Atopic Dermatitis in Children

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DERMATOLOGY

HARVARD MEDICAL SCHOOL

Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Advisory board of Sanofi, Incyte, and Arcutis.

Consultant for Dermavant, O'Glacee, and iRhythm

Consultant and speaker for National Eczema Association.

Investigator for Lilly, Pfizer, Abbvie, and SmartPractice.

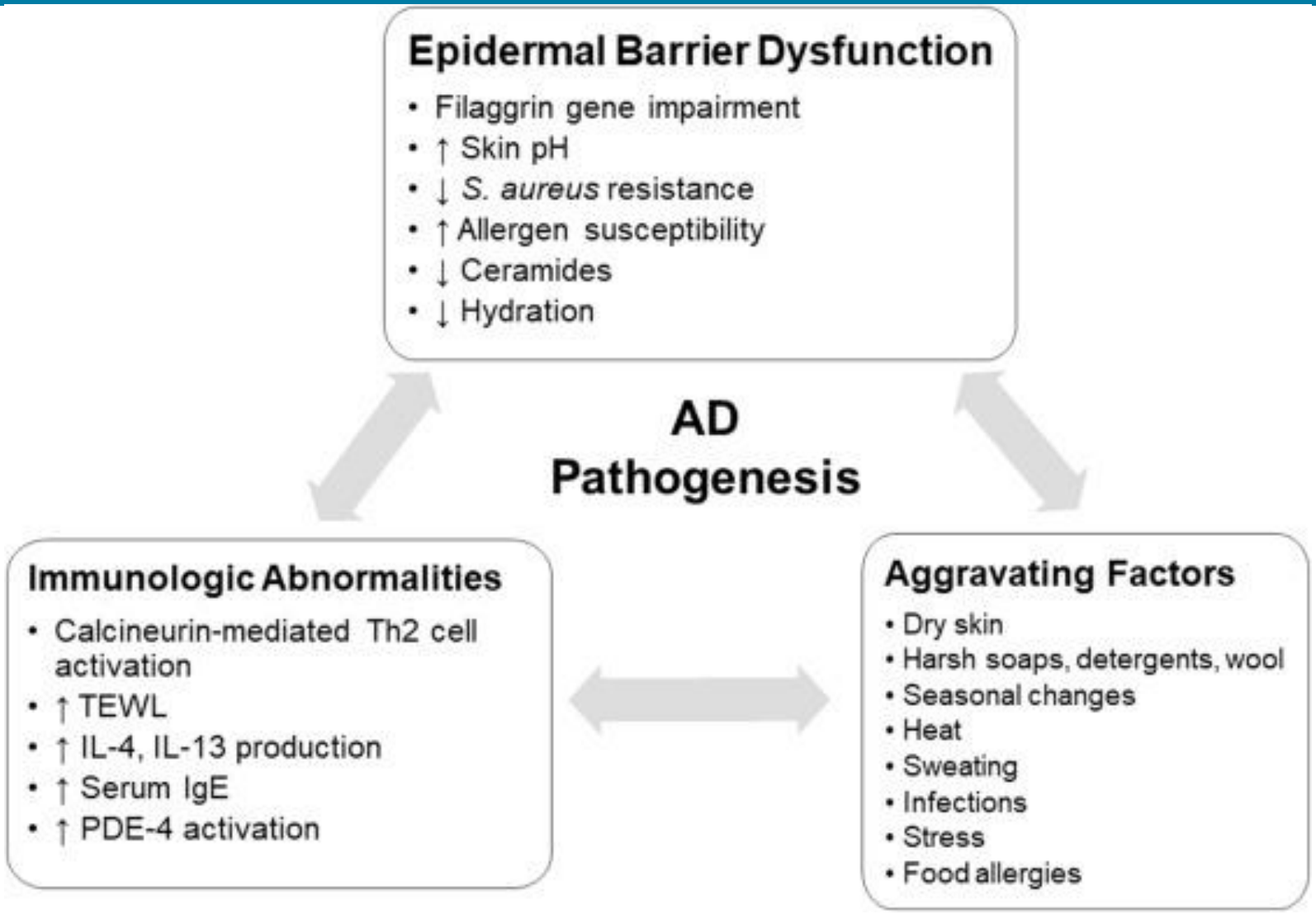
Overview

- Quick overview of atopic dermatitis in children
- Natural history and pathogenesis of atopic dermatitis
- Discuss treatment options (old and new) for children with atopic dermatitis

What Is Atopic Dermatitis?

- Common, chronic inflammatory skin disease that can start at ANY time
- Itchy, scaly, red, rash that can appear *anywhere*
- Worse with dry air, forced heat, and stress
- Often there is a family history

Andrews' Diseases of the Skin Clinical Atlas



Sayaseng KY, Vernon P. Pathophysiology and Management of Mild to Moderate Pediatric Atopic Dermatitis. J Pediatr Health Care. 2018 Mar-Apr;32(2):S2-S12.

Management of Atopic Dermatitis

Dermatologists  **Allergists**

Atopic Dermatitis

- About 10% of the population have atopic dermatitis OVERALL
  - **20-25% of Children**
  - 10% of all adults
- Different presentation in infants, children, and adults
- Chronic relapsing course

Natural History

- Atopic dermatitis starts around 3-6 months of age for most children
- Most will develop atopic dermatitis by age 5
- 10-30% of children with atopic dermatitis continue to have it as adults (therefore most resolve)
- Location changes

Phases of Atopic Dermatitis

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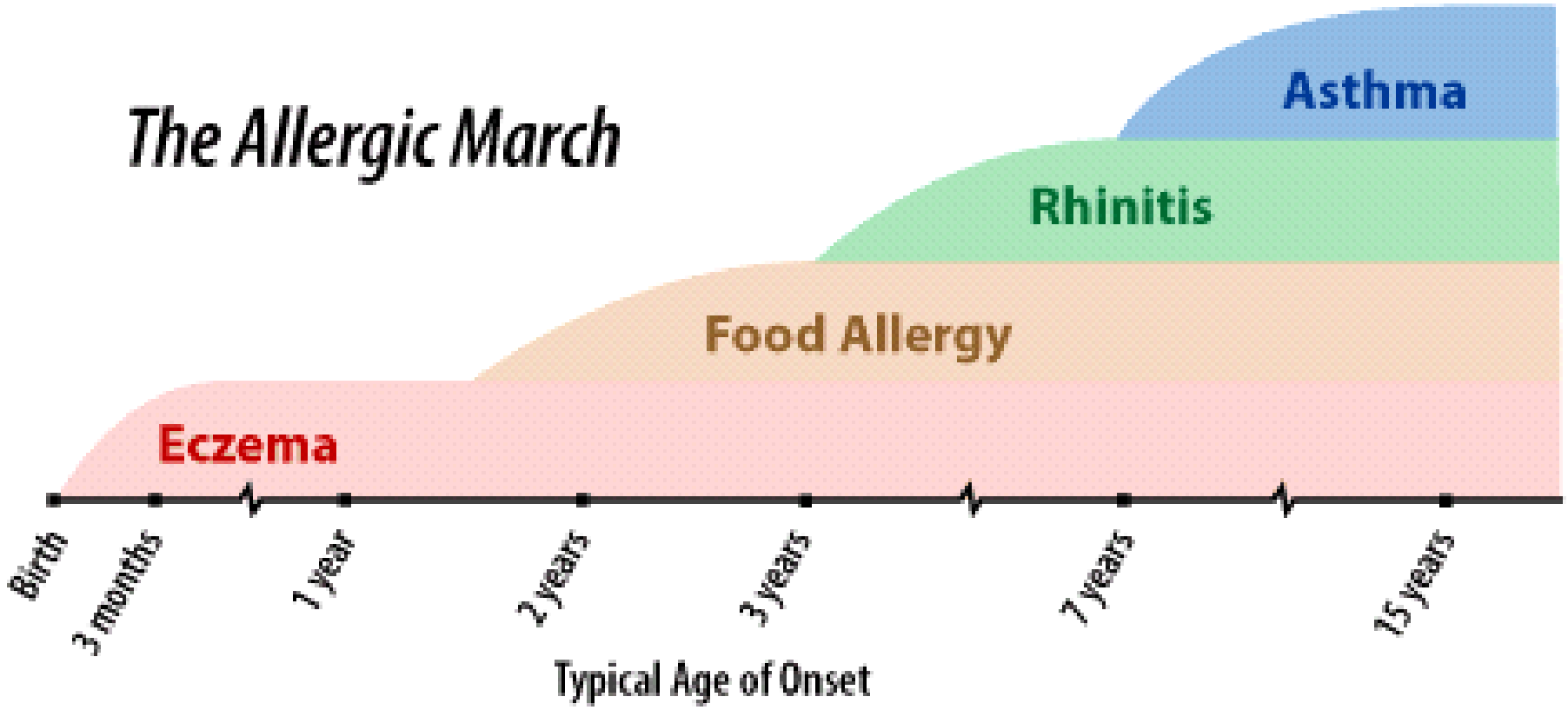
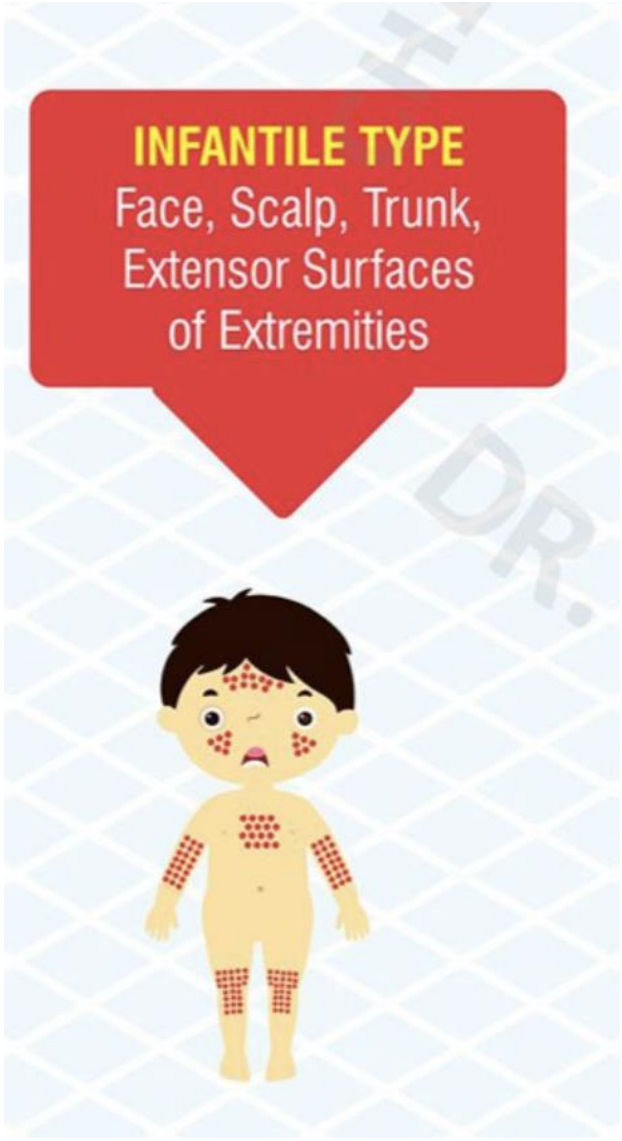
Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet. 2020 Aug 1;396(10247):345-360. doi: 10.1016/S0140-6736(20)31286-1. Erratum in: Lancet. 2020 Sep 12;396(10253):758. PMID: 32738956.



