Atopic Dermatitis: 2023 AAD Guidelines

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Disclosures

- Investigator: Regeneron (Dupilumab), Pfizer (Abrocitinib); Galderma (Nemolizumab); UCB (Certrolizumab); Castle
- Consultant: Lilly (Tralokinumab); Leo (Lebrikizumab); Arcutis (Roflumilast); Dermavent (Tapinarof)
- Speaker’s Bureau: Beiersdorf
- My own opinions unless otherwise stated

Outline

- Comorbidities beyond the atopic march
- COVID and AD
- Therapeutic advances
  - Topical
  - Systemic
- Pipeline

American Academy of Dermatology AD Guidelines

- 2014: Four part publication
  - Diagnosis and Assessment: Eichenfield et al
  - Topical therapies: Eichenfield et al
  - Phototherapy and systemic therapies: Sidbury et al
  - Prevention of flares and adjunctive therapies: Sidbury et al

- 2022: Planned 4 part publication
  - Comorbidities: Davis DM et al, JAAD, 2022
  - Topical Therapy: under review, planned publication Dec 2022
  - Systemic Therapy: manuscript being prepared; planned Mar 2023
  - Pediatrics: Literature search complete, planned late 2023

2022 Guideline Methodology

- 12 committee members
  - 11 dermatologists (adult and pediatric), 1 allergist/pediatrician

- GRADE to assess strength of evidence
  - **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment and **E**valuation
  - Systematic and transparent effort to define quality of evidence (Used by UpToDate among many other organizations)
  - GRADE for prognosis used to assess comorbidity literature
  - Downgrades
    - Risk of bias
    - Imprecision
    - Inconsistency
    - Indirectness
    - Publication bias

AAD Guidelines: Part 1, Comorbidities

Many recent studies

2014 Guidelines:

- Physicians should be aware of and assess for conditions associated with atopic dermatitis such as rhinitis/conjunctivitis; asthma; food allergy; sleep disturbance; depression; other neuropsychiatric conditions; and it is recommended that physicians discuss them with the patient as part of the treatment/management plan when appropriate

Eichenfield LE et al, Part 1 AD Guidelines J Am Acad Dermatol 2014;70(2):338-51 Table VI

Is associated
Is probably associated
May be associated
Is uncertain
May not

Table III AD Comorbidity Statements

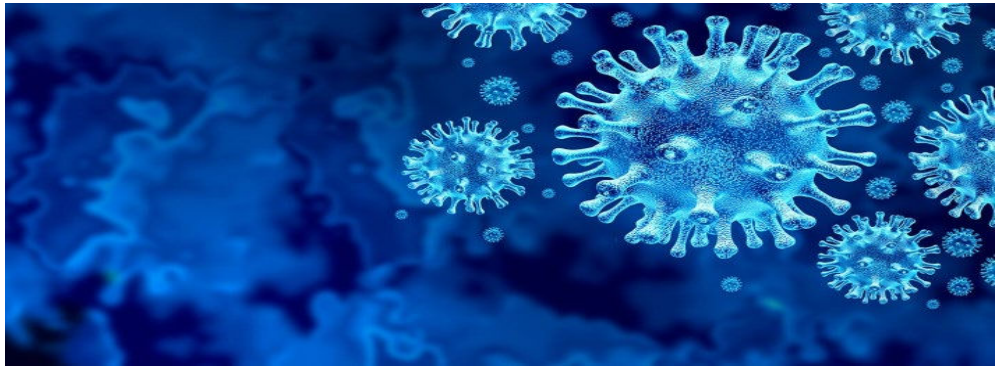
Atopic	Immune	Mental Health	ADHD and Autism spectrum	Cardio Vascular	Metabolic	Bone	Infection
Asthma	Alopecia areata	Depression	ADHD	HTN	Obesity	Osteoporosis	Skin infection
Food allergy	Urticaria	Anxiety	Autism	Coronary artery disease	Dyslipidemia	Fractures	
Allergic rhinitis		Suicide		Myocardial infarction	Diabetes		
Eosinophilic esophagitis		Alcohol abuse		Stroke			

Davis DM et al, JAAD, 2022

AAD Guidelines: Comorbidities takeaway

- No surprise: food allergy, asthma
- Newer associations: ADHD, depression, anxiety, cardiovascular conditions, metabolic syndrome, substance abuse, osteoporosis and fractures
- Actionable: *
  - Situational (eg child not focused in school);
  - Tween or teen (screen for depression);
  - Adult (consider with other CV risk factors)
  - Will non steroidal treatments like dupilumab impact bone outcomes?
  - Consider earlier, more aggressive treatment of inflammation to mitigate extracutaneous outcomes? A la psoriasis

COVID and AD



- Best practice has been evolving
  - Are AD patients at unique risk? (eg as with some infections like HSV)
  - Does dupilumab use impact that risk?
  - Does vaccine pose risks?
  - Does dupilumab prevent normal vaccine response?

- Wu J et al. The risk of COVID 19 infection in patients with atopic dermatitis: a retrospective cohort study. J Am Acad Dermatol 2022;86(1):243245
- Wollenberg A et al. European Task Force on Atopic Dermatitis statement on severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection and atopic dermatitis. JEADV 2020;34(6):e241-2
- Gresham LM et al. An evidence-based guide to SARS-CoV-2 vaccination of patients on immunotherapies in dermatology. J Am Acad Dermatol 2021;84(6):1652-66

Atopic Dermatitis and COVID 19

- Wu et al population-based study
  - Adults 20 years + with AD diagnosis (n = 39,417) prior to 2020 vs no AD diagnosis (n =397,293)
  - Laboratory confirmed COVID cases between Jan 1,2020—April 17, 2021
  - Compare rates of infection
  - AD group RR 1.18 $\{CI_{95}1.12\text{-}1.24\}$ $p < 0.0001$
  - Dupilumab use RR 0.66 $\{CI_{95}0.52\text{-}0.83\}$ $p< 0.0001$ vs no systemic medication
    - IL 4 activity associated with severe COVID
- Limitation: AD patients had higher number of comorbidities

Wu J at al, JAAD, 2022

European Guidelines: Atopic Dermatitis Therapeutic Ladder

Treatment recommendation for atopic eczema: adult

- For every phase, *additional* therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with [1]
- Licensed indication are marked with [2], off-label treatment options are marked with [3]

SEVERE: SCORAD >50 / or persistent eczema	Hospitalization; systemic immunosuppression: cyclosporine A [2], short course of oral glucocorticosteroids[2], dupilumab [1,2], methotrexate[3], azathioprin [3], mycophenolate mofetil [3]; PUVA [1]; alitretinoin [1,3]
MODERATE: SCORAD 25-50 / or recurrent eczema	Proactive therapy with topical tacrolimus [2] or class II or class III topical glucocorticosteroids [3], wet wrap therapy, UV therapy (UVB 311 nm, medium dose UVA1), psychosomatic counseling, climate therapy
MILD: SCORAD <25 / or transient eczema	Reactive therapy with topical glucocorticosteroids class II [2] or depending on local cofactors: topical calcineurin inhibitors [2], antiseptics incl. silver [2], silver coated textiles [1]
BASELINE: Basic therapy	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

PUVA = UVA and psoralens; SCORAD = Severity Scoring of Atopic Dermatitis; UV = ultraviolet. Wollenberg A, et al. *J Eur Acad Dermatol Venereol.* 2018;32(5):657-682.

