distribution
- Intermittent flares
- Associated skin conditions (minor diagnostic criteria)
- Skin infections
- Associated morbidities

Siegfried EC, Hebert AA. *J Clin Med.* 2015;4:884-917. Ring J, et al. *J Eur Acad Dermatol Venereol.* 2012;26:1045-1060.

The Inflammatory Loop in AD



IL = interleukin; ILC = innate lymphoid cell;
PAMPs = pathogen-associated molecular patterns;
T_H = T helper; TSLP = thymic stromal lymphopoietin;
DC = dendritic cell

Dainichi T, et al. *Nat Immunol*. 2018;19:1286-1298.

Please click here to watch a brief animation exploring the pathophysiology of atopic dermatitis

Evaluation and Diagnosis

Atopic Dermatitis: Diagnosis Features

Features to be considered in diagnosing patients with AD

- **ESSENTIAL FEATURES**; must be present:
  - Pruritus
  - Eczema (acute, subacute, chronic):
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

  Patterns include:
  1) facial, neck, and extensor involvement in infants and children;
  2) current or prior flexural lesions in any age group;
  3) sparing of groin and axillary regions.

- **IMPORTANT FEATURES**; seen in most cases, adding support to the diagnosis:
  - Early age of onset
  - Atopy
    - Personal and/or family history
    - IgE reactivity
  - Xerosis

- **ASSOCIATED FEATURES** ; these clinical associations help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD for research and epidemiologic studies:
  - Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
  - Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
  - Ocular / periorbital changes
  - Other regional findings (e.g., perioral changes / periauricular lesions)
  - Perifollicular accentuation / lichenification / prurigo lesions

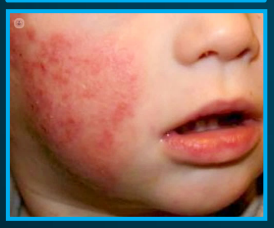
- **EXCLUSIONARY CONDITIONS;** it should be noted that a diagnosis of AD depends on excluding conditions such as:
  - scabies
  - seborrheic dermatitis
  - contact dermatitis (irritant or allergic)
  - ichthyoses
  - cutaneous T-cell lymphoma
  - psoriasis
  - photosensitivity dermatoses
  - immune deficiency diseases
  - erythroderma of other causes

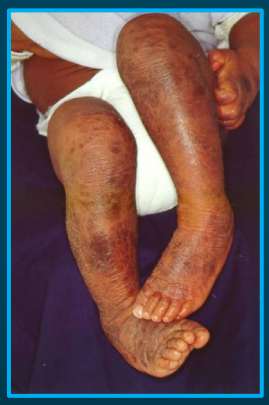
Eichenfield LF, et al. *J Am Acad Dermatol.* 2003;49:1088-1095. Eichenfield LF, et al. *J Am Acad Dermatol.* 2014;70:338-351.

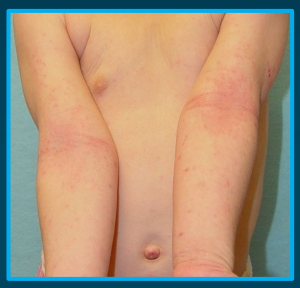
Classic AD Distribution Changes With Age

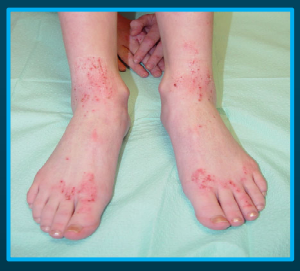
Infants: face, extensor extremities

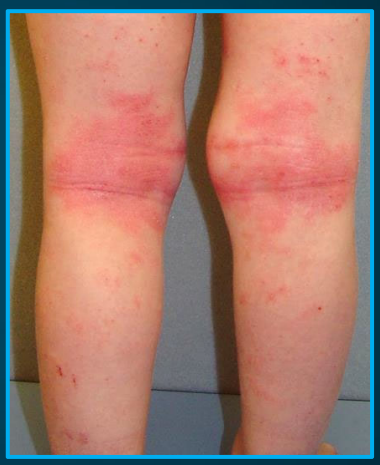
Children: wrists, ankles, antecubital and popliteal fossae





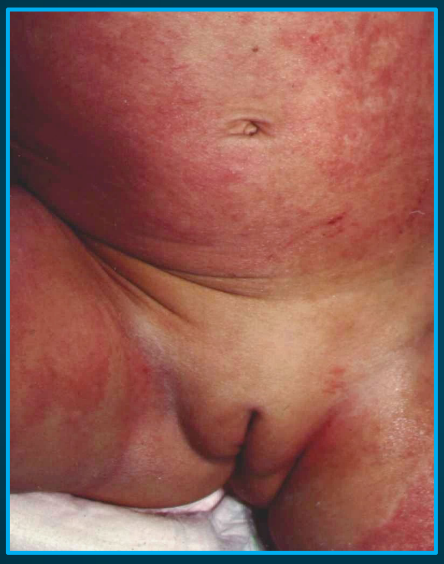


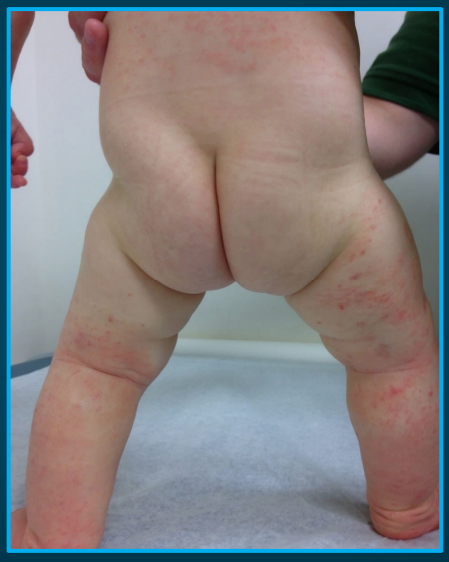




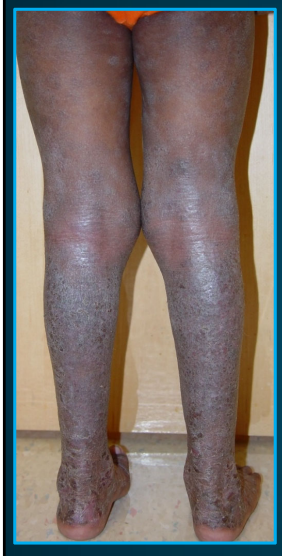
AD across the lifespan (https://atopicdermatitis.net/across-lifespan). Accessed January 26, 2021.