(Diagram courtesy of LEAP Study, Evelina Children's Hospital, London)

Infantile Atopic Dermatitis

- Most common age of onset
- “Born with it”
- Beginning of the Atopic March
  - Followed by food allergies, asthma, rhinitis



https://www.ankitparakh.com/conditions-treated/allergies/atopic-dermatitis/

Andrews' Diseases of the Skin Clinical Atlas

Childhood Atopic Dermatitis

- Children 2-12 years old
- Moves to skin fold areas (wrist, neck, arm pits (antecubital fossa), knee pits (popliteal fossa), ankles, feet)
- Less red and weepy than infantile atopic dermatitis

https://www.ankitparakh.com/conditions-treated/allergies/atopic-dermatitis/

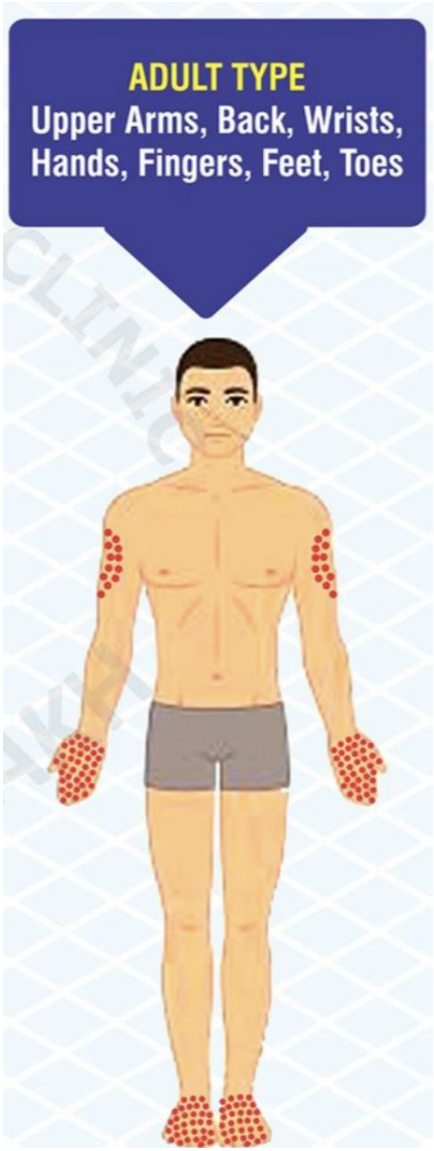
Andrews' Diseases of the Skin Clinical Atlas

Adult Atopic Dermatitis

- Distribution in adults involves the hands, feet, face, neck, and other flexural areas similar to childhood

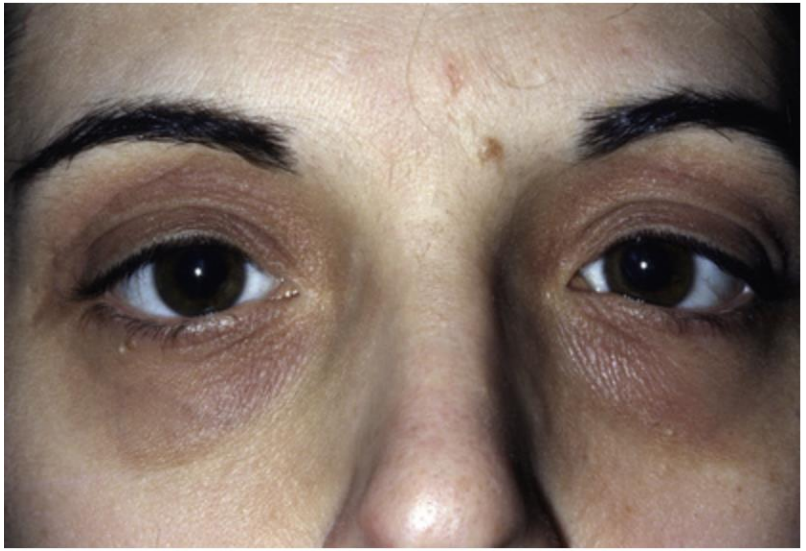
- More hands/feet involvement likely due to occupation/chores

- More prevalent than once thought ~10%



https://www.ankitparakh.com/conditions-treated/allergies/atopic-dermatitis/

Andrews' Diseases of the Skin Clinical Atlas



Associated Skin Findings w/ AD

- Not diagnostic but SUGGESTIVE of atopic dermatitis
  - Keratosis Pilaris
  - Hyperlinear palms
  - Dennie-Morgan Lines
  - White dermatographism
  - Pityriasis alba

Keratosis Pilaris

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Hyperlinear Palms

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Dennie-Morgan Lines

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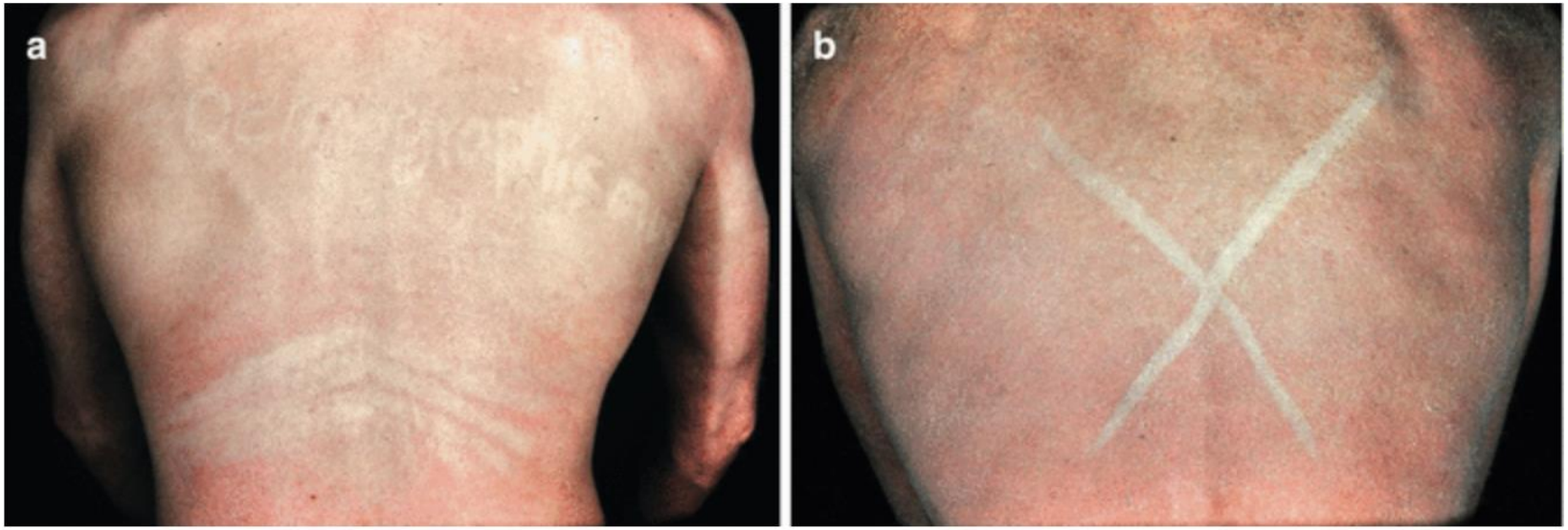
White Dermatographism



https://plasticsurgerykey.com/clinical-symptoms-of-atopic-eczema-2/

Pityriasis Alba

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Treatment Options

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- Gentle Skin Care Recommendations
- Topical Steroids
- Light Therapy
- Systemic medications
- Biologics

Dry Skin – A Hallmark

- Worse in the winter
- Worse with low humidity and high forced heat
- Harsh soaps, detergents, fabrics (wool) → broken skin barrier → increased water loss

Basics of Gentle Skin Care

- Bathe with gentle soaps (non-fragranced, hypoallergenic)
- Use lukewarm water in the shower/bath
- Moisturize within 2-3 minutes THICK emollients (petrolatum based)
  - Ointments (more oil and less water) > Creams > Lotions (more water and alcohol)
- Use a humidifier in the wintertime

- 13 year old female with a long history of atopic dermatitis since childhood that primarily affects the face and the flexural folds of the body (elbows, knees).

- Previously treated with crisaborole and topical calcineurin inhibitors (tacrolimus and pimecrolimus) without significant benefit

- Additionally, she notes that crisaborole, tacrolimus, and pimecrolimus causes burning and discomfort

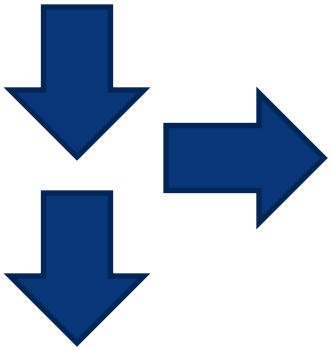
- https://www.byrdie.com/thmb/HBZ3qsjmYdYybZ6TOniRRXb6D3k=/1500x0/filters:no_upscale():max_bytes(150000):strip_icc()/ellefanningfb-8c9f4368c6424513b57260ac9374c93e.jpg

Where do you go next?

- https://www.pinnaclepromotions.com/blog/wp-content/uploads/2018/03/512690298.jpg

Lifestyle Management: Bathing, Moisturizing, Humidifier, Bleach Baths

Topical Treatments: Steroids, Calcineurin Inhibitors, Topical JAKi, PDE4 inhibitors



Phototherapy: nbUVB, PUVA

Systemic DMARDs: methotrexate, azathioprine, mycophenolate mofetil, cyclosporine

Biologics: Dupilumab, Tralokinumab

JAK inhibitors: Upadacitinib, Abrocitinib

Meta-Analysis > J Allergy Clin Immunol. 2023 Dec;152(6):1493-1519.
doi: 10.1016/j.jaci.2023.08.030. Epub 2023 Sep 9.