Topical Therapy

Prescription Non-Steroidal Options

- Topical Calcineurin Inhibitors (TCI)
  - Tacrolimus ointment is the only one indicated for moderate to severe AD
  - Pimecrolimus 1% cream is indicated for mild to moderate AD

- TCIs are not approved < 2 years, carry boxed warning
  - Guideline language---

- Crisaborole 2% ointment, Ruxolitinib 1.5 % cream for mild to moderate

Crisaborole and Infants: CrisADe-CARE 1 study

137 infants (mean age = 13.6 months) mild to moderate AD (> 5% BSA)

- 21 in PK cohort
- Moderate cohort with > 35% BSA included in PK group

- Crisaborole 2% oint BID x 28 days

- Safety (primary), efficacy, PK

- Schlessinger J et al. Safety, Effectiveness, and Pharmacokinetics of Crisaborole in Infants aged 3 to < 24 months with Mild-to-Moderate AD: A phase IV Open-Label Study (CrisADe-CARE1) Am J Clin Dermatol 2020

Crisaborole and Infants: CrisADe-CARE 1 study

- Systemic exposure comparable to patients > 2 yo
- Application site concerns:
  - pain 3.6%
  - discomfort: 2.9%
  - erythema, “reaction”, irritation, pruritus (5.8%)
- No safety signals
- Efficacy similar to phase 3 trials
- FDA approval expanded down to 3 months of age
- Schlessinger J et al. Am J Clin Dermatol 2020

Crisaborole Summary

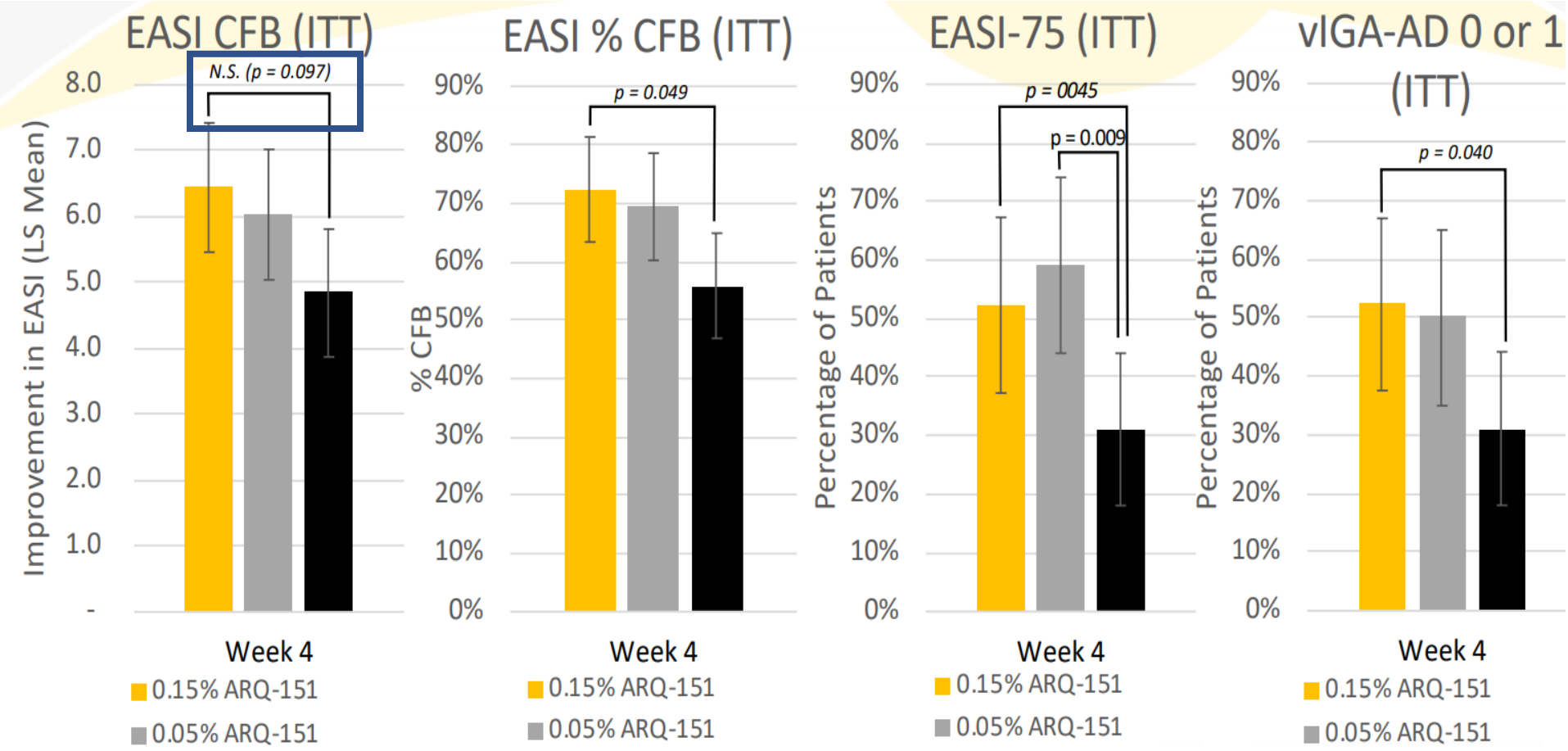
- How well does it work?
  - Variable
  - HC 1%-Triamcinolone 0.1%
  - Surprising benefit on hands; stinging limits eyelids
  - No black box
  - FDA Approved in infants (3 months)

- Stinging
  - More than 4.4%!
  - Strategize to minimize
    - Keep in refrigerator
    - Pre-treat with TCS

- Cost; odd step therapy requirements

Other PDE4 inhibitors*

Phase 2b trial roflumilast (more potent than crisaborole)



- ≥12 yrs old
- 1.5-35% BSA
- IGA 2-3

- No significant application site reactions (burn/sting)
- No evidence of adverse events of oral PDE4 inhibitor