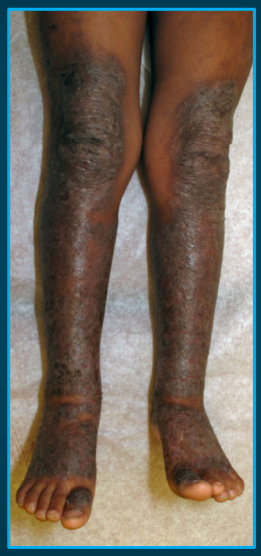
Diaper-Area Sparing: A Diagnostic and Therapeutic Feature

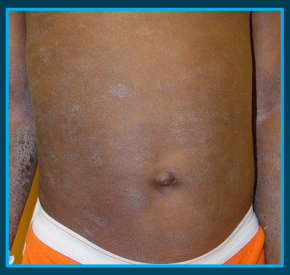


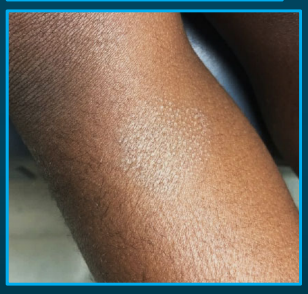


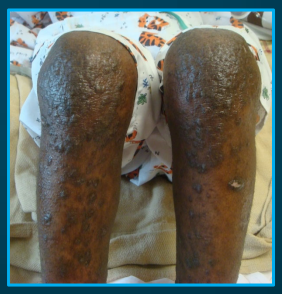
More Common Features in Skin of Color











- Follicular/papular and nummular morphology
- Obscured erythema
- Prominent lichenification
- Dyspigmentation

Boguniewicz M, et al. *J Allergy Clin Immunol Pract.* 2017;5:1519-1531. Poladian K, et al. *Cutis.* 2019;104:164-168. Siegfried EC, Hebert AA. *J Clin Med.* 2015;4:884-917.

Phenotypic Mimics

Otherwise healthy

- **Pityriasis alba**
- **Keratosis pilaris**
- **Ichthyosis vulgaris**
- Lichen simplex chronicus
- Contact dermatitis
- Psoriasiform overlap
- Seborrheic dermatitis
- Tinea
- Scabies

Unhealthy

- Immune deficiencies
- Nutritional deficiencies
- Cutaneous T-cell lymphoma
- Genodermatoses

Siegfried EC, Hebert AA. *J Clin Med.* 2015;4:884-917. Wine SJ, Steinberg S. *Can Fam Physician.* 1972;18:65-66. Purohit MP. Lichen simplex chronicus. DoveMed. 2018 (www.dovemed.com/diseases-conditions/lichen-simplex-chronicus). Fields D. NEWS Medical. 2019 (www.news-medical.net/health/Types-of-Genodermatoses.aspx). All URLs accessed January 26, 2021.

Patient Impact

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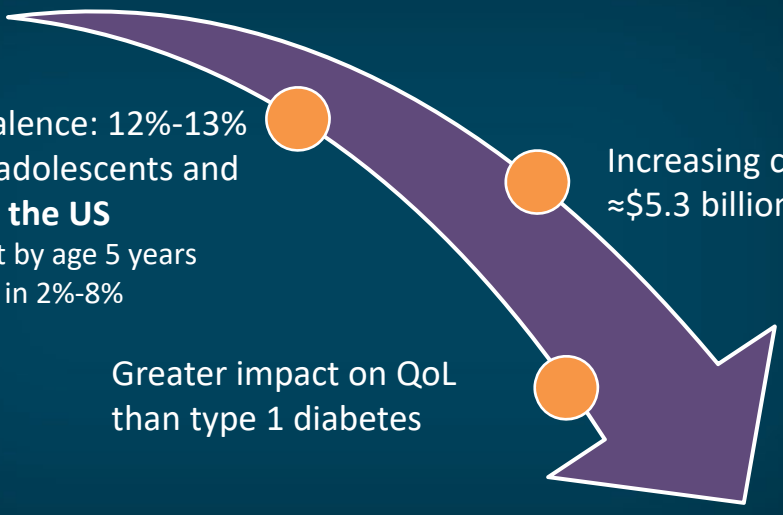
Please click here to watch a brief animation looking at the 5 I's and patient-centered treatment

Impact of AD



Increasing prevalence: 12%-13% in children and adolescents and >7% in adults in **the US**

- 85% present by age 5 years
- Adult-onset in 2%-8%

Increasing costs: ≈$5.3 billion/year

Greater impact on QoL than type 1 diabetes

Silverberg JI. *Ann Allergy Asthma Immunol.* 2019;123:144-151. Silverberg JI, et al. *Ann Allergy Asthma Immunol.* 2018;121:340-347. Drucker AM, et al. *J Invest Dermatol.* 2017;137:26-30. Arkwright PD, et al. *J Allergy Clin Immunol Pract.* 2013;1:142-151.

Associated Morbidities

Atopic	Others[1,2,6,7]
• **Allergic rhinitis** (≈50% prevalence)[1] • **Allergic conjunctivitis**[2] • **Asthma** (≈22%-30% prevalence)[1,3,4] • **Primary eosinophilic gastrointestinal disorders**[2] • **Food allergy**[5]	• **Mental/behavioral health** • **Skin infections** • **Allergic contact dermatitis** • **Immune deficiency** • **Cataracts**

1. Whiteley J, et al. *Curr Med Res Opin.* 2016;32:1645-1651. 2. Silverberg JI. *Cutis.* 2019;104:142-143. 3. Silverberg JI, Hanifin JM. *J Allergy Clin Immunol.* 2013;132:1132-1138. 4. Wang D, Beck LA. *Am J Clin Dermatol.* 2016;17:425-443. 5. Greenhawt M. *Allergy Asthma Proc.* 2010;31:392-297. 6. Silverberg NB. *Cutis.* 2016;97:408-412. 7. De Benedetto A, et al. *J Invest Dermatol.* 2009;129:14-30.

Management

Standard Treatment Strategies: 5 "I"s

Impaired skin barrier function

Ointment emollient, wet wraps, ambient humidity

Itch (and scratching)

Non-sedating antihistamines for urticarial component, N-acetylcysteine*

Interrupted sleep

Short-term sedating antihistamines, sleep hygiene

Inflammation

- Bleach baths
- Avoid topical allergens
- TCSs/calcineurin inhibitors/ crisaborole
- Systemic anti-inflammatory medication

Infection/risk (*Strep, HSV, molluscum, tinea*)

- Bleach baths
- Surveillance testing
- Appropriate antimicrobial medication

**N-acetylcysteine not FDA approved for AD.*

FDA = US Food and Drug Administration; HSV = herpes simplex virus; TCS = topical corticosteroid.