Topical treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials

- Chu DK, Chu AWL, Rayner DG, Guyatt GH, Yepes-Nuñez JJ, Gomez-Escobar L, Pérez-Herrera LC, Díaz Martinez JP, Brignardello-Petersen R, Sadeghirad B, Wong MM, Ceccacci R, Zhao IX, Basmaji J, MacDonald M, Chu X, Islam N, Gao Y, Izcovich A, Asiniwasis RN, Boguniewicz M, De Benedetto A, Capozza K, Chen L, Ellison K, Frazier WT, Greenhawt M, Huynh J, LeBovidge J, Lio PA, Martin SA, O'Brien M, Ong PY, Silverberg JI, Spergel JM, Smith Begolka W, Wang J, Wheeler KE, Gardner DD, Schneider L. Topical treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials. J Allergy Clin Immunol. 2023 Dec;152(6):1493-1519. doi: 10.1016/j.jaci.2023.08.030. Epub 2023 Sep 9. PMID: 37678572.

Expanding World of Topical Therapies

		Atopic Dermatitis Severity SCORAD (0–103)	Itch NRS (0–10)	Sleep Disturbance NRS (0–10)	Eczema-Related Quality of Life DLQI (0–30)	Atopic Dermatitis Flare	Any Adverse Event	Discontinuation due to Adverse Event
		MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	RD (95%CrI)	RD (95%CrI)	RD (95%CrI)
Baseline		25.96	5.40	4.89	9.43	95 per 1000	305 per 1000	28 per 1000
JAK Inhibitors								
Delgocitinib Cream		-5.64 (-8.36 to -2.91)						
Delgocitinib Ointment		-9.98 (-13.81 to -6.15)	-1.47 (-2.17 to -0.77)		-7.41 (-10.16 to -4.66)	-74 (-84 to -51)	-37 (-93 to 25)	-21 (-25 to -15)
Ruxolitinib		-4.82 (-5.65 to -4.00)	-2.11 (-2.96 to -1.26)	-0.57 (-1.15 to 0.02)	-4.82 (-6.35 to -3.44)	-74 (-84 to -51)	-37 (-93 to 25)	-21 (-25 to -15)
PDE4 Inhibitors								
Crisaborole		-4.89 (-8.69 to -1.08)	-0.64 (-1.11 to -0.15)		-1.23 (-2.34 to -0.09)	-59 (-81 to -12)	43 (-32 to 124)	9 (-15 to 58)
Difamilast		-5.41 (-9.12 to -1.68)	-1.26 (-2.09 to -0.42)		-1.55 (-3.00 to -0.03)	-45 (-71 to 2)	-41 (-110 to 39)	-17 (-22 to -9)
Lotamilast		-2.89 (-8.84 to 3.06)	0.04 (-1.53 to 1.62)			-23 (-80 to 196)	6 (-153 to 211)	-10 (-25 to 28)
Roflumilast		-2.15 (-4.20 to -0.12)	-1.55 (-3.39 to 0.29)				177 (-38 to 408)	23 (-27 to 367)
Topical Calcineurin Inhibitors								
Pimecrolimus		-7.23 (-8.76 to -5.72)	-1.61 (-2.00 to -1.21)	-2.13 (-3.15 to -1.01)	-1.44 (-2.38 to -0.62)	-53 (-66 to -39)	21 (-15 to 59)	-11 (-16 to -3)
Tacrolimus 0.1% (High Dose)		-13.05 (-15.15 to -10.95)	-2.27 (-2.84 to -1.70)		-3.65 (-5.59 to -1.83)	-70 (-85 to -41)	29 (-18 to 79)	-15 (-19 to -10)
Tacrolimus 0.03% (Low Dose)		-9.38 (-11.22 to -7.55)	-1.97 (-2.44 to -1.50)	-0.17 (-1.97 to 1.60)	-1.72 (-3.47 to -0.02)	-70 (-85 to -41)	29 (-18 to 79)	-15 (-19 to -10)
Topical Corticosteroids								
Conventional TCS Potency Classification →	High	**TCS Group 1**	-17.81 (-21.32 to -14.30)	-2.34 (-4.37 to -0.32)				-96 (-179 to 11)	-25 (-27 to -18)
		TCS Group 2	-13.82 (-18.74 to -8.89)	-3.39 (-5.02 to -1.76)				-16 (-278 to 479)	
	Medium (Moderate or Mid)	**TCS Group 3**	-11.57 (-14.80 to -8.37)	-2.37 (-3.18 to -1.57)	-0.22 (-2.23 to 1.72)	-1.23 (-3.71 to 1.17)	-11 (-83 to 312)	-62 (-138 to 24)	-12 (-23 to 9)
		TCS Group 4	-12.26 (-15.02 to -9.50)	-2.62 (-3.26 to -1.98)		-5.96 (-8.53 to -3.56)	-66 (-92 to 49)	-76 (-142 to -1)	85 (-15 to 381)
		TCS Group 5	-8.46 (-10.90 to -6.03)	-2.09 (-2.54 to -1.64)	-0.92 (-2.57 to 0.71)	-3.82 (-6.21 to -1.44)	-83 (-92 to -57)	-102 (-138 to -63)	-18 (-23 to -12)
	Low	**TCS Group 6/7**	-4.68 (-7.10 to -2.29)	-1.33 (-1.89 to -0.76)	0.32 (-1.51 to 2.10)	-1.48 (-3.38 to 0.34)	-13 (-78 to 234)	-33 (-105 to 47)	-6 (-18 to 13)
Other								
Antibiotic		-1.48 (-6.77 to 3.81)	-0.32 (-2.15 to 1.51)		-1.33 (-3.35 to 0.69)	-56 (-94 to 499)	50 (-153 to 306)	229 (-5 to 834)
Prescription Moisturizers		-1.94 (-4.83 to 0.95)	-1.63 (-2.28 to -0.97)			-60 (-82 to -5)	-8 (-111 to 111)	-10 (-23 to 17)
Tapinarof		-11.26 (-16.55 to -6.03)	-1.93 (-2.99 to -0.89)			-64 (-88 to 20)	155 (19 to 299)	-14 (-23 to 9)

High to moderate certainty evidence	Low to very low certainty evidence
Among the most effective	Possibly among the most effective
Among the intermediate (superior) effective	Possibly among the intermediate (superior) effective
Among the intermediate (inferior) effective	Possibly among the intermediate (inferior) effective
Not clearly different from control	Possibly not clearly different from control

Beyond Topical Steroids

- **Topical Calcineurin Inhibitors**
- Tacrolimus 0.03% (2y+) and 0.1% (15y+) ointment
- Pimecrolimus 1% (2y+) cream
- ***Almost always prescribed for those < 2 years***

- **Topical PDE4 inhibitor**
- Crisaborole (3 months +)
- ***Burns and low efficacy***

PDE4 Inhibitors

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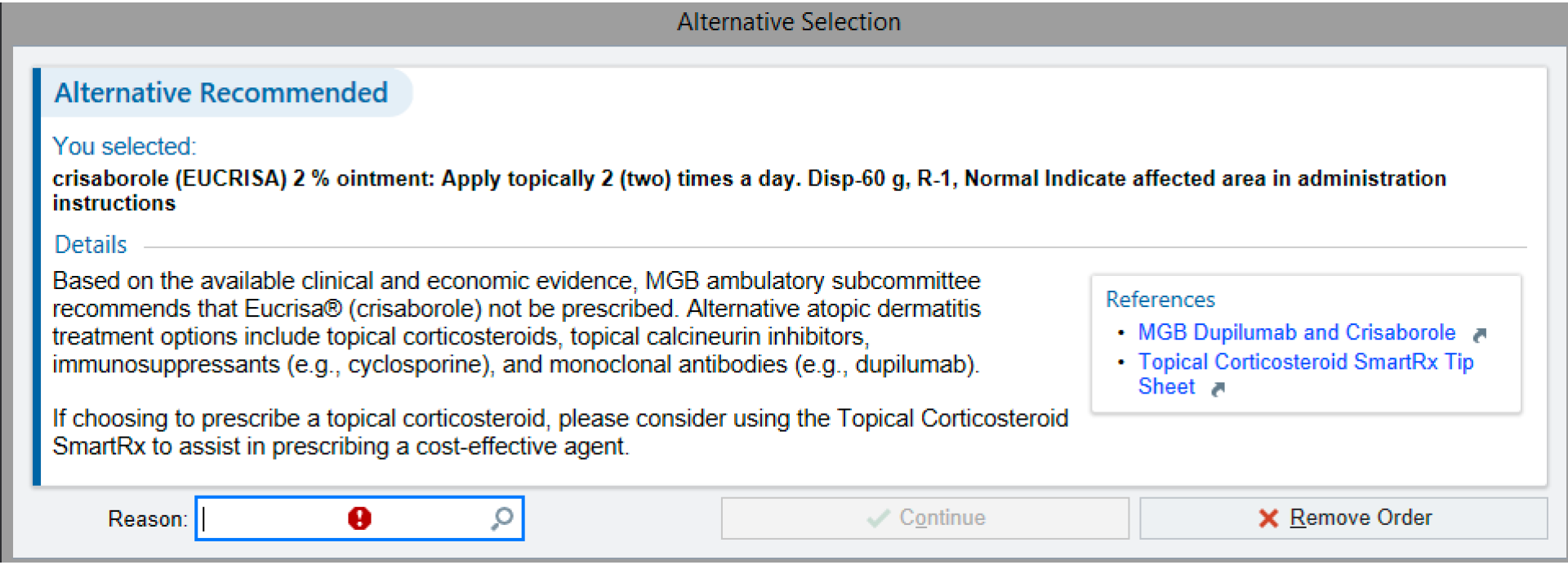


Topical Steroids

Eczema

Classification of Topical Corticosteroids

Class	Potency	Examples (Not exclusive)	Caution
1	**Superpotent**	Clobetasole Propionate, Halobetasole Propionate	*Avoid in children, face, folds, near genitals.*
2	**Potent**	Betamethasone dipropionate, Halcinonide, Flucinonide	*Avoid in children, face, folds, near genitals.*
3	**Upper Mid Strength**	Betamethasone Valerate	*Use cautiously in children. Avoid on face, folds, near genitals*
4	**Mid Strength**	Mometasone, Beclomethasone, Fluocinolone 0.25%, Triamcinolone acetonide, Methyl Prednisolone acetonate	*They may be used in children for a short duration. Not to be used on face and body folds.*
5	**Lower Mid Strength**	Hydrocortisone butyrate, Fluticasone propionate	*Can be used in all ages and on the face and folds for a short duration*
6	**Mild**	Desonide, Flucinolone 0.1%	*Can be used in all ages and on the face and folds for a short duration*
7	**Least Potent**	Hydrocortisone 1%	*This can be used in all, the only one that may be bought over the counter.*

https://skin-care-tips-from-dermatologist.com/topical-corticosteroids-double-edged-swords/