*Other PDE4 inhibitors are E6005 and OP-15406

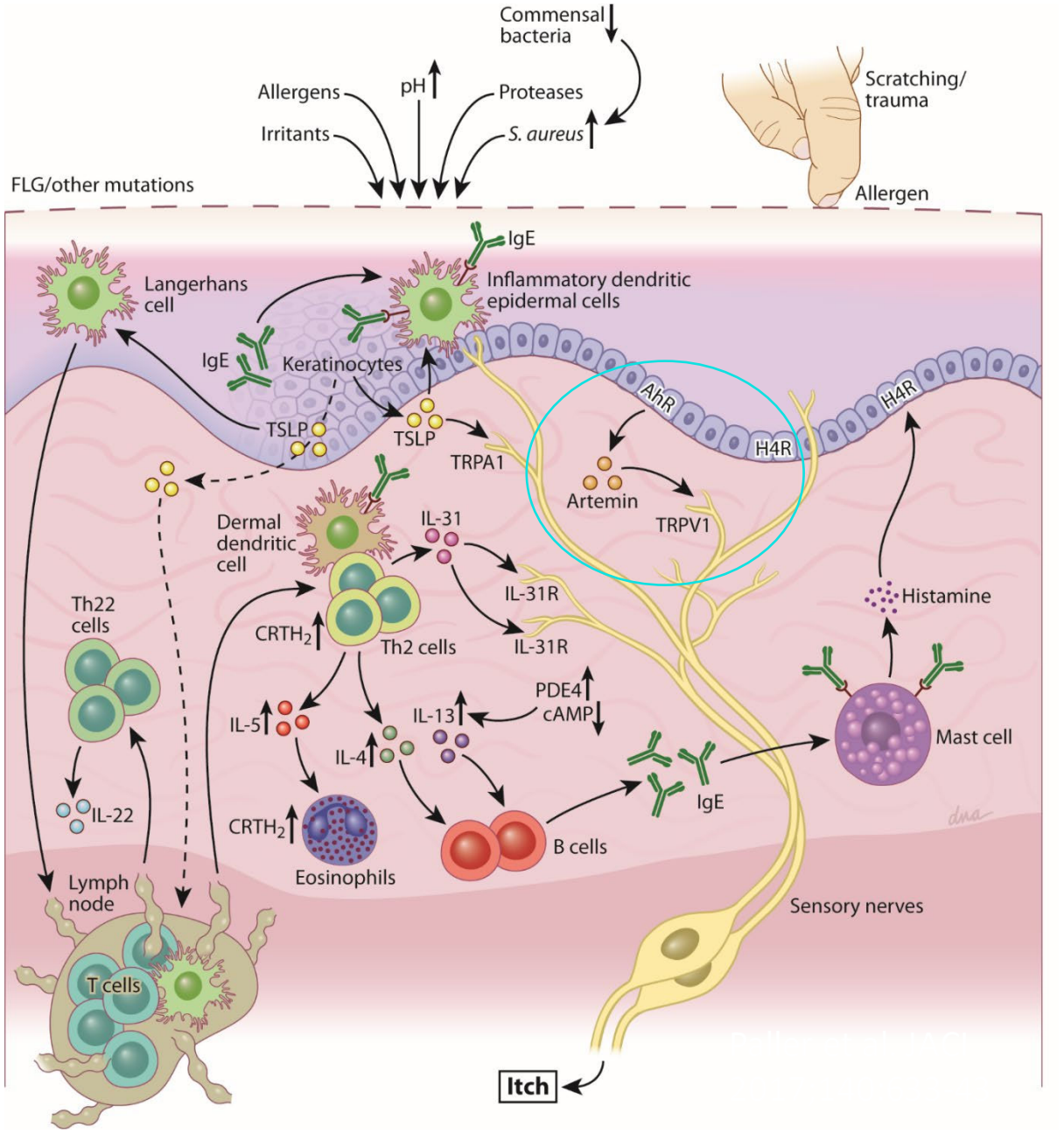
Difamilast 1% ointment in adults: Phase 3

- RDBPC trial in patients aged 15-70 with mild to moderate AD
  - Mean age = 31.7 years
  - 182 patients in each arm
- Difamilast 1% ointment BID vs vehicle x 4 weeks
- Patients who achieved IGA clear or almost clear with at least 2-grade improvement
  - 38.4 vs 12.6% p< 0.0001
- No serious Aes; no application site concerns
- Saeki H et al. Difamilast ointment in adult patients with atopic dermatitis: a phase 3 randomized, double blind, vehicle-controlled trial. J Am Acad Dermatol 2022 Mar;86(3):607-614

Therapeutic Aryl Hydrocarbon Modulating Agent (TAMA)

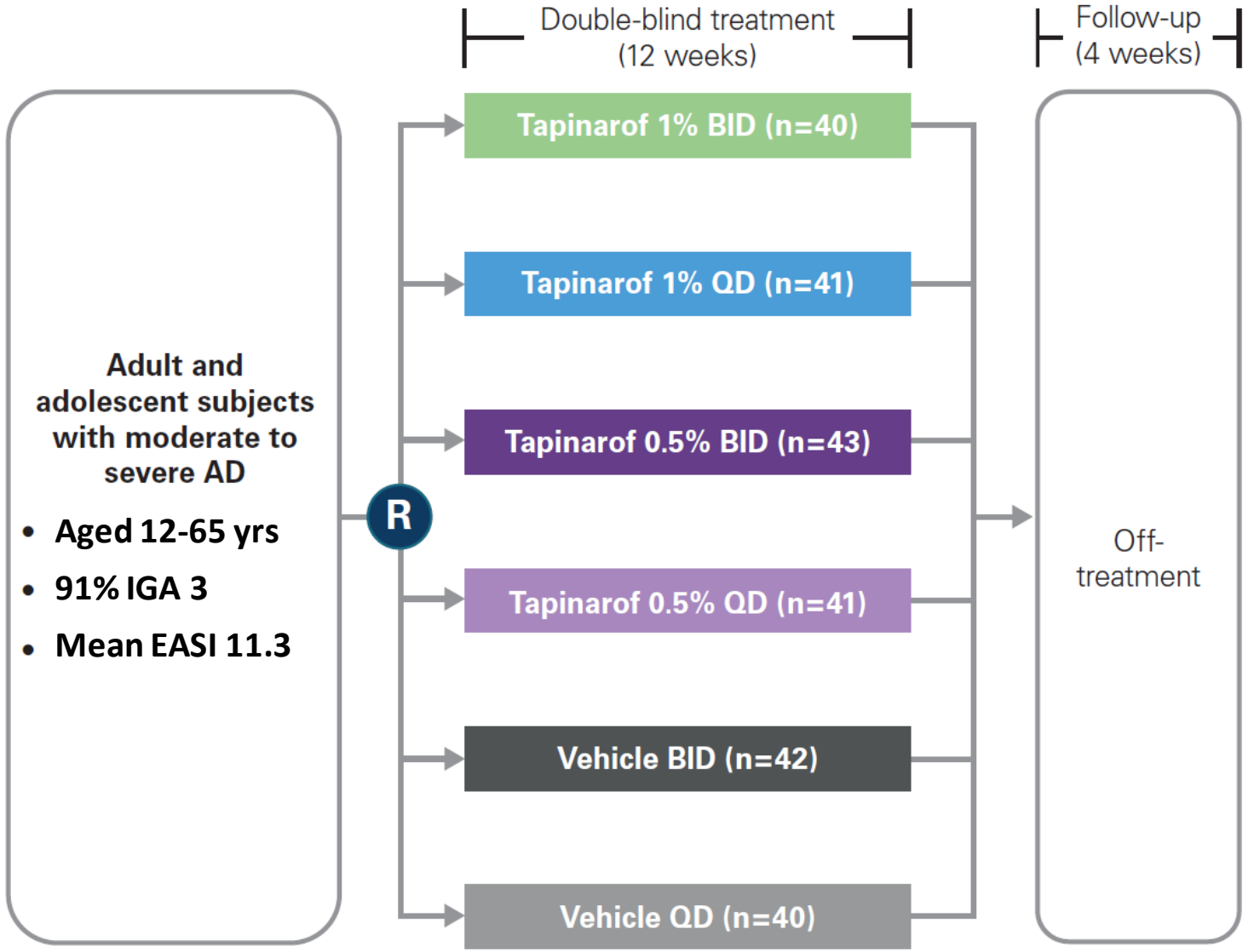
New class that agonizes the epidermal Aryl Hydrocarbon Receptor, leading to inhibition of Th2 pathway cytokines and improvement of skin barrier function, as well as anti-oxidant activity