Original concept acknowledgement to Dr. Margaret Lee and Dr. Lisa Shen. Lio PA, et al. *J Allergy Clin Immunol Pract.* 2014;2:361-369. Janeczek M, et al. *J Clin Aesthet Dermatol.* 2019;12:20-26.

Assessment of Disease Severity

- Validated AD-specific severity scales
  - **SCORAD** (**SCOR**ing **A**topic **D**ermatitis index): includes extent, sleep, and itch
  - **EASI** (**E**czema **A**rea and **S**everity **I**ndex): includes extent
  - **IGA** (**I**nvestigator's **G**lobal **A**ssessment): simple 0- to 5-point scale
- Modified forms used in clinical trials
- SCORAD and EASI are too cumbersome for clinical practice
- IGA is simple, useful, and may be required for insurance authorization

Siegfried EC, et al. *Pediatr Dermatol.* 2018;35:303-322. Chopra R, et al. *Br J Dermatol.* 2017;177:1316-1321. Brunk D. *Dermatol News.* 2020 (www.mdedge.com/dermatology/article/220713/atopic-dermatitis/expert-discusses-her-approach-using-systemic-agents). Accessed January 26, 2021. Silverberg JI, et al. *Br J Dermatol.* 2019;181:80-87.

AD Severity Informs *Customized* Stepped Therapy

	MILD	MODERATE	SEVERE
Maintenance	**Skin care** Daily bath (bleach optional) Liberal, frequent moisturizer use **Trigger avoidance** Irritants, potential topical allergens, low ambient humidity **Consider comorbidities**	**Add bleach baths, wet wraps** **Maintenance TCI or crisaborole** • Up to twice daily • Monitor quantities **Intermittent TCS** • Medium potency • 15 days/month • Monitor quantities	**Specialist referral** **Consider comorbidities** **Short-term aggressive treatment** • Wet wraps • Hospitalization **Phototherapy** **Systemic immunosuppressants** • Cyclosporine A* • Methotrexate* • Mycophenolate mofetil* • Azathioprine* **Dupilumab**
Flare	**TCS** • Low-to-medium potency • PRN up to 15 days/month • Monitor quantities	**TCS** • Medium-to-high potency • Consider complicating factors	**Other considerations** • Nonadherence • Infection • Misdiagnosis • Contact allergy

PRN = as needed; TCI = topical calcineurin inhibitor.

*Not FDA approved for AD.

Adapted from Boguniewicz M, et al. *Ann Allergy Asthma Immunol*. 2018;120:10-22.e2.

Emollient Options

- Affordability
- Tactile acceptance
- Low allergenicity
- Options
  - Non-allergenic: plain petroleum jelly, plain mineral oil (beware tocopherol), Vanicream™ Moisturizing Ointment (formerly Vaniply™ Ointment)
  - Physiologic lipids (eg, CeraVe®, EpiCeram®); equimolar ratio of ceramides, cholesterol, fatty acids for benefit
  - pH <5 (A-Mantle™)
  - Colloidal oatmeal (Aveeno®)
  - Prescription skin-barrier devices (Hylatopic®, Mimyx®, Atopiclair®)
- Wet wraps

Elias PM, et al. *Skin Pharmacol Physiol.* 2019;32:1-7. Dhandha MM, Siegfried EC. *Skin.* 2017;1:48-51 (www.jofskin.org/index.php/skin/article/download/4/pdf). URLs accessed January 26, 2021. Cincinnati Childrens. (https://www.cincinnatichildrens.org/health/e/eczema). Accessed January 26, 2021.

Safe and Effective Use of Topical Medications in Children

How much, how often, how to monitor?

Medication	Quantity	Frequency	Possible Safety Monitoring	Prescribing Guideline
Corticosteroids	15-60 g/month (based on age/body site/potency)	15 days/month	AM cortisol	Potency and age group specific
Calcineurin inhibitors	100-200 g/month; Supplied in 30- to 100-g tubes	BID	Tacrolimus peak	≥2 years*
PDE-4 inhibitors	100-200 g/month; Supplied in 60- to 100-g tubes	BID	—	≥3 months

Refer to individual medication prescribing information for approved indications and guidelines for treatment.

*Tacrolimus 0.03% is indicated for children 2-15 years; 0.1% is indicated for adults.

AM = morning; BID = twice daily; PDE-4 = phosphodiesterase-4.

Carr WW. *Paediatr Drugs*. 2013;15:303-310. Eichenfield LF, et al. *J Am Acad Dermatol*. 2014;71:116-132. Schwartz RA. Pediatric atopic dermatitis medication. Medscape. 2020 (https://emedicine.medscape.com/article/911574-medication). Accessed January 26, 2021. Pharmacist's Letter. 2012 (http://snapaprn.org/docs/SNAP%20Comparison%20of%20Topical%20Steroids.pdf). Accessed January 26, 2021. National Eczema Society. Factsheet. 2019 (https://eczema.org/wp-content/uploads/Topical-steroids-Sep-19-1.pdf). Accessed January 26, 2021.

Optimizing Long-Term Control

Address only intermittent flares

Prescription antibiotics, potent TCS, and prednisone

Yields alternating roller-coaster improvement and flares

Practice daily skin care

Use adequate amounts of topical medication

Recognize and avoid triggers

Maintains control

Wollenberg A, et al. *J Eur Acad Dermatol Venereol*. 2016;30:729-747. Torrelo A, et al. *Actas Dermosifiliogr*. 2013;104:409-417. Thaci D, et al. *J Eur Acad Dermatol Venereol*. 2010;24:1040-1046. Sidbury R, et al. *J Am Acad Dermatol*. 2014;71:1218-1233.

Implementing Shared Decision-Making in Practice

Invite the patient to participate

↓

Present options

↓

Provide information on benefits and risks

↓

Assist patients in evaluating options based on their goals and concerns

↓

Facilitate deliberation and decision-making

↓

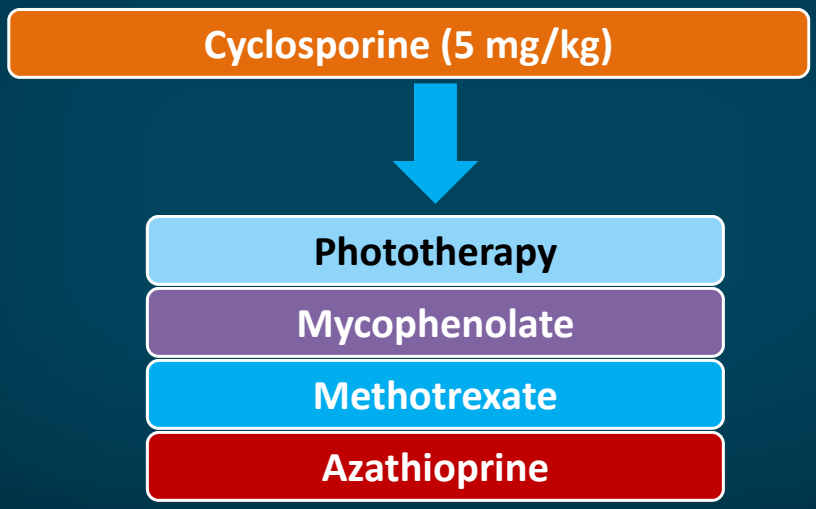
Assist patients to follow through on the decision

National Learning Consortium. Shared decision making. 2013. (www.healthit.gov/sites/default/files/nlc_shared_decision_making_fact_sheet.pdf). Accessed 2/11/2020.