Side Effect of TOPICAL Steroids

- Moderate use will not lead to substantial systemic absorption
  - Twice a day for 2 weeks/month for example (excludes face and groin)
- Skin thinning – looks more “vein-y” or translucent
- Stretch marks may appear
- Chronic steroid use on the face → acne
- Increased risk of glaucoma and cataracts if extensively used in and around the eyes

https://www.e-ijd.org/articles/2014/59/5/images/IndianJDermatol_2014_59_5_456_139872_u5.jpg

https://img.grepmed.com/uploads/2082/dermatology-skinrash-clinical-atrophy-steroid-original.jpeg

Non-Steroidal Options

= Medium Potency Steroid

= Low Potency Steroid

Non-Steroidal Options

= Low Potency Steroid

Non-Steroidal Options

https://www.medscape.com/viewarticle/978653

Phototherapy

- 2nd line treatment
- 2-3x/week for 1-3 minutes each treatment
- Takes about 4-6 weeks to work
- After 12 weeks, 50% or more improvement

Tintle S, Shemer A, Suárez-Fariñas M et al. Reversal of atopic dermatitis with narrow-band UVB phototherapy and biomarkers for therapeutic response. J Allergy Clin Immunol. 2011 Sep;128(3):583-93.e1-4.

DMARDs

- Methotrexate- @12 weeks → 42% improvement
  - Works slowly
  - ”Safe” to use longer term

- Cyclosporine- @6 weeks → 55% improvement
  - Works quickly
  - Use < 12 months ideally

- Azathioprine- @12 weeks → 37% improvement
  - Works slowly
  - ”Safe” to use longer term

- Prednisone- Almost always see improvement but rebound flare
  - Works quickly
  - NOT safe for long term use

Sidbury R, Davis DM, Cohen DE et al; American Academy of Dermatology. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014 Aug;71(2):327-49.

Newer Therapies

1. Novel topical agents (and soon available) for the treatment of pediatric atopic dermatitis
    - **Ruxolitinib** (FDA approved)
    - **Roflumilast** (approval pending)
    - **Tapinarof** (approval pending)

2. Novel systemic agents for pediatric atopic dermatitis relative to dupilumab
    - **Tralokinumab** (FDA Approved)
    - **Abrocitinib** (FDA Approved)
    - **Upadacitinib** (FDA Approved)
    - **Lebrikizumab** (approval pending)
    - **Amlitelimab** (approval pending)

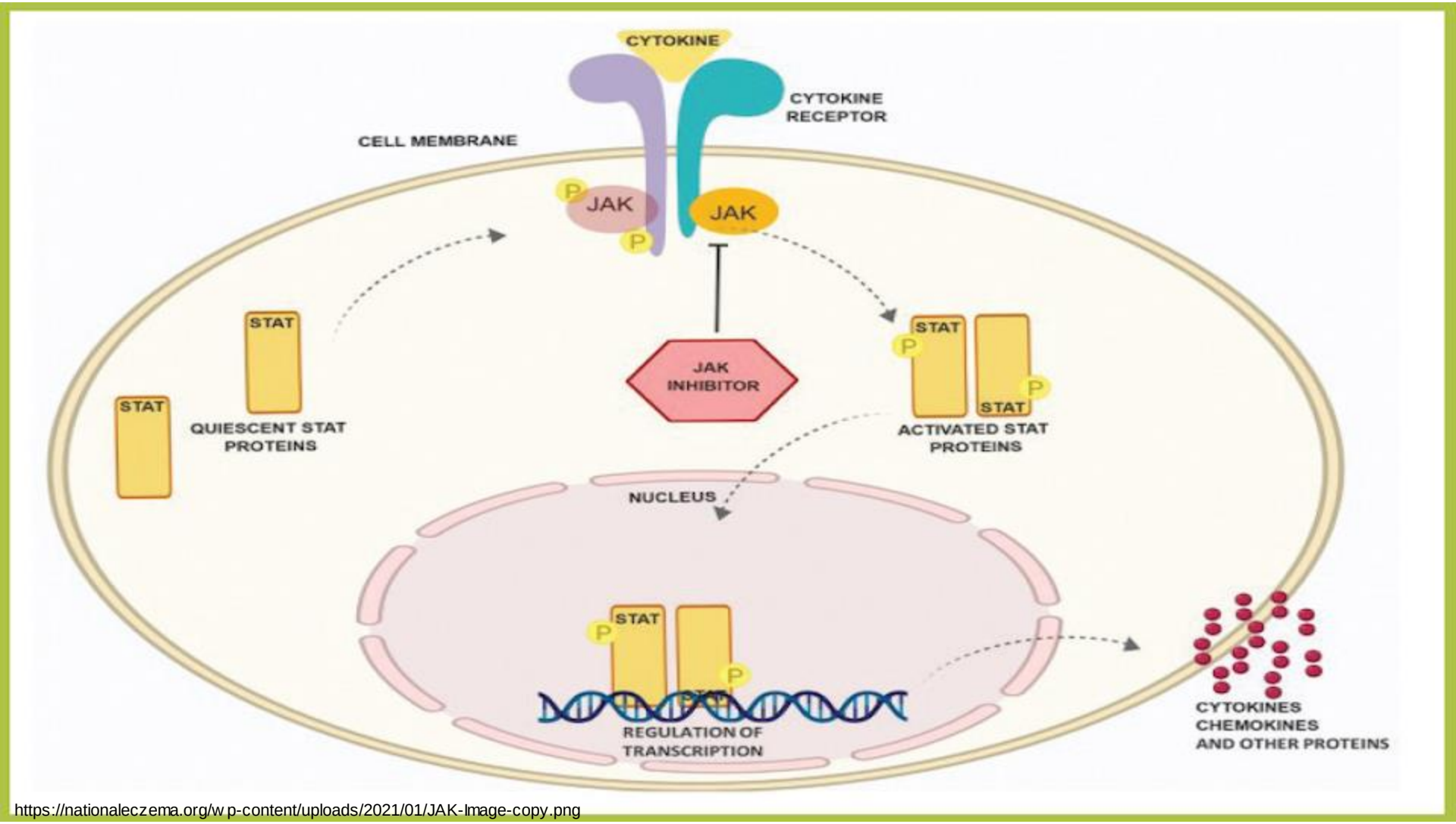
Ruxolitinib (Opzelura)

- Selective **JAK 1/2 inhibitor** FDA approved for mild to moderate atopic dermatitis in children > 12 years of age
- Twice a day application for up to 20% BSA
- No stinging or burning on application
- BLACK BOX WARNING…but why?

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

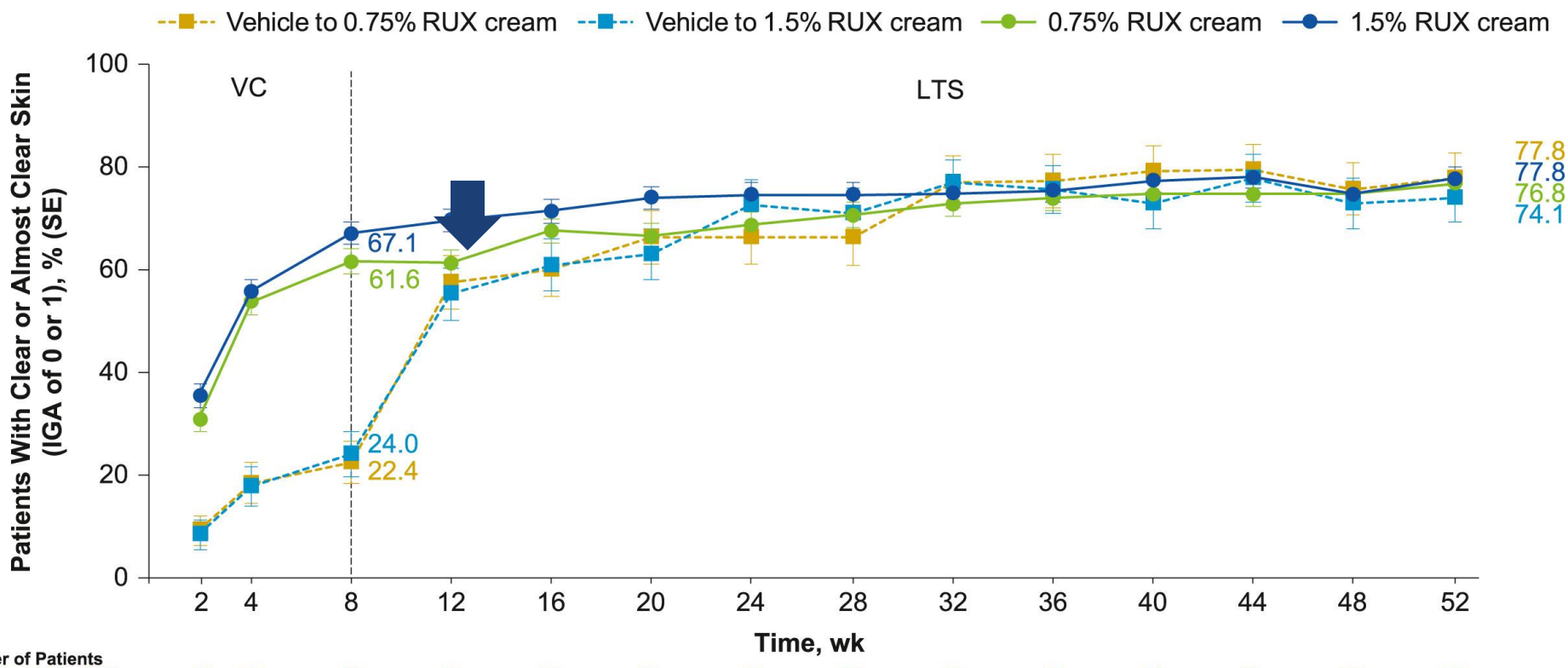
See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving Janus kinase inhibitors for inflammatory conditions. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.2)**
- **Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.3)**
- **Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.4)**
- **Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal, have occurred in patients treated with Janus kinase inhibitors for inflammatory conditions. (5.5)**