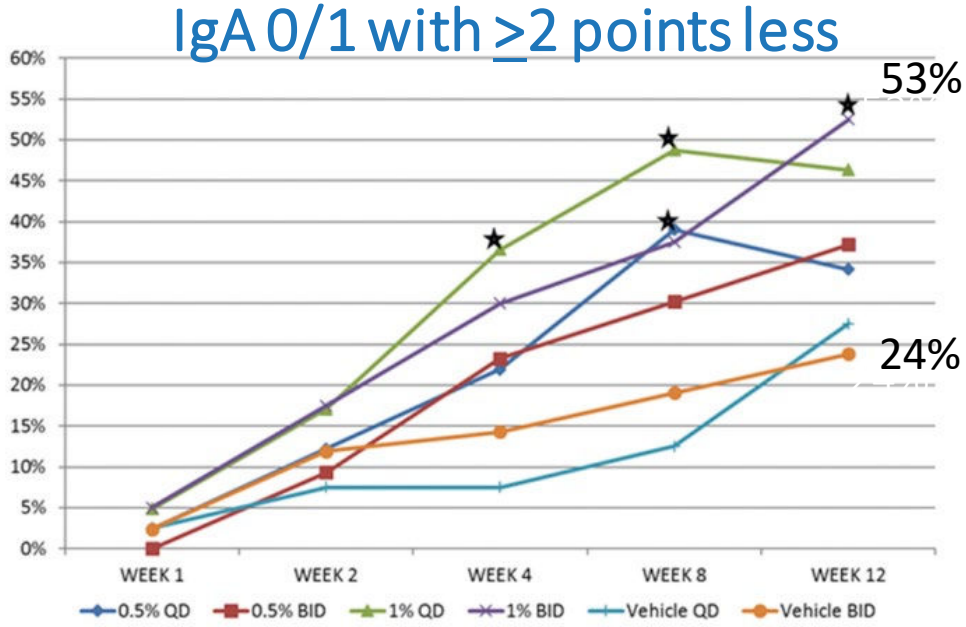
AHR regulates expression of Artemin, which activates TRPV1



Tapinarof First Therapeutic Aryl Hydrocarbon modulating Agent (TAMA)

Phase 2b study of 247 subjects





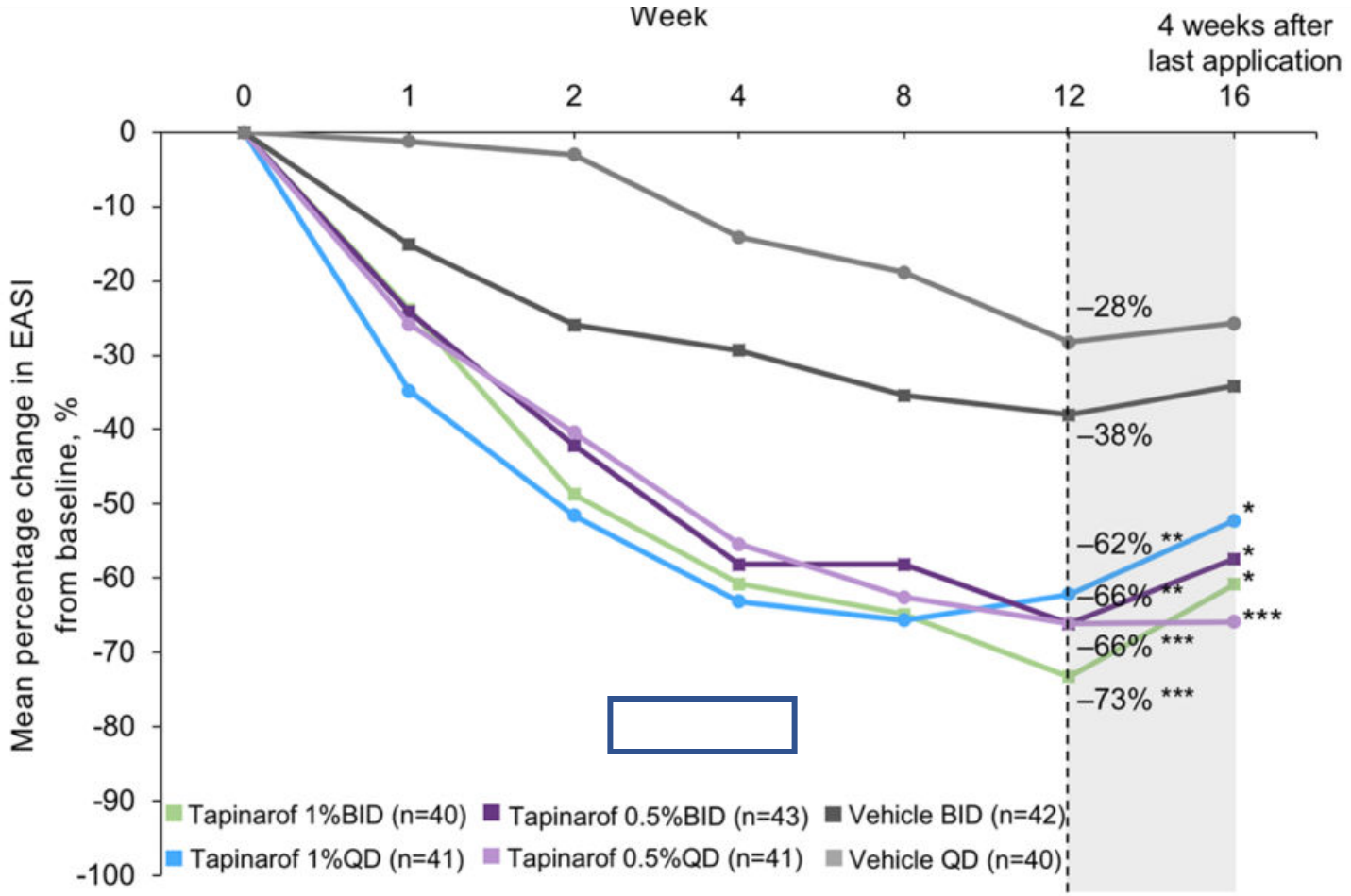
*p<0.001

	Tapinarof 1% bid	Vehicle bid
IGA 0 or 1	53%*	24%
EASI-75	60%*	26%

Peppers et al. J Am Acad Dermatol 2019;80:89-98

Tapinarof: Therapeutic Aryl Hydrocarbon modulating Agent (TAMA)