New and Targeted Therapy

Mark Boguniewicz, MD
Professor, Division of Allergy-Immunology
Department of Pediatrics
National Jewish Health
and University of Colorado School of Medicine
Denver, CO

Conventional Systemic Treatment Algorithm



Cyclosporine, mycophenolate, methotrexate, and azathioprine are not FDA approved for AD.

Discontinuation Rates of Immunosuppressive Therapies

	CsA (N=356) (at 6-Year Follow-up)[1]	AZA (N=94) (at 3-Year Follow-up)[2]	MTX (N=89) (at 2-Year Follow-up)[3]	EC-MPS (N=84) (at 3-Year Follow-up)[2]
AE	22%	36%	25%	14%
Inefficacy	16%	19%	15%	38%
Controlled AD	26%	11%	6%	11%
Other reasons	11%	6%	7%	4%

Cyclosporine, mycophenolate, methotrexate, and azathioprine are not FDA approved for AD.

AE = adverse event; AZA = azathioprine; CsA = cyclosporine A; EC-MPS = enteric-coated mycophenolate sodium; MTX = methotrexate.

1. van der Schaft J, et al. *Br J Dermatol.* 2015;172:1621-1627. 2. van der Schaft J, et al. *Br J Dermatol.* 2016;175:199-202. 3. Politiek K, et al. *Br J Dermatol.* 2016;174:201-203.

Dupilumab

- A human monoclonal antibody against IL-4 receptor α
- Inhibits signaling of IL-4 and IL-13
- FDA approved for moderate-to-severe AD in adults in March 2017, for aged ≥12 years in 2019, and for aged ≥6 years in 2020
- Also FDA approved for moderate-to-severe eosinophilic asthma (≥12 years) and for add-on maintenance therapy for CRSwNP (adults)
- SC injection every 2 or 4 weeks, based on patient weight

CRSwNP = chronic rhinosinusitis with nasal polyposis; SC = subcutaneous.

Dupilumab (Dupixent®) PI 2020 (https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf). Press release. May 26, 2020 (https://www.prnewswire.com/news-releases/fda-approves-dupixent-dupilumab-as-first-biologic-medicine-for-children-aged-6-to-11-years-with-moderate-to-severe-atopic-dermatitis-301065273.html). All URLs accessed January 21, 2021.

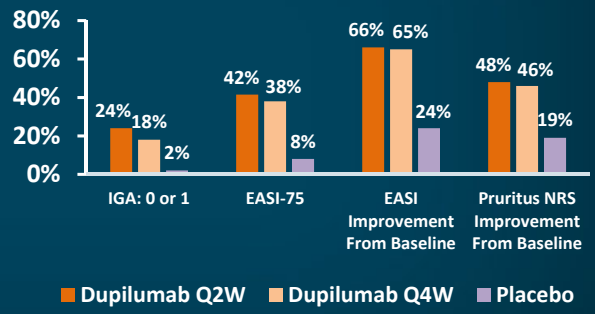
Dupilumab: Select Clinical Trials in Pediatric Patients

Phase 3 Trial (Jul 2020)[1]
- 16-week trial in 251 patients aged 12-17 years
- Dupilumab 200 or 300 mg Q2W
- Dupilumab 300 mg Q4W
- Placebo

Phase 3 Trial (Nov 2020)[2]
- 16-week trial of 367 patients aged 6-11 years with concomitant TCS
- 67%-70% achieved EASI 75 (27% PBO)
- 31%-33% achieved IGA 0/1 (11% PBO)
- 51%-58% achieved ≥4-pt itch reduction (12% PBO)

Additional Trials
- Case series (6 patients; 7-15 years): efficacy/safety over 8.5 months[3]
- Phase 3 open-label extension (6 months - 17 yrs): underway[4]
- Phase 2 and 3 (6 months-6 years): underway

Dupilumab vs Placebo: Clinical Endpoints

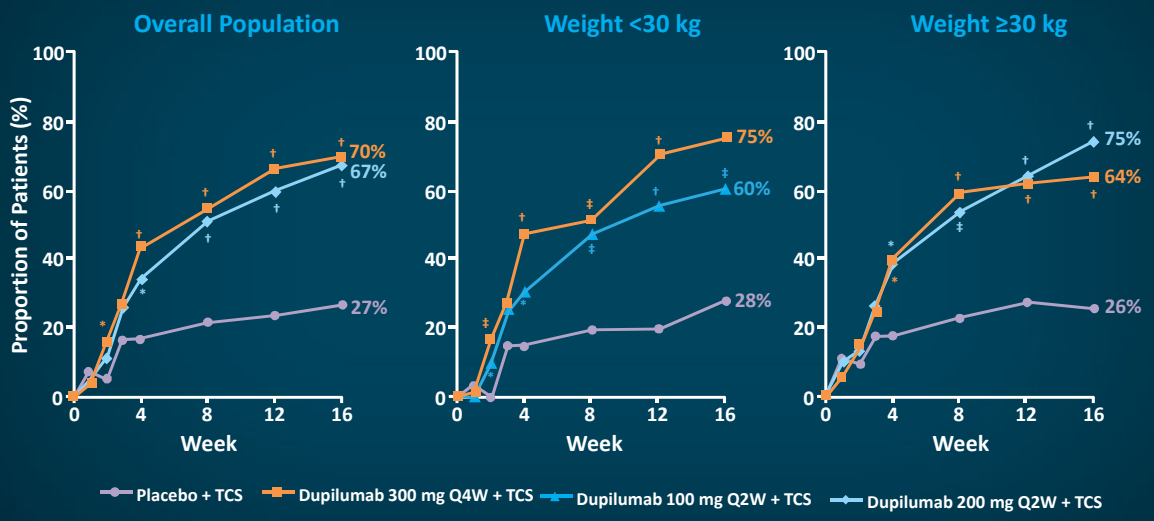


All *P*< .001 vs placebo; dupilumab is FDA approved for moderate-to-severe AD in patients aged ≥6 years.