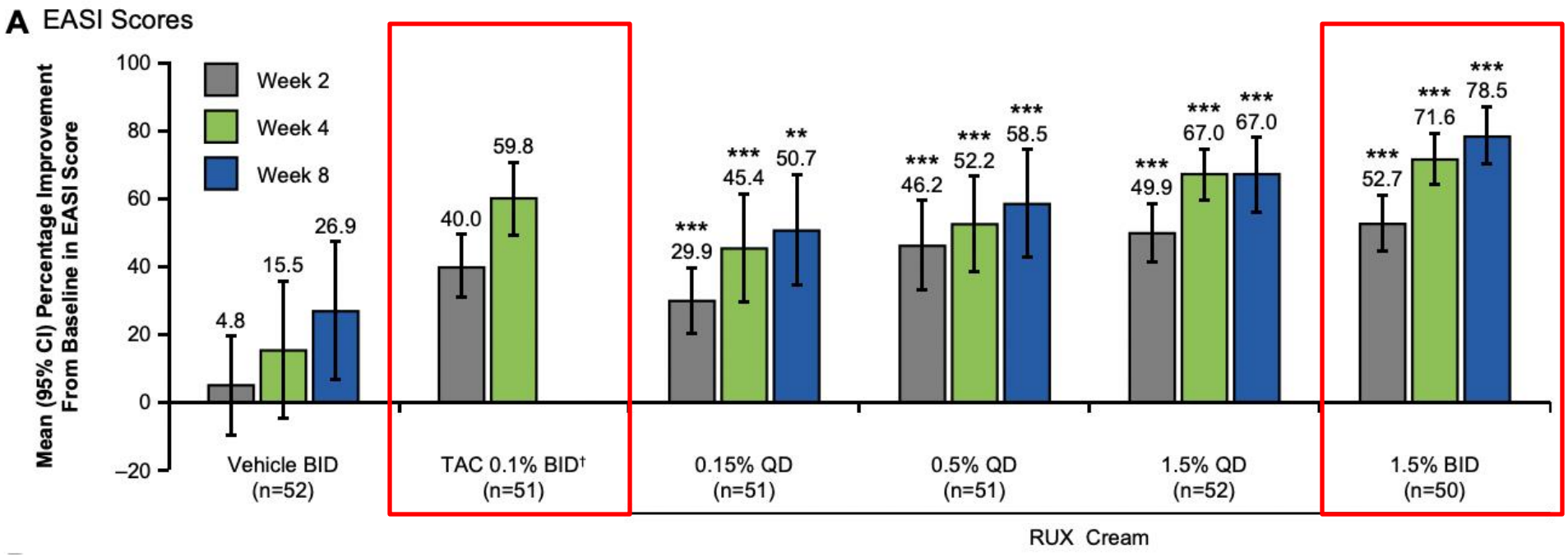
https://nationaleczema.org/wp-content/uploads/2021/01/JAK-Image-copy.png

Ruxolitinib- Efficacy Data



Number of Patients														
Vehicle to 0.75% RUX cream	98	98	98	92	90	86	83	74	70	66	67	68	70	72
Vehicle to 1.5% RUX cream	96	96	96	94	92	92	88	86	87	82	81	81	81	81
0.75% RUX cream	409	409	409	395	383	370	345	333	316	307	312	320	316	323
1.5% RUX cream	428	428	428	408	399	392	374	354	342	342	332	343	326	342

Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Forman SB, Kuligowski ME, Kallender H, Sun K, Ren H, Simpson EL. Long-term safety and disease control with ruxolitinib cream in atopic dermatitis: Results from two phase 3 studies. J Am Acad Dermatol. 2023 May;88(5):1008-1016. doi: 10.1016/j.jaad.2022.09.060. Epub 2022 Nov 26. PMID: 36574595.



Through week 4 (green bar), ruxolitinib cream 1.5% applied BID had similar or higher reduction in EASI than triamcinolone (not statistically sig however)

- Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME; INCB 18424-206 Study Investigators. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. J Allergy Clin Immunol. 2020 Feb;145(2):572-582. doi: 10.1016/j.jaci.2019.08.042. Epub 2019 Oct 17. PMID: 31629805.

Safety Data- Phase 3 Studies

	0.75% Ruxolitinib cream (n = 601)	1.5% Ruxolitinib cream (n = 598)
Notable serious infections[†]	4 (0.7)	1 (0.2)
Serious pneumonia	3 (0.5)	1 (0.2)
Sepsis	1 (0.2)	0
Viral skin infections	6 (1.0)	11 (1.8)
Herpes zoster	3 (0.5)	5 (0.8)
Herpes simplex	2 (0.3)	6 (1.0)
Molluscum contagiosum	1 (0.2)	0
Malignancies[‡,§]	4 (0.7)	2 (0.3)
Basal cell carcinoma	2 (0.3)	0
Squamous cell carcinoma of the skin	2 (0.3)	2 (0.3)
Squamous cell carcinoma	0	1 (0.2)
Renal cell carcinoma	1 (0.2)	0
MACE[‖]	2 (0.3)	1 (0.2)
Myocardial infarction	1 (0.2)	0
Cerebrovascular accident	1 (0.2)	1 (0.2)
Thrombotic events[‡,‖]	1 (0.2)	1 (0.2)
Deep vein thrombosis	0	1 (0.2)
Pulmonary embolism	1 (0.2)	1 (0.2)
Thrombocytosis[¶]	2 (0.3)	2 (0.3)
Cytopenias[‡,#]	24 (4.0)	15 (2.5)
Erythropenia	12 (2.0)	3 (0.5)
Neutropenia	12 (2.0)	12 (2.0)
Thrombocytopenia	3 (0.5)	0
Lipid elevations[‡]	11 (1.8)	9 (1.5)
Liver enzyme elevations[‡]	18 (3.0)	12 (2.0)

52 Week Safety Data

Most common treatment-relatec AE[§]	
Neutropenia	4 (0.9)
Application site pain[‖]	4 (0.9)
Application site pruritus	0
Oral herpes	0
Application site folliculitis	1 (0.2)
Skin bacterial infection	2 (0.4)
Alopecia	0
Application site erythema	0
Dermatitis acneifor	2 (0.4)
Herpes simplex	2 (0.4)
Skin papilloma	0
Patients who discontinued due t a TEAE	1 (0.2)
Patients with serious TEAE[¶,#]	8 (1.8)

- Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Forman SB, Kuligowski ME, Kallender H, Sun K, Ren H, Simpson EL. Long-term safety and disease control with ruxolitinib cream in atopic dermatitis: Results from two phase 3 studies. J Am Acad Dermatol. 2023 May;88(5):1008-1016. doi: 10.1016/j.jaad.2022.09.060. Epub 2022 Nov 26. PMID: 36574595.

Interpretation of Ruxolitinib Data

- Ruxolitinib is an excellent option for topical treatment of atopic dermatitis in children > 12 years of age
- Equal in strength to topical triamcinolone (medium potency steroid)
- Low risk of side effects especially given low systemic absorption
- No lab monitoring needed
- Currently seeking approval for 2-12 years of age

Dupilumab- THE GOLD STANDARD

MASSACHUSETTS GENERAL HOSPITAL
DERMATOLOGY

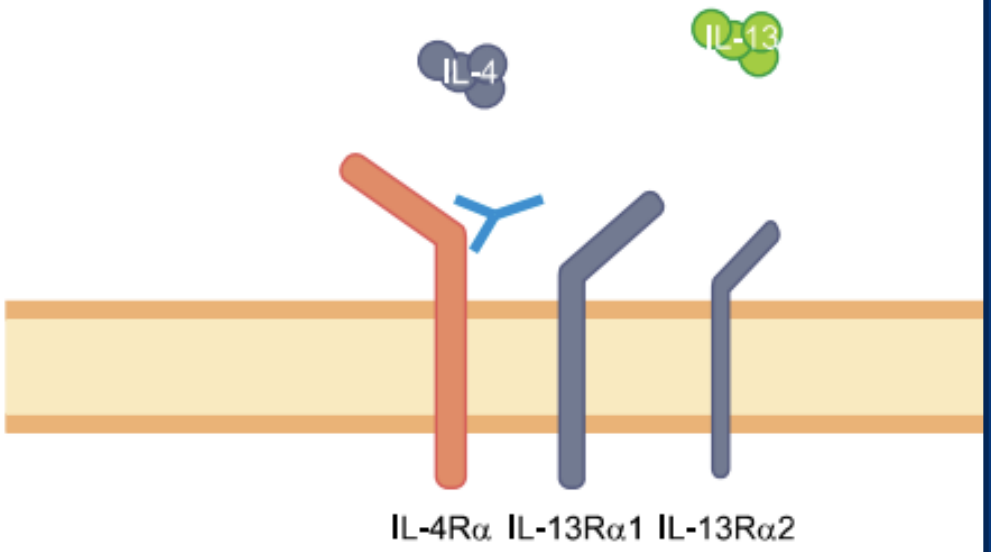
- FDA approved for children with eczema over **6 months of age**
  - Approved for PRURIGO NODULARIS
  - Eosinophilic esophagitis, asthma, chronic nasal rhinosinusitis with polyposis