Change in EASI



- Tapinarof (5%) vs. vehicle (0%) was folliculitis (mild)
- **Minimal application site stinging/burning**

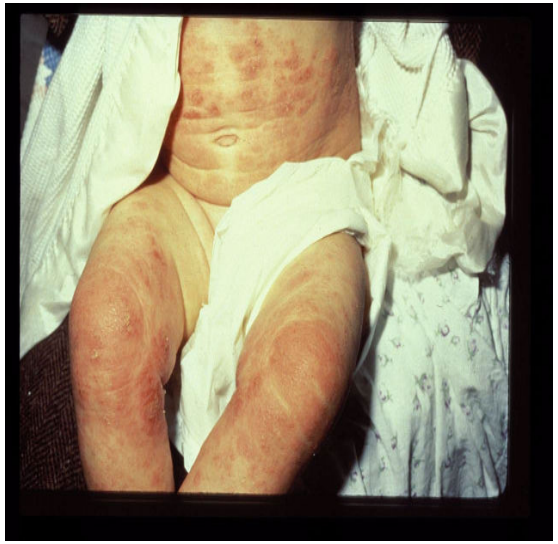
Paller et al. J Am Acad Dermatol 2021;Mar 84(3):632-638

Has the patient truly failed topical therapy? Or are they just afraid of it?

- Bos study: parents and health care providers completed Topicop
  - Corticosteroid phobia is a concern for primary care providers too
  - Nurse provider rates in this study identical to parents (44%)

- Embrace concerns but try to disarm them
  - Convince! Do not merely dismiss

- Bleach baths are non steroidal!



- Bos B et al. Corticosteroid phobia in parents of young children with atopic dermatitis and their health care providers. Pediatr Dermatol 2019;36(1):100-104

Systemic Therapy

- Who should get it?
    - Consider prior failures, severity, risk/benefit, QUALITY OF LIFE
- Which agent is best? Which are FDA approved?
- Are older immunosuppressant agents still used?
- Newest data on biologics

- Simpson E et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. J Am Acad Dermatol 2017;77(4):623-33

American Academy of Dermatology (AAD) Guidelines for AD

Guidelines update is now in press

2014 publication: Cyclosporine, methotrexate, mycophenolate mofetil, azathioprine

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Since that publication: Dupilumab (>6 mo), tralokinumab (12 yr +), upadacitinib (>12 yr), abrocitinib (12 yr +)

Sidbury R et al. *J Am Acad Dermatol.* 2014;71(6):1218-1233.
Drucker AM, et al. *JAMA Dermatol*. 2020;156(6):659-667.
Davis DM, et al. 2023 *J Am Acad Dermatol Nov 7*

Implications for Vaccine Schedules for Children on Biologic Therapies

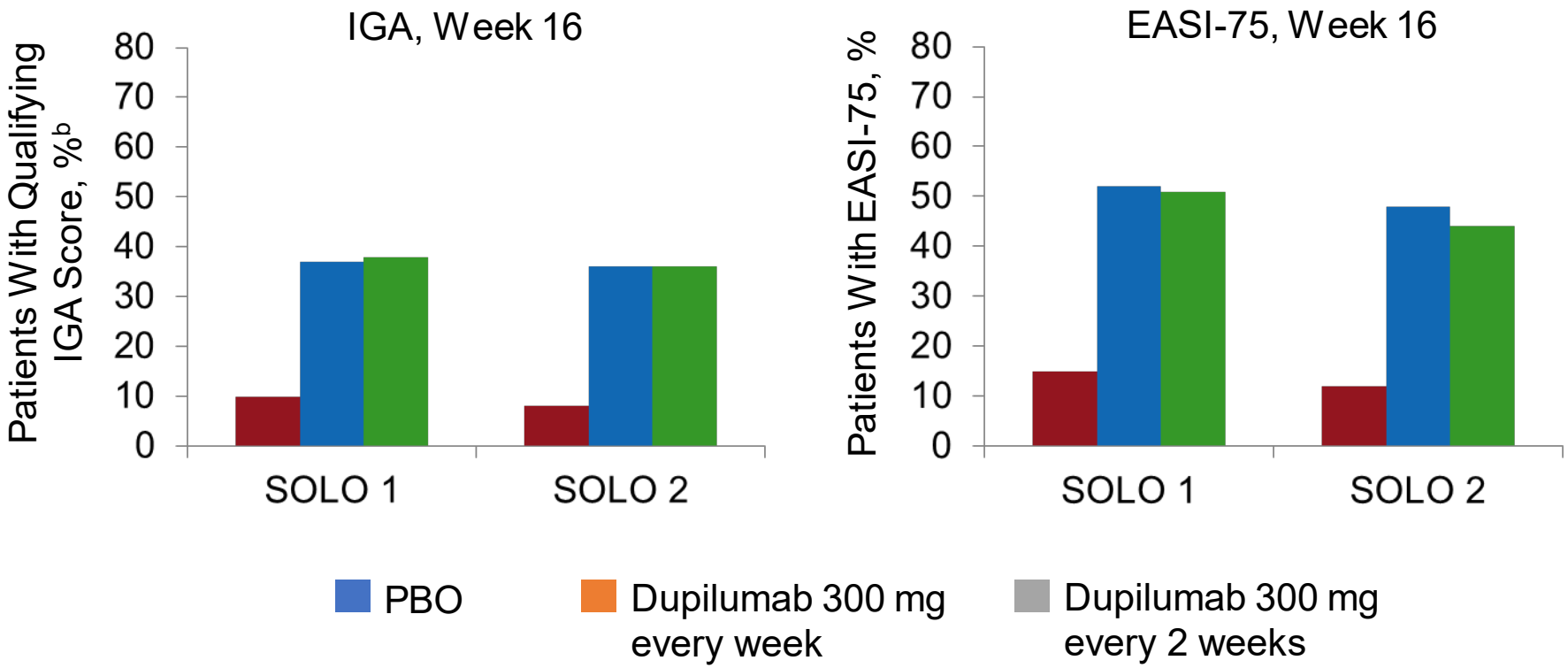
- Current guidelines specify that biologics not be interrupted for administration of any inactivated vaccines, including seasonal inactivated influenza vaccination
  - Youngest patients are dosed monthly
  - Vaccinate at mid-point

- Current recommendation is to vaccinate at least 4 weeks before initiation of dupilumab and consider the need for live vaccines on a case-by-case basis

AAD Guidelines

- For adults with moderate to severe AD, we recommend dupilumab, tralokinumab
  - Pediatric language will mirror this
- Strength of recommendation: strong
- Certainty of evidence: moderate