NRS = Numeric Rating Scale; Q2W = every 2 weeks; Q4W = every 4 weeks; PBO = placebo.

1. Simpson E, et al. *JAMA Dermatol*. 2020;156(1):44-56. 2. Paller A, et al. JAAD. 2020;83(5):1282-93. 3. Treister AD, et al. *Pediatr Dermatol*. 2019;36:85-88. 4. https://clinicaltrials.gov/ct2/show/NCT02612454

Proportions of Children Aged 6-11 Years Achieving EASI-75



*$P \leq .05$; †$P \leq .0001$; ‡$P \leq .001$ vs placebo + TCS.

Paller AS, et al. *J Am Acad Dermatol*. 2020;83:1282-93.

Dupilumab Adolescent Data

- 12- to 17-year-olds with moderate-to-severe AD, 1:1:1 placebo, 300 mg SC every 4 weeks or 200 mg/300 mg SC every 2 weeks
- For most endpoints, patients with the every-2-week regimen was superior to patients with the every-4-week regimen
- Safety profile was acceptable: Conjunctivitis and injection site reactions were higher vs placebo, but AD exacerbation and non-herpetic skin infections were lower vs placebo
- Both placebo-corrected efficacy and safety of dupilumab in adolescents were similar to those in adults

Simpson EL, et al. *JAMA Dermatol*. 2020;156:44-56.

Dupilumab: Safety

- It appears much safer than conventional immunosuppressants, but other potential considerations include:
  - Conjunctivitis in up to 10% of patients[1,2]
    - Higher rates in those with higher baseline AD severity and/or history of conjunctivitis
    - Mostly mild to moderate
    - In dupilumab trials in other type 2 diseases (eg, asthma, CRSwNP), incidence similar to placebo
  - Head/neck erythema[3,4]
  - Injection site reaction/systemic reactions
  - Cost may be a factor
  - Injection

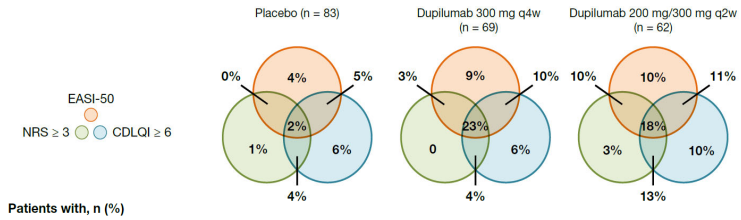
1. Akinlade B, et al. *Br J Dermatol*. 2019;181:459-473. 2. Achten R, et al. *J Allergy Clin Immunol Pract*. 2020;S2213-2198(20)31091-6.
3. de Beer F, et al. *JAAD Case Rep*. 2019;5:888-891. 4. de Wijs L, et al. *Br J Dermatol*. 2020;183:745-749.

Therapeutic Targets in AD: Beyond IGA ≤1

IGA score of ≤1 (clear/almost clear skin) is the standard measure in clinical trials[1,2]

- Outcomes measures in those with **IGA ≥1** are still important!
- EASI, Peak Pruritus NRS, affected BSA, POEM, and DLQI
- IGA ≤1 endpoint underestimates clinically relevant treatment effects

Patients in IGA >1 subgroup who achieved EASI-50, ≥3-point improvement in Peak Pruritus NRS, or ≥6-point improvement in CDLQI



Patients with, n (%)	Placebo (n = 83)	Dupilumab 300 mg q4w (n = 69)	Dupilumab 200 mg/300 mg q2w (n = 62)
EASI-50 only	3 (4%)	6 (9%)	6 (10%)
EASI-50 and CDLQI ≥ 6	4 (5%)	7 (10%)	7 (11%)
CDLQI ≥ 6 only	5 (6%)	4 (6%)	6 (10%)
CDLQI ≥ 6 and Peak Pruritus NRS ≥ 3	3 (4%)	3 (4%)	8 (13%)
Peak Pruritus NRS ≥ 3 only	1 (1%)	0	2 (3%)
Peak Pruritus NRS ≥ 3 and EASI-50	0	2 (3%)	6 (10%)
EASI-50 and CDLQI ≥ 6 and NRS ≥ 3	2 (2%)	16 (23%)	11 (18%)

BSA = body surface area; CDLQI = Children's DQLI; DLQI = Dermatology Quality of Life Index; EASI-50 = 50% improvement from baseline in EASI; POEM = patient-oriented eczema measure.

1. Silverberg J, et al. *Br J Dermatol*. 2019;181:80-87. 2. Paller A, et al. *Am J Clin Dermatol*. 2020;21:119-131.

Does Dose Reduction Maintain Efficacy?

Worm et al, 2020:

- 422 adult patients responding to dupilumab, and continuing *once weekly or once every 2 weeks* maintained optimal efficacy
- EASI 75:
  - Negligible changes with above dosing regimens (−0.06%; $P < .001$ vs placebo)
  - Dose-dependent worsening with other doses (Q4wks: −3.84%; Q8wks: −6.84%)
- Adverse events: 70.7% weekly or Q2wks; 73.6% Q4wks; 75.0% Q8wks; 81.7% placebo.
- Similar conjunctivitis rates
- Antidrug antibody incidence lower with more frequent regimens (weekly: 1.2%; Q2wks: 4.3%; Q4wks: 6.0%; Q8wks: 11.7%; PBO: 11.3%)

Worm M, et al. *JAMA Dermatol*. 2020;156(2):131-43.