- Inhibitor of the α subunit of IL4 and IL13

- **Market standard to which all new therapies are being compared**

Dupilumab

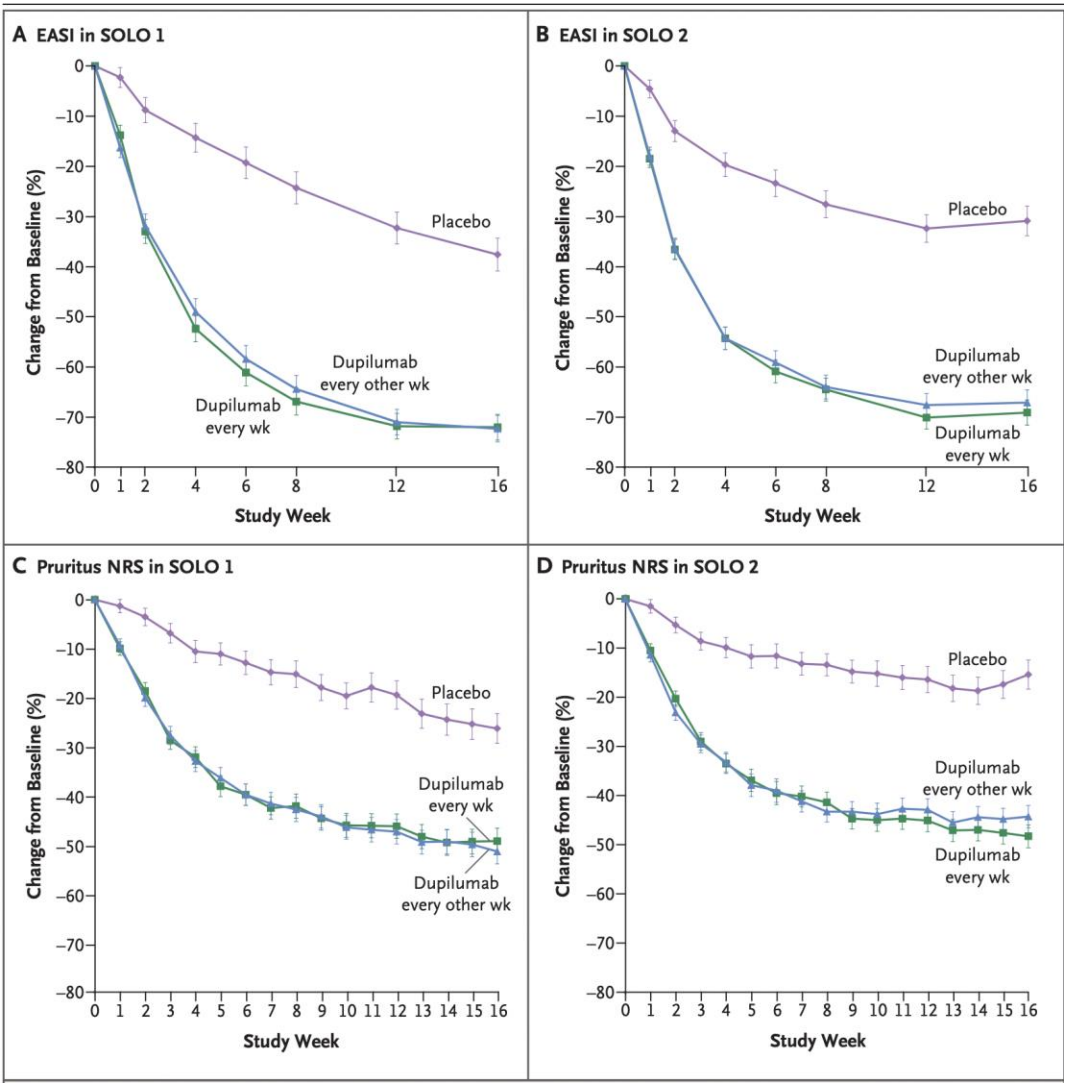
Binds IL-4α, blocking IL-13 and IL-4 signaling



Ahn J, Choi Y, Simpson EL. Therapeutic New Era for Atopic Dermatitis: Part 1. Biologics. Ann Dermatol. 2021 Feb;33(1):1-10. doi: 10.5021/ad.2021.33.1.1. Epub 2020 Dec 30. PMID: 33911806; PMCID: PMC7875213.

Dupilumab Lab Monitoring?

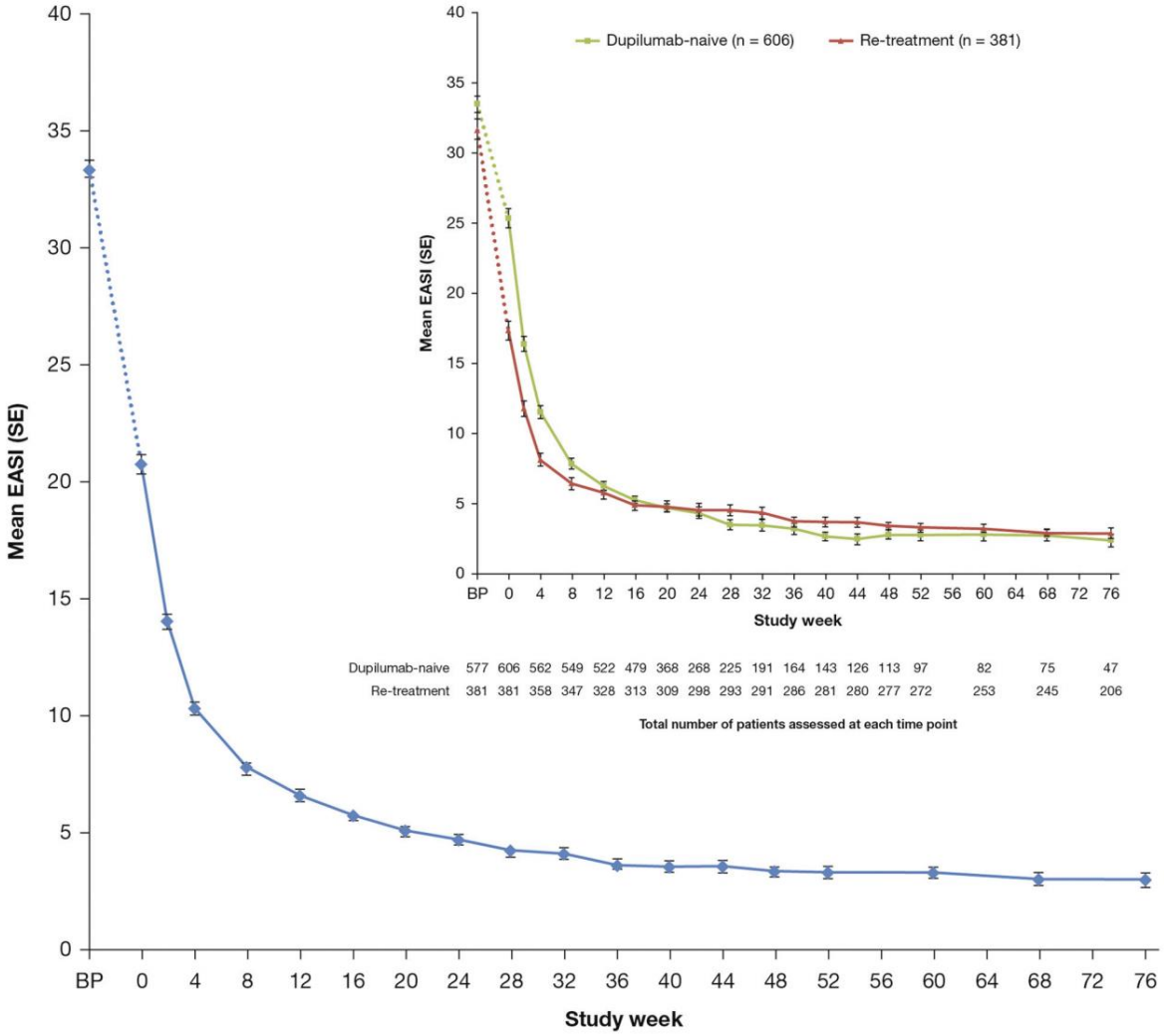
https://mobile.twitter.com/nothing



After 16 weeks, dupilumab led to a 60-70% improvement in EASI scores

Within 2 weeks, pruritus decreased in patients on dupilumab with an improvement of >40% after 16 weeks

Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JI, Deleuran M, Kataoka Y, Lacour JP, Kingo K, Worm M, Poulin Y, Wollenberg A, Soo Y, Graham NM, Pirozzi G, Akinlade B, Staudinger H, Mastey V, Eckert L, Gadkari A, Stahl N, Yancopoulos GD, Ardeleanu M; SOLO 1 and SOLO 2 Investigators. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med. 2016 Dec 15;375(24):2335-2348. doi: 10.1056/NEJMoa1610020. Epub 2016 Sep 30. PMID: 27690741.



Even at 6 years, efficacy is maintained and stopping/ restarting did not impact efficacy

Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, Bissonnette R, Reich K, Soong W, Hussain I, Foley P, Hide M, Bouaziz JD, Gelfand JM, Sher L, Schuttelaar MLA, Wang C, Chen Z, Akinlade B, Gadkari A, Eckert L, Davis JD, Rajadhyaksha M, Staudinger H, Graham NMH, Pirozzi G, Ardeleanu M. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. J Am Acad Dermatol. 2020 Feb;82(2):377-388. doi: 10.1016/j.jaad.2019.07.074. Epub 2019 Jul 30. PMID: 31374300.

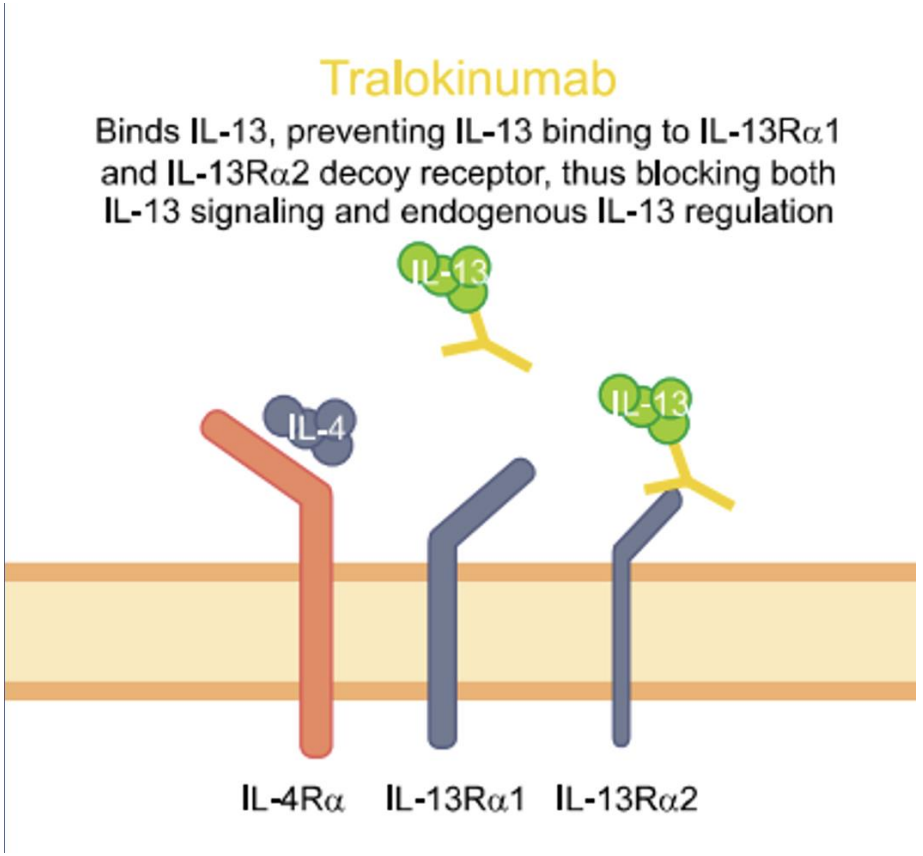
https://www.utphysicians.com/wp-content/uploads/2022/10/givingawaytreats-featured.jpg