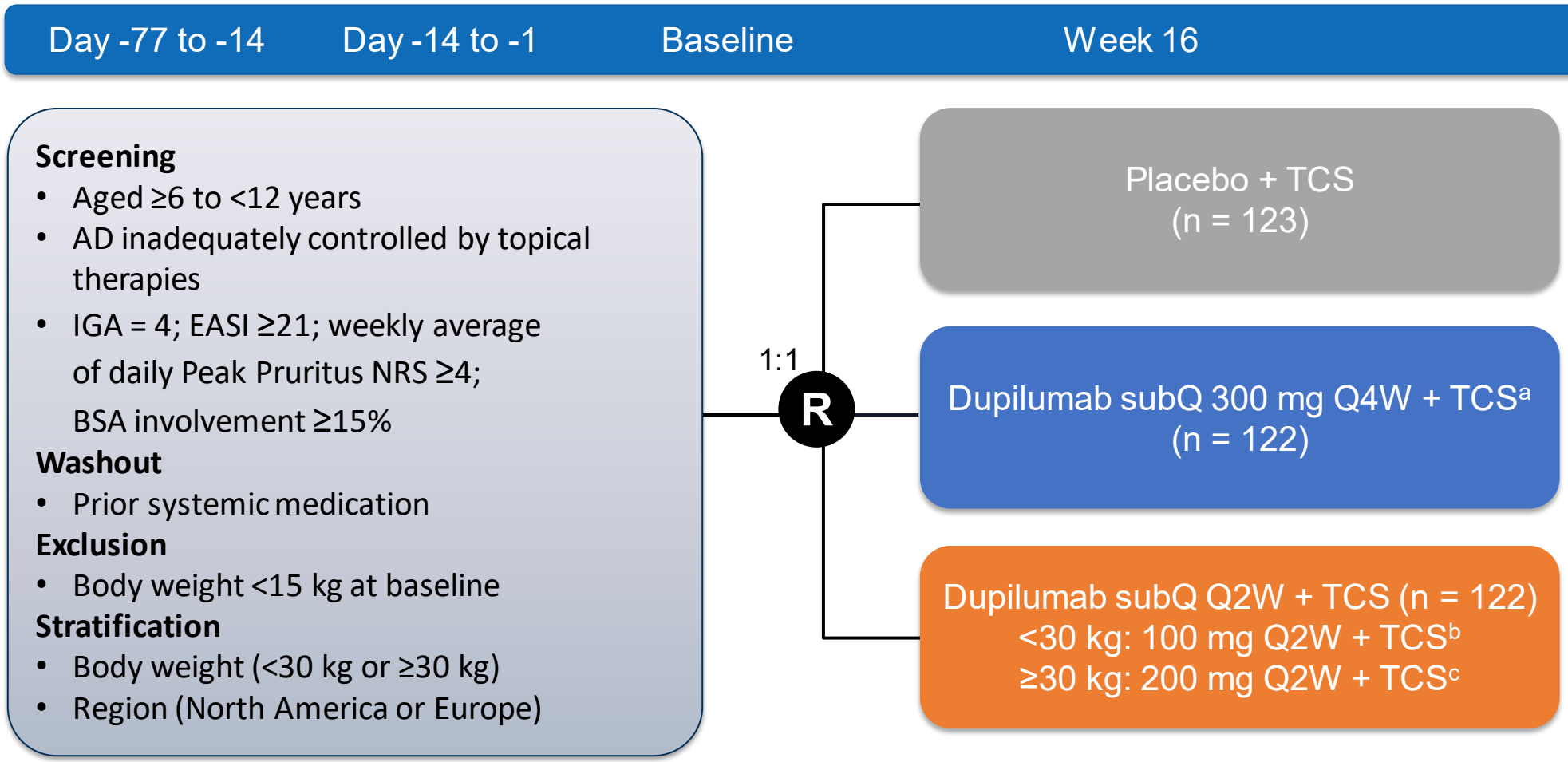
Dupilumab Monotherapy: SOLO 1 and SOLO 2 Trials



- Significant improvements in itch, DLQI, POEM, HADS-A, and HADS-D scores also observed
- Decreases in rescue medication use with dupilumab versus PBO

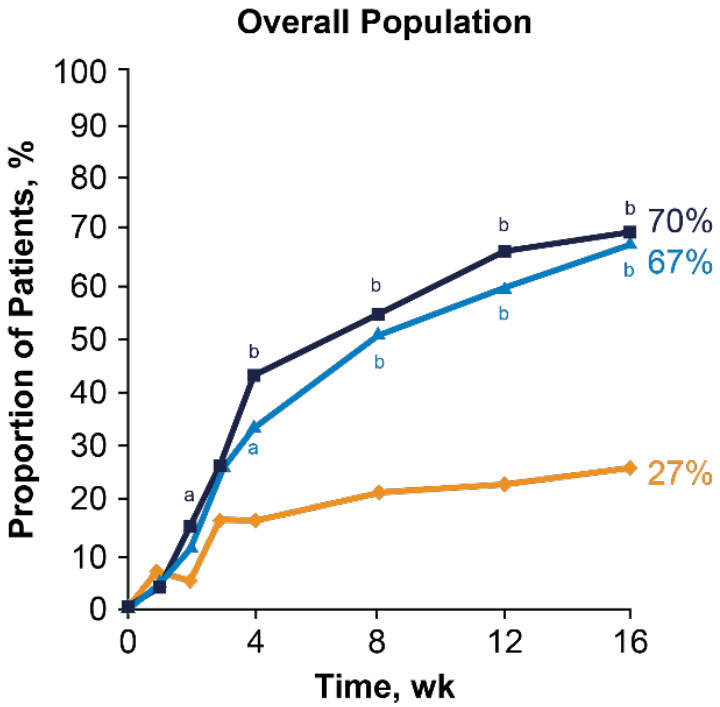
Simpson E et al, NEJM, 2016

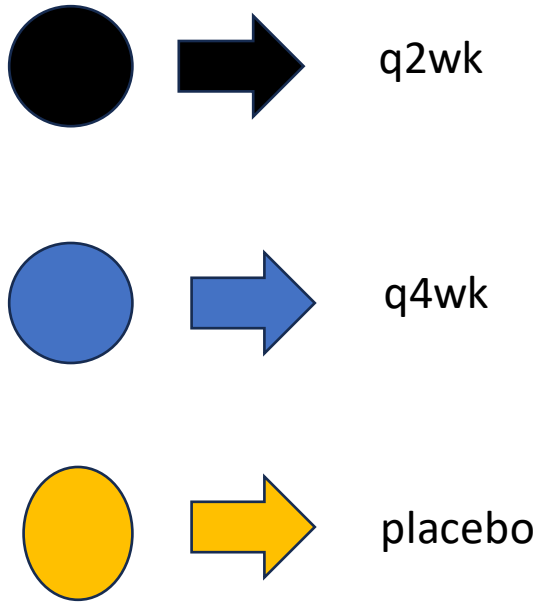
Dupilumab in Patients Aged 6-12 Years



Paller AS et al. *J Am Acad Dermatol*. 2020;83:1282-1293.