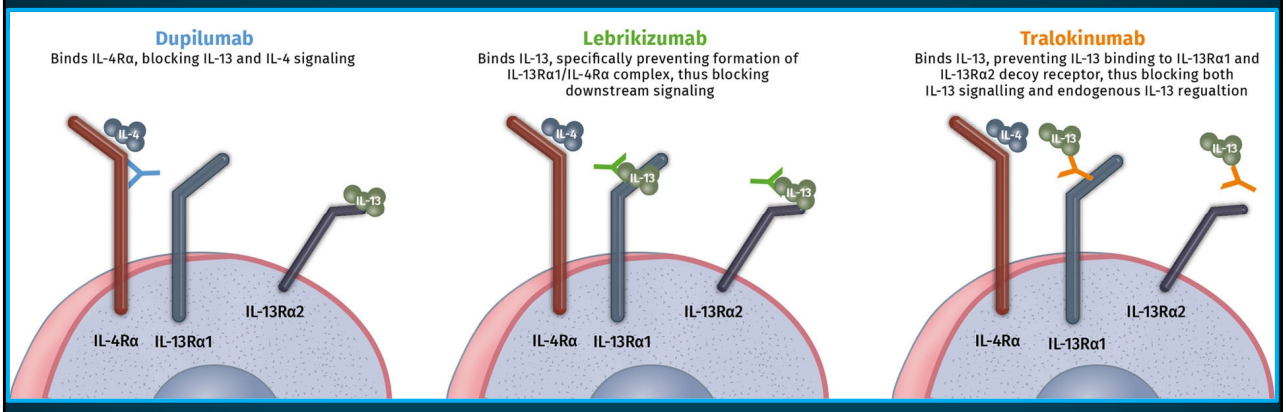
Pipeline: Selected Agents

Drug	Target
TOPICAL	
Delgocitinib	JAK1, JAK2, JAK3, and TYK2
E6005	PDE-4
OPA-15406	PDE-4
Ruxolitinib	JAK1 and JAK2
Tapinarof	AHR ligand
ORAL	
Abrocitinib	JAK1
ASN002	JAK
Baricitinib	JAK1 and JAK2
Upadacitinib	JAK1
SYSTEMIC INJECTION	
Lebrikizumab	IL-13
Nemolizumab	IL-31
Tralokinumab	IL-13

AHR = aryl hydrocarbon receptor; TYK2 = tyrosine kinase 2.

National Eczema Association. Eczema treatments (https://nationaleczema.org/research/eczema-treatment-research). Accessed January 26, 2021. Vakharia PP, Silverberg JI. *Lancet Child Adolesc Health*. 2019;3:343-353.

Not Identical Mechanisms



Lebrikizumab does not prevent binding to Rα2 → no increased levels of IL-13

Tralokinumab prevents the binding to Rα2 → thus increased total IL-13 levels

What does this mean?

We don't know!

Rα = receptor α.

Moyle M, et al. *Exp Dermatol*. 2019;28:756-768.

Emerging Agent: Tralokinumab (Anti–IL-13)

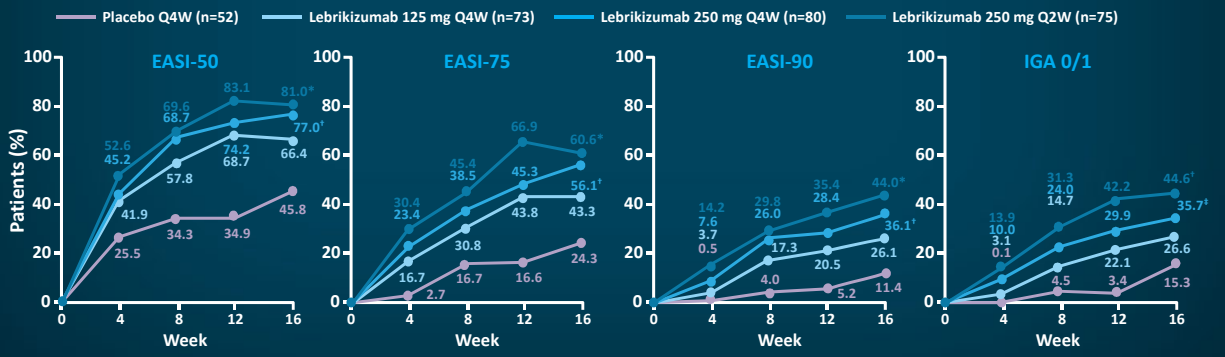
Study	Treatment	IGA 0/1 Response at Week 16	EASI-75 Response at Week 16
ECZTRA 1[1]	Tralokinumab	16%	25%
	Placebo	7%	13%
	Placebo-adjusted response	**9%**	**12%**
ECZTRA 2[1]	Tralokinumab	22%	33%
	Placebo	11%	11%
	Placebo-adjusted response	**11%**	**22%**
ECZTRA 3[2]	Tralokinumab	39%	56%
	Placebo	26%	36%
	Placebo-adjusted response	**13%**	**20%**

- ECZTRA 1/2: 51%-60% maintained response over 52 weeks
- ECZTRA 3: 78%-93% maintained response over 32 weeks

1. Wollenberg A, et al. *Br J Dermatol*. 2020;Sep 30. doi:10.1111/bjd.19574. 2. Silverberg JI, et al. *Br J Dermatol*. 2020 Sep 30. doi:10.1111/bjd.19573.

Emerging Agent: Lebrikizumab (Anti–IL-13)

- A phase 2, randomized, monotherapy trial in 280 adults with moderate-to-severe AD inadequately controlled with TCS
- At week 12, significantly more patients achieved EASI-50/75/90 with lebrikizumab 250 mg every 2 weeks or every 4 weeks vs placebo

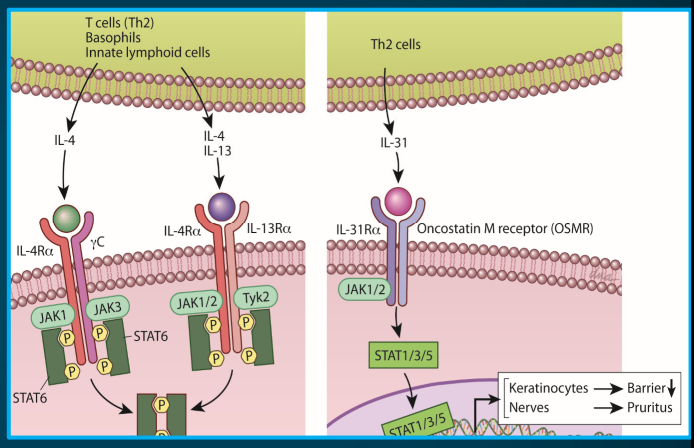


EASI-90 = 90% improvement from baseline in EASI.*$P < .001$; †$P < .01$; ‡$P < .05$ vs placebo.

Guttman-Yassky E, et al. *JAMA Dermatol*. 2020:156:411-420.

Janus-Associated Kinase (JAK)