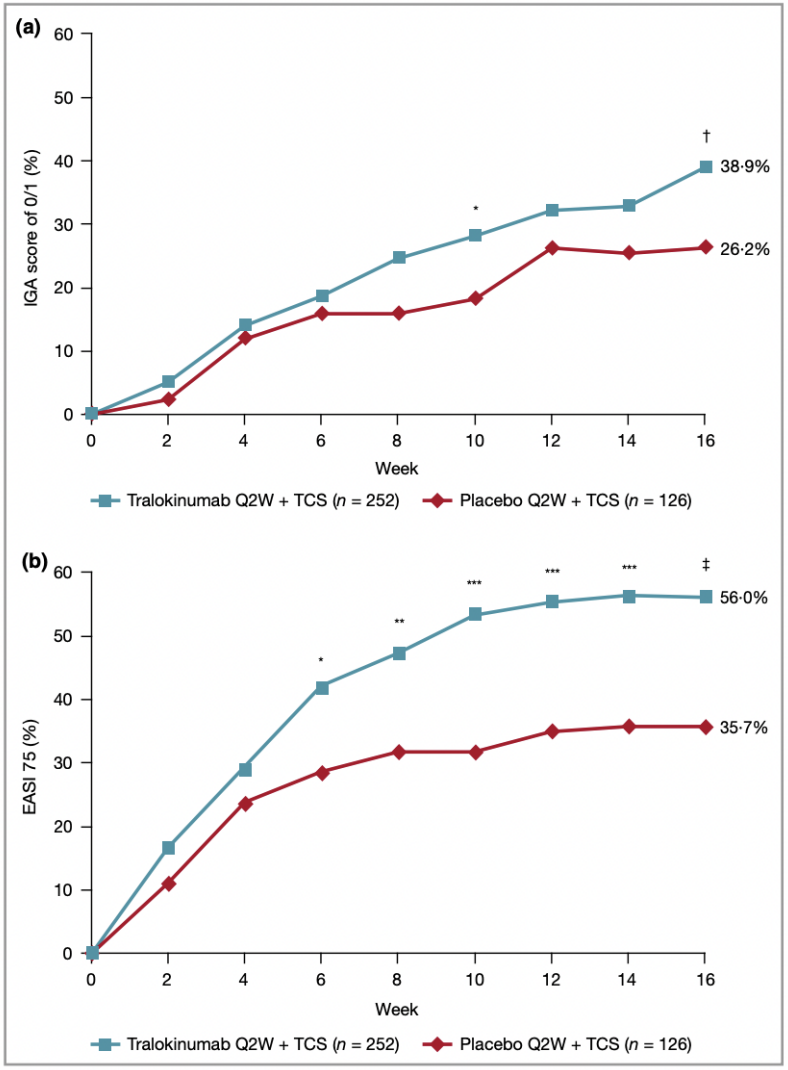
If it's so good, why do we need others

- Not everyone improves… (fail rate ~10-20%)
- Side effects: Allergic conjunctivitis or head and neck dermatitis
- Fear of injections

Tralokinumab- IL13 inhibitor

- FDA approved for > 12 years of age
- High affinity IL-13 inhibitor (high concentration of IL13 in AD skin)
- VERY similar efficacy to dupilumab
- 300mg loading and 150mg every other weeks in children > 12



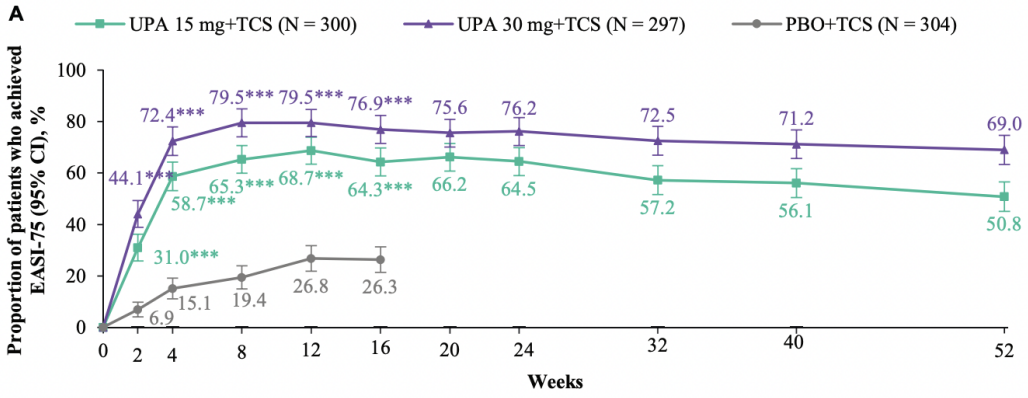


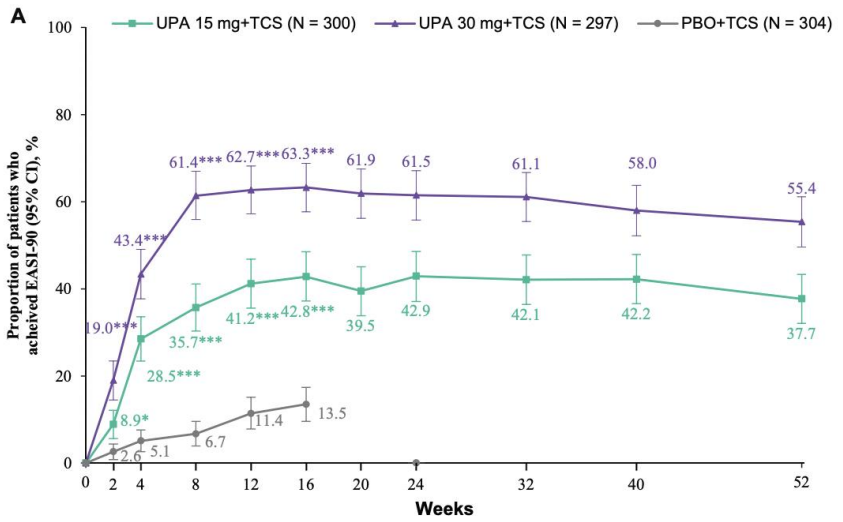
EASI 75 similar to that of dupilumab. No head to head studies

Silverberg JI, Toth D, Bieber T, Alexis AF, Elewski BE, Pink AE, Hijnen D, Jensen TN, Bang B, Olsen CK, Kurbasic A, Weidinger S; ECZTRA 3 study investigators. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol. 2021 Mar;184(3):450-463. doi: 10.1111/bjd.19573. Epub 2021 Feb 22. PMID: 33000503; PMCID: PMC7986183.

Systemic JAKi for Atopic Dermatitis

Upadacitini
JAK 1 inhibi
> 12 years c
15 or 30mg
FDA Black B
PO



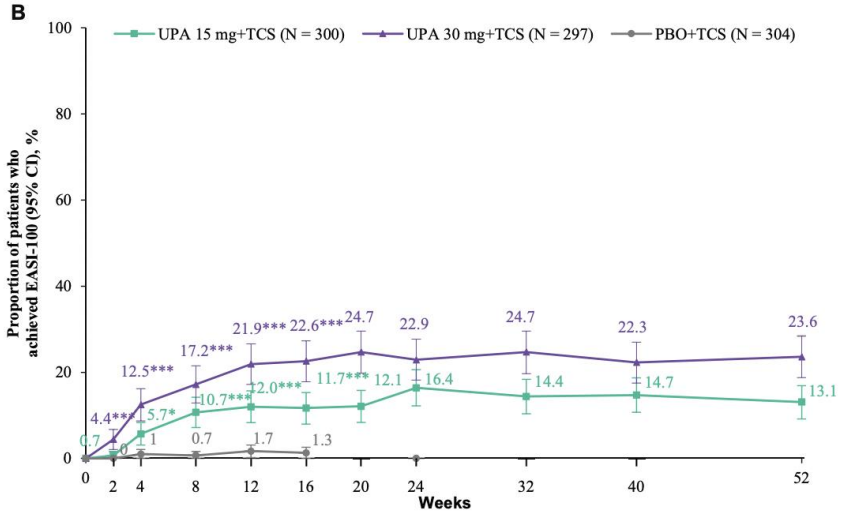


UPADACITINIB

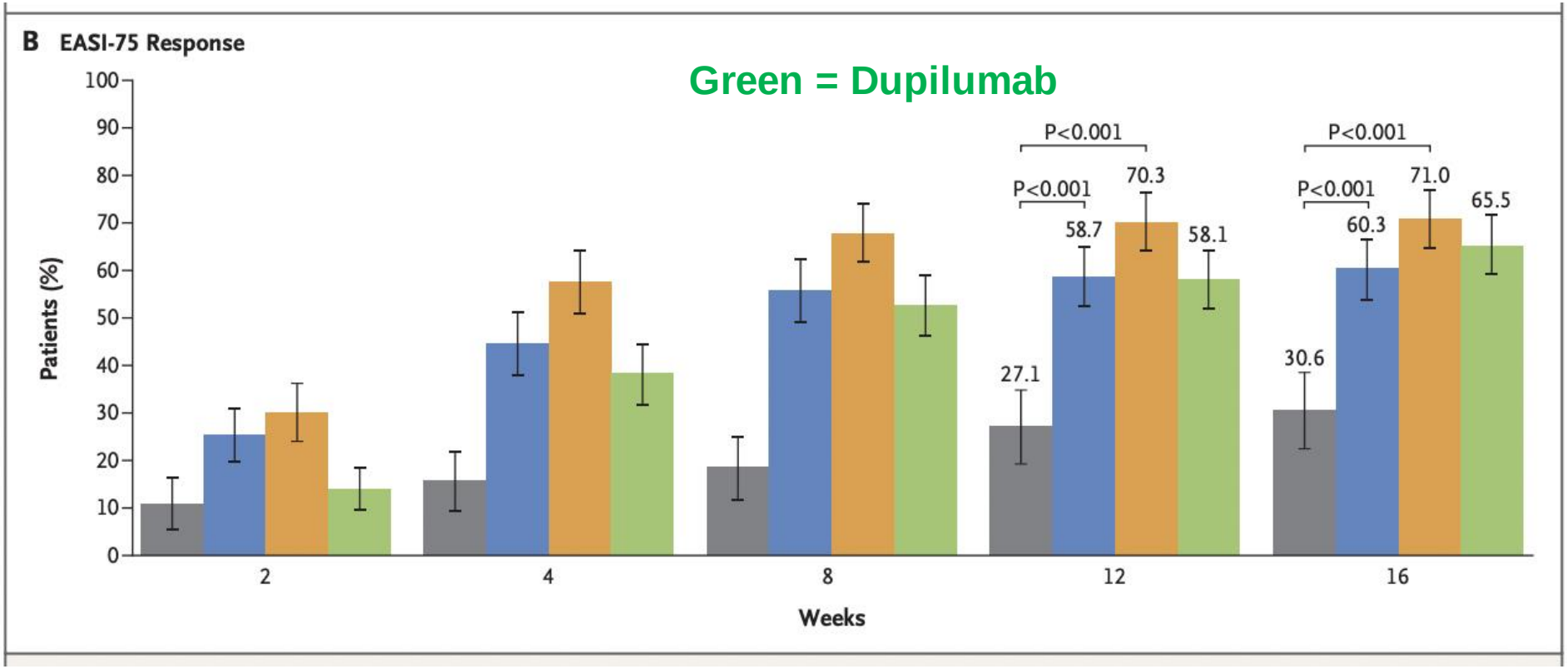
EASI 75- 50.8/69% (15 vs 30mg)