Proportion of Patients Achieving EASI-75





Paller AS et al, JAAD, 2020

Safety in Patients Aged 6-12 Years

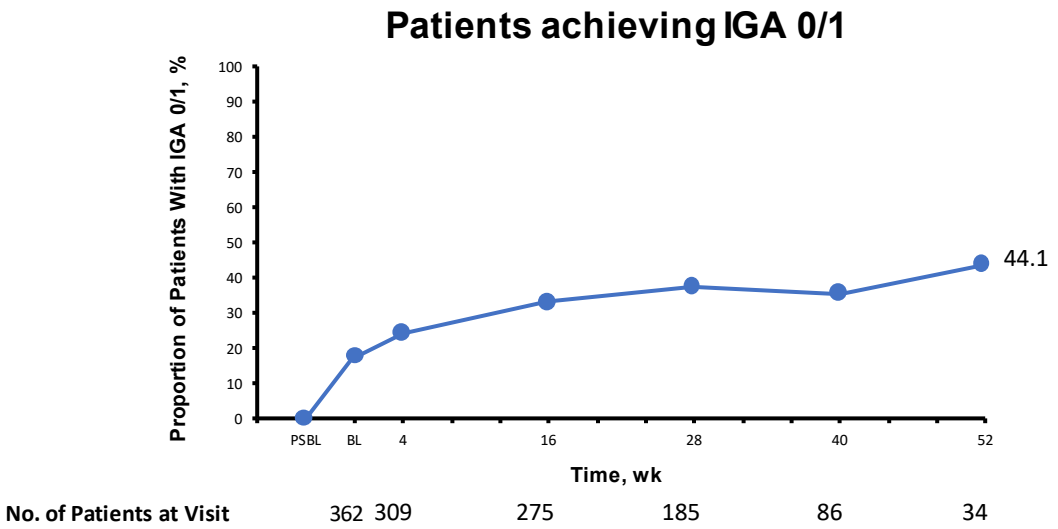
	Placebo + TCS (n = 120)	Dupilumab 300 mg Q4W + TCS (n = 120)	Dupilumab 100 or 200 mg Q2W + TCS (n = 122)
Patients with ≥1 TEAE, n (%)	88 (73.3)	78 (65.0)	82 (67.2)
Patients with ≥1 serious TEAE, n (%)	2 (1.7)	2 (1.7)	0
Patients with ≥1 TEAE leading to permanent tx discontinuation, n (%)	2 (1.7)	0	2 (1.6)
Deaths	0	0	0
TEAEs (PT) reported in ≥5% of patients, n (%)			
Atopic dermatitis, exacerbation	17 (14.2)	8 (6.7)	10 (8.2)
Asthma	12 (10.0)	2 (1.7)	4 (3.3)
Nasopharyngitis	8 (6.7)	15 (12.5)	8 (6.6)
URTI	12 (10.0)	13 (10.8)	10 (8.2)
Viral URTI	6 (5.0)	2 (1.7)	1 (0.8)
Vomiting	8 (6.7)	6 (5.0)	6 (4.9)
Cough	9 (7.5)	3 (2.5)	5 (4.1)
Headache	10 (8.3)	6 (5.0)	7 (5.7)

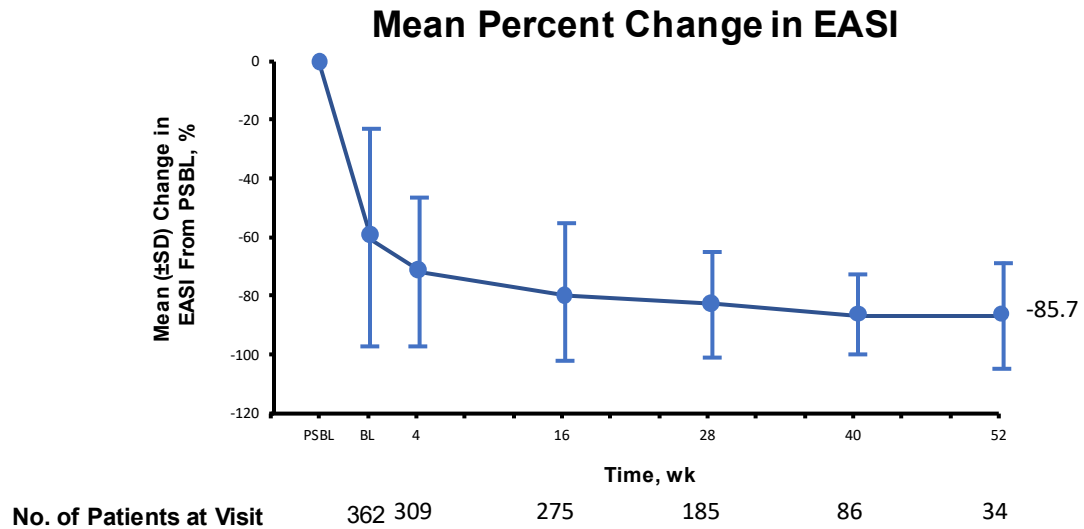
Baseline Weight <30 kg	Placebo + TCS (n = 60)	Dupilumab 300 mg Q4W + TCS (n = 60)	Dupilumab 100 mg Q2W + TCS (n = 63)
Patients with ≥1 TEAE, n (%)	43 (71.7)	39 (65.0)	46 (73.0)
TEAEs (PT), n (%)			
Atopic dermatitis	7 (11.7)	4 (6.7)	8 (12.7)
Asthma	7 (11.7)	0	4 (6.3)
Rhinitis allergic	2 (3.3)	1 (1.7)	3 (4.8)
Food allergy	0	1 (1.7)	3 (4.8)
Conjunctivitis cluster[a]	2 (3.3)	4 (6.7)	13 (20.6)
Herpes infections (HLT)	3 (5.0)	0	3 (4.8)

Baseline Weight ≥30 kg	Placebo + TCS (n = 60)	Dupilumab 300 mg Q4W + TCS (n = 60)	Dupilumab 200 mg Q2W + TCS (n = 59)
Patients with ≥1 TEAE, n (%)	45 (75.0)	39 (65.0)	36 (61.0)
TEAEs (PT), n (%)			
Atopic dermatitis	10 (16.7)	4 (6.7)	2 (3.4)
Asthma	5 (8.3)	2 (3.3)	0
Rhinitis allergic	3 (5.0)	2 (3.3)	1 (1.7)
Food allergy	0	0	0
Conjunctivitis cluster[a]	3 (5.0)	4 (6.7)	5 (8.5)
Herpes infections (HLT)	3 (5.0)	2 (3.3)	1 (1.7)

Long-Term Treatment With Dupilumab Showed Sustained Improvement in Patients Aged ≥6 to <12 Years With Moderate to Severe AD[1]

LIBERTY AD PED-OLE: Patients were treated with 200/300 mg of dupilumab every 2 weeks or 300 mg of dupilumab every 4 weeks and had participated in previous dupilumab trials





Liberty AD Study 6 m—6 yr: Efficacy

- All primary and secondary endpoints were met
- At 16 weeks, in patients treated with dupilumab
  - 28% achieved clear or almost-clear skin (IGA 0 or 1) vs 4% with placebo
  - 70% average improvement from baseline in EASI 75 vs 20% placebo
  - 49% average improvement from baseline in itch vs 2% placebo
  - Significantly improved measures of observed patient outcomes (eg, sleep, skin pain, health-related quality of life) as well as caregiver-reported health-related quality of life
- A lower rate of skin infections was also seen in the dupilumab arm (12%) vs placebo (24%)

Paller AS et al. RAD 2021. Abstract 690.