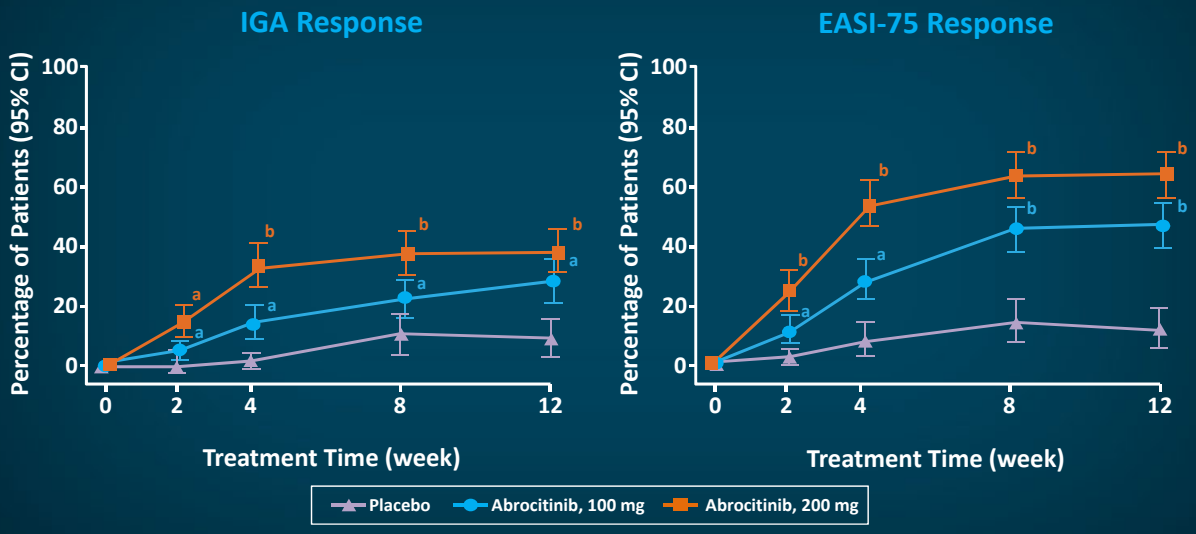
- The JAK-STAT pathway is a conserved master regulator of immunity and myeloproliferation
- JAK inhibitors are used to treat several hematologic and inflammatory diseases
- Small molecules (including JAK inhibitors) show improvement in AD disease scores, patient-reported outcomes, and QoL



STAT = signal transducer and activator of transcription.

Cotter DG, et al. *J Am Acad Dermatol*. 2018;78(3 suppl 1):S53-S62. Mobasher P, et al. *J Dermatolog Treat*. 2019;30:550-557. Paller AS, et al. *J Allergy Clin Immunol*. 2017;140:633-643.

Abrocitinib

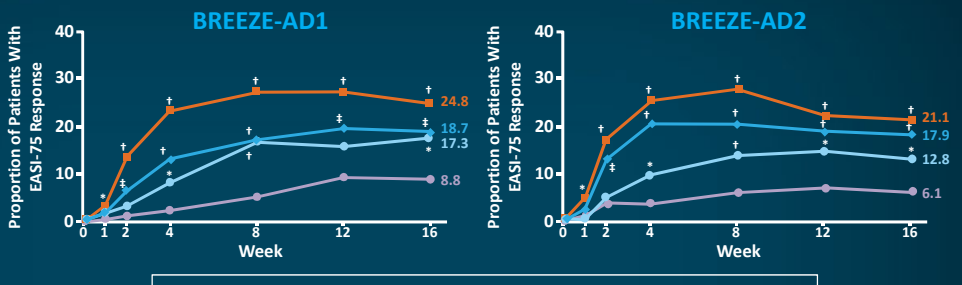


[a]*P*<.05; [b]*P*<.001 vs placebo.

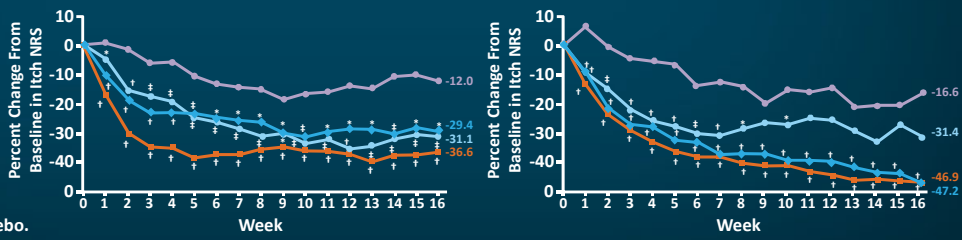
Silverberg JI, et al. *JAMA Dermatol*. 2020;156:863-873.

Baricitinib: BREEZE-AD1/AD2

EASI-75 Response



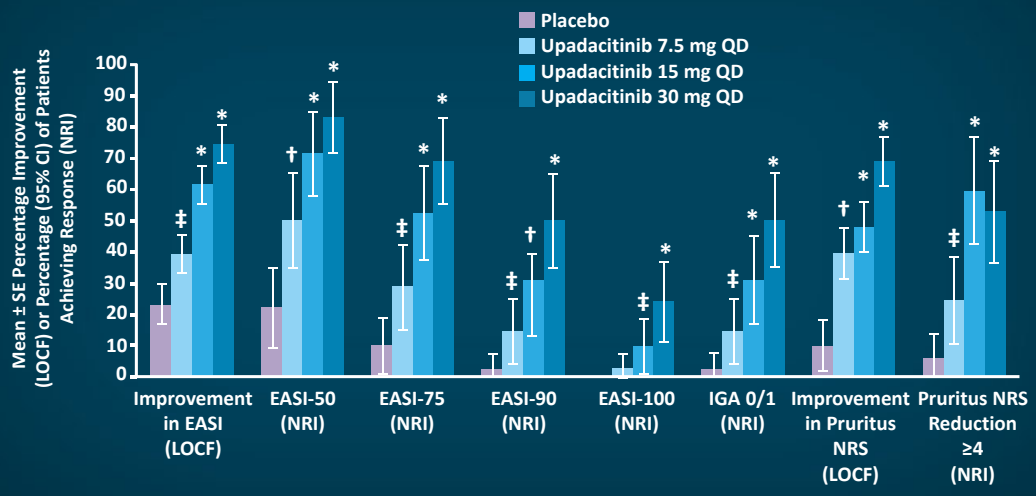
% Change From Baseline: Itch NRS



*P≤ .05; †P≤ .001; ‡P≤ .01 vs placebo.

Simpson EL, et al. *Br J Dermatol*. 2020;183:242-255.

Upadacitinib: Outcomes at Week 16 in Adults



*$P \leq .001$; †$P \leq .01$; ‡$P \leq .05$ for upadacitinib vs placebo.

LOCF = last observation carried forward; NRI = nonresponder imputation; QD = daily; SE = standard error.

Guttman-Yassky E, et al. *J Allergy Clin Immunol*. 2020;145:877-884.

JAK Inhibitors: Topical

- **Delgocitinib**
  - Dose ranging (0.25%-3% ointment) twice daily vs vehicle vs tacrolimus 0.1% x 4 weeks
  - All doses > vehicle in EASI (73% vs 12% in 3% group)
  - Tacrolimus = 62% reduction
  - No serious AEs
- **Ruxolitinub**
  - Phase 2 randomized, dose-ranging, vehicle- and active-controlled study to evaluate safety and efficacy in adult patients
    - 1.5% twice-daily group > vehicle in EASI (71.6% improvement at 4 weeks) and noninferior to triamcinolone cream 0.1%
  - Phase 1 study in children aged 2-7 years and 2 phase 3 studies in patients aged ≥12 years (TruE-AD1 and TruE-AD2) are underway

Nakagawa H, et al. *Br J Dermatol*. 2018;178:424-432. Bissonnette R. *Br J Dermatol*. 2018;178:321.

JAK Inhibitors: Key Adverse Events
≥3% (any dose) and >Placebo

- **Abrocitinib[1]**
  - Nausea, nasopharyngitis, headache, URTI, dermatitis atopic, acne, vomiting, upper abdominal pain, elevated CPK, folliculitis, thrombocytopenia
- **Baricitinib[2]**
  - Nasopharyngitis, headache, diarrhea, herpes simplex, URTI, influenza, oral herpes, UTI, folliculitis
- **Upadacitinib[3]**
  - URTI, AD worsening, acne, headache, nasopharyngitis, elevated CPK, nausea, diarrhea, influenza, oropharyngeal pain

- Serious AE's were rare, similar to placebo, and usually unrelated to treatment

URTI = upper respiratory tract infection; CPK = creatinine phosphokinase; UTI = urinary tract infection

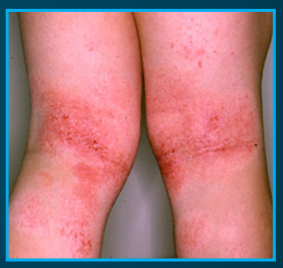
1. Silverberg J, et al. *JAMA Dermatol*. 2020;156(8):873. 2. Bieber T, et al. JEADV. 2021;35:476-85. 3. Guttman-Yassky E, et al. *J Allergy Clin Immunol*. 2020;145:877-884.

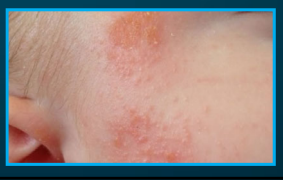
Case Study

Peter A. Lio, MD
Clinical Assistant Professor, Dermatology and Pediatrics
Northwestern University Feinberg School of Medicine
Medical Dermatology Associates of Chicago
Chicago, IL

Case Study

A 3-year-old child comes to your clinic after several months of experiencing an itchy rash on the neck, face, upper back, antecubital fossae, upper and lower legs with predilection for popliteal fossae. Treatments tried so far include essential oils without improvement.





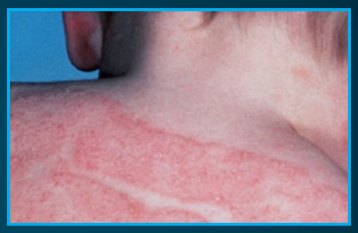
The next best step in treatment would be:

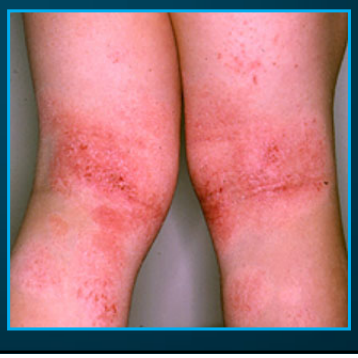
A) Emollient barrier cream
B) Topical therapy, emollient, and gentle skin care
C) Oral corticosteroids
D) Systemic therapy
E) Referral for allergy testing

Photos: National Eczema Association

Atopic Dermatitis

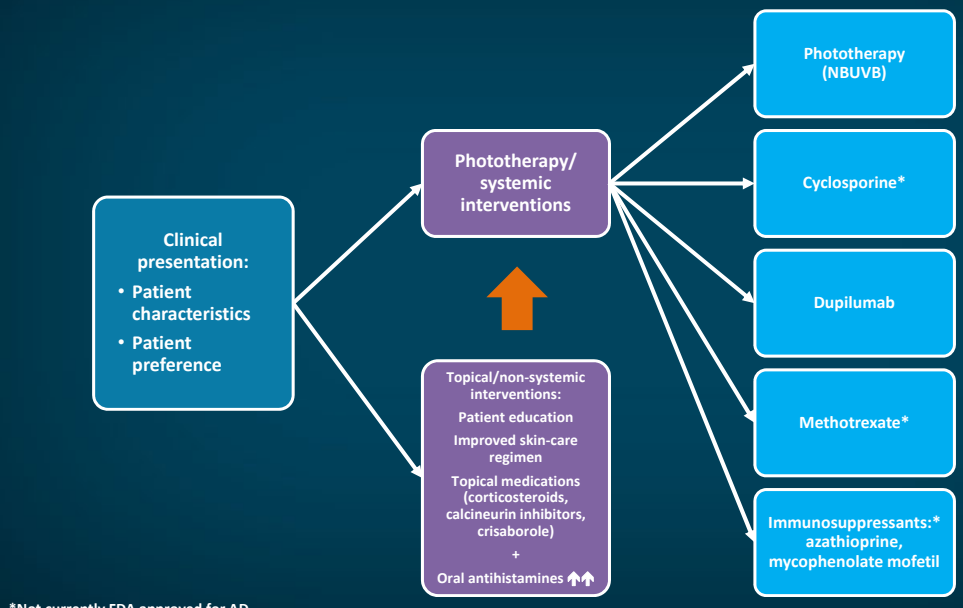
- Gentle skin care—avoid irritants (fragrance, etc)
- Emollient to replace defective barrier—twice daily
- Topical therapy: TCSs, topical calcineurin inhibitors, etc.
- ± Bleach baths, topical antibiotics
- Oral corticosteroids can lead to AD flares upon treatment withdrawal





Photos: National Eczema Association

Management and Treatment Decisions



*Not currently FDA approved for AD

Conclusions

- AD is a chronic disease with a significant impact on QoL
- A **pro**active approach is more effective than **re**active treatment
- Proactive treatment is stepwise and based on severity
- Management can be ***difficult*** and potentially complicated by conflicting messages from different care-team members (clinicians and family)
- **Adherence** is **key** to successful therapy
- Evolving biomarkers and targeted treatments promise to revolutionize treatment

Thank You!

Moderate-to-Severe Atopic Dermatitis:

Targeting the Underlying Inflammatory Processes to Improve Patient Outcomes

YOUTUBE: 360° VIRTUAL ANIMATIONS

ATOPIC DERMATITIS PATIENT FACTORS: **https://youtu.be/dq_LngHSPFI**

ATOPIC DERMATITIS PATHOLOGY: **https://youtu.be/X6w3OZEIMLA**

Use your device's QR code scanner to view this 360° content in the **YOUTUBE APP!**

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Moderate-to-Severe Atopic Dermatitis:

Targeting the Underlying Inflammatory Processes to Improve Patient Outcomes

For more information and additional resources please visit

https://atopicdermatitis.posterprogram.com