Dupilumab for 6 mo---6 years

	Dupilumab plus topical corticosteroid (n=83)	Placebo plus topical corticosteroid (n=79)	Overall (n=162)
Age, years	4·2 (3·1–4·8; 0·8–5·8)	3·8 (2·9–4·8; 0·6–5·9)	4·0 (3·1–4·8; 0·6–5·9)
Age at disease onset, months			
<6	50 (60%)	57 (72%)	107 (66%)
≥6	33 (40%)	22 (28%)	55 (34%)
Age group			
≥6 months to <2 years*	6 (7%)	5 (6%)	11 (7%)
≥2 years to <6 years	77 (93%)	74 (94%)	151 (93%)
Gender			
Male	44 (53%)	55 (70%)	99 (61%)
Female	39 (47%)	24 (30%)	63 (39%)
Race			
White	58 (70%)	53 (67%)	111 (69%)
Black or African American	14 (17%)	16 (20%)	30 (19%)
Asian	6 (7%)	4 (5%)	10 (6%)
Native Hawaiian or other Pacific islander	0	1 (1%)	1 (1%)
Not reported	2 (2%)	1 (1%)	3 (2%)
Other	3 (4%)	4 (5%)	7 (4%)
Ethnicity			
Not Hispanic or Latino	72 (87%)	70 (89%)	142 (88%)
Hispanic or Latino	11 (13%)	9 (11%)	20 (12%)
Bodyweight, kg	17·1 (4·4)	16·7 (3·6)	16·9 (4·0)
Bodyweight group, kg			
≥5 to <15	26 (31%)	25 (32%)	51 (31%)
≥15 to <30	57 (69%)	54 (68%)	111 (69%)
BMI, kg/m²	17·0 (5·6)	16·2 (1·9)	16·6 (4·2)

Meta-Analysis of Dupilumab Adverse Effects

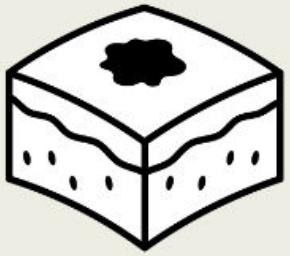
- Eight RCTs
- Reduced risk
  - Skin infection (RR 0.54)
- Increased risk
  - Conjunctivitis (RR 2.64)
  - Headache (RR 1.47)
  - Injection site reaction
- Little effect on other infections

- Ou Z et al. Adverse events of dupilumab in adults with moderate to severe atopic dermatitis: a meta-analysis. Int Immunopharm 2018;54:303-310

Updates on Tralokinumab – Safety and Efficacy in Adolescents

POPULATION

149 Males, 140 Females

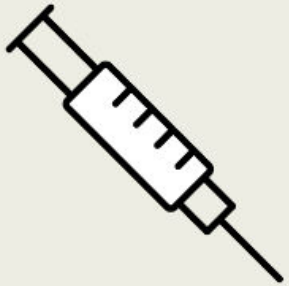


Pediatric patients aged 12 to 17 y with moderate to severe atopic dermatitis

Median (IQR) age, 15 (13-16) y

INTERVENTION

301 Patients randomized



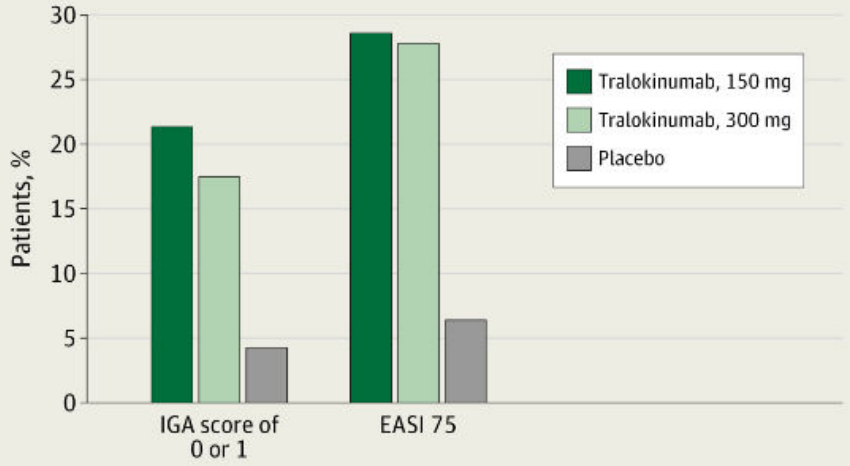
99 Tralokinumab, 150 mg
Subcutaneous tralokinumab, 150 mg, every 2 wk

98 Tralokinumab, 300 mg
Subcutaneous tralokinumab, 300 mg, every 2 wk

95 Placebo
Subcutaneous placebo, every 2 wk

FINDINGS

Proportions of patients achieving IGA score of 0 or 1 and EASI 75 at wk 16 without rescue medication were significantly greater with tralokinumab than placebo



Tralokinumab, 150 mg, difference vs placebo:
IGA score of 0 or 1, 17.5%; *P*<.001; EASI 75, 22.5%; *P*<.001

Tralokinumab, 300 mg, difference vs placebo:
IGA score of 0 or 1, 13.8%; *P*<.002; EASI 75, 22.0%; *P*<.001

SETTINGS / LOCATIONS

72 Centers across 10 countries

PRIMARY OUTCOME

Proportions of patients achieving Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and/or 75% improvement in Eczema Area and Severity Index (EASI 75) at wk 16

Paller AS, et al. *JAMA Dermatol*. 2023;159(6):596-605.

Tralokinumab approved to 12 years of age

- Approved by FDA to 12 yo December 15, 2023

- Dosing
  - Load: 2 x 150mg
  - Maintenance: 1 x 150 mg every 2 weeks
  - Monthly dosing possible

- Efficacy (monotherapy)
  - IGA 0/1: 21% vs 9% p <0.001 at 16 weeks (90% of this cohort maintained control at 32 weeks)
  - EASI75: 33% vs 10 % p< 0.001

- Ocular adverse events occur
  - AEs > 1% included conjunctivitis, URI, injection site reactions, eosinophilia

Adverse Events

Adverse Events	Ecztra 1 + 2 Tralo 300 mg q2wk N = 1180 (%)	Ecztra 1 + 2 Placebo N = 388 (%)	Ecztra 3 Tralo 300 mg Q2wk + TCS N = 243 (%)	Ecztra 3 Placebo + TCS N = 123 (%)
URI	281 (23.8)	79(20.4)	73(30)	19(15.4)
Conjunctivitis	88(7.5)	12(3.1)	33(13.6)	6(4.9)
Injection site reaction	87(7.4)	16(4.1)	27(11.1)	1(0.8)
Eosinophilia	17(1.4)	2(0.5)	3(1.2)	0

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Summary

- Be aware of newer comorbidities like ADHD, depression
- Address steroid phobia
- Crisaborole for infants, ruxolitinib are newest topical advances
- Dupilumab for infants, tralokinumab to 12 years of age


Thank you