EASI 90- 37.7/55.4%

EASI 100- 13.1/23.6%



Silverberg JI, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, Costanzo A, Rosmarin D, Lynde C, Liu J, Gamelli A, Zeng J, Ladizinsl Upadacitinib plus topical corticosteroids in atopic dermatitis: Week 52 AD Up study results. J Allergy Clin Immunol. 2022 Mar ;149(3): 10.1016/j.jaci.2021.07.036. Epub 2021 Aug 14. PMID: 34403658.



Abrocitinib 100mg and 200mg > placebo

- 60.3% (100/blue) and 71% (200/orange) reaching EASI75 vs 30.6% in placebo group

- Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, Kataoka Y, Chu CY, DiBonaventura M, Rojo R, Antinew J, Ionita I, Sinclair R, Forman S, Zdybski J, Biswas P, Malhotra B, Zhang F, Valdez H; JADE COMPARE Investigators. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. N Engl J Med. 2021 Mar 25;384(12):1101-1112. doi: 10.1056/NEJMoa2019380. PMID: 33761207.

Upadacitinib- Clinical Trials Side Effects

MASSACHUSETTS GENERAL HOSPITAL DERMATOLOGY

Table 3: Adverse Reactions Reported in ≥ 1% of Patients with Atopic Dermatitis Treated with RINVOQ 15 mg or 30 mg

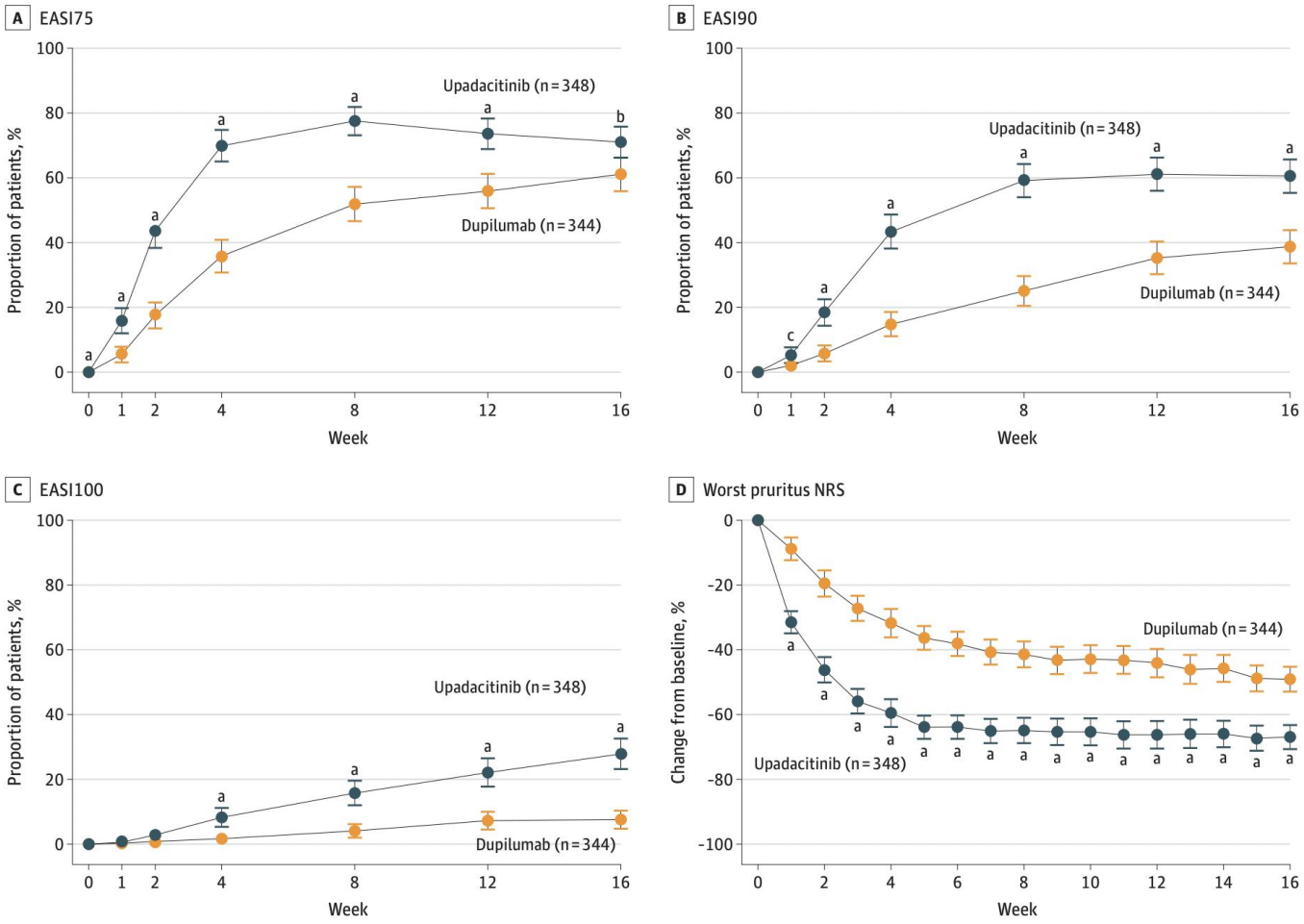
Adverse Reaction	Placebo	RINVOQ 15 mg	RINVOQ 30 mg
	n=902 (%)	n=899 (%)	n=906 (%)
Upper respiratory tract infection (URTI)*	17	23	25
Acne**	2	10	16
Herpes simplex***	2	4	8
Headache	4	6	6
Increased blood creatine phosphokinase	2	5	6
Cough	1	3	3
Hypersensitivity****	2	2	3
Folliculitis	1	2	3
Nausea	1	3	3
Abdominal pain*****	1	3	2
Pyrexia	1	2	2
Increased Weight	1	2	2
Herpes zoster******	1	2	2
Influenza	<1	2	2
Fatigue	1	1	2
Neutropenia	<1	1	2
Myalgia	1	1	2
Influenza like illness	1	1	2

Rinvoq Package Insert

Comparative Studies of JAKi vs Dupilumab

- 24 week head to head, phase 3b, multicenter, randomized, double blinded, double dummy, active controlled clinical trial comparing upadacitinib (30mg) vs dupilumab (300 mg) in ADULTS

Blauvelt A, Teixeira HD, Simpson EL, Costanzo A, De Bruin-Weller M, Barbarot S, Prajapati VH, Lio P, Hu X, Wu T, Liu J, Ladizinski B, Chu AD, Eyerich K. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2021 Sep 1;157(9):1047-1055. doi: 10.1001/jamadermatol.2021.3023. Erratum in: JAMA Dermatol. 2022 Feb 1;158(2):219. Erratum in: JAMA Dermatol. 2022 Feb 1;158(2):219. PMID: 34347860; PMCID: PMC8340015.



Upadacitinib 30mg superior to dupilumab in ALL metrics

	Dupi	UPA
AEs of special interest		
Serious infections	2 (0.6)	4 (1.1)
Opportunistic infection, excluding tuberculosis and herpes zoster[c]	0	1 (0.3)
Herpes zoster	3 (0.9)	7 (2.0)
Active tuberculosis	0	0
Nonmelanoma skin cancer[d]	1 (0.3)	0
Malignant neoplasm, excluding NMSC	0	0
Lymphoma	0	0
Hepatic disorder[e]	4 (1.2)	10 (2.9)
Adjudicated gastrointestinal perforations	0	0
Anemia	1 (0.3)	7 (2.0)
Neutropenia	2 (0.6)	6 (1.7)
Lymphopenia	0	2 (0.6)
Creatine phosphokinase elevation	10 (2.9)	23 (6.6)
Renal dysfunction	1 (0.3)	1 (0.3)
Adjudicated major adverse cardiovascular events	0	0
Adjudicated venous thromboembolic events	0	0

	Dupi	UPA
TEAEs reported by ≥5% in either treatment group		
Acne[f]	9 (2.6)	55 (15.8)
Dermatitis atopic	29 (8.4)	24 (6.9)
Upper respiratory tract infection	13 (3.8)	22 (6.3)
Blood CPK level increased	10 (2.9)	23 (6.6)
Nasopharyngitis	22 (6.4)	20 (5.7)
Headache	21 (6.1)	14 (4.0)
Conjunctivitis	29 (8.4)	5 (1.4)

Abrocitinib vs Dupilumab?

MASSACHUSETTS GENERAL HOSPITAL
DERMATOLOGY

- Abrocitinib 200mg > dupilumab at decreasing itch score
- However, not statistically significantly better when it came to EASI 75 or IGA
- Side effect profile similar to upadacitinib

Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, Kataoka Y, Chu CY, DiBonaventura M, Rojo R, Antinew J, Ionita I, Sinclair R, Forman S, Zdybski J, Biswas P, Malhotra B, Zhang F, Valdez H; JADE COMPARE Investigators. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. N Engl J Med. 2021 Mar 25;384(12):1101-1112. doi: 10.1056/NEJMoa2019380. PMID: 33761207.

- Living network meta-analysis

- Comparative efficacy necessary but not always available
  - High cost
  - Not advantageous for drug companies (what if your drug is weaker)

Conclusions and relevance: In this systematic review and meta-analysis, abrocitinib, 200 mg; and upadacitinib, 30 mg daily, were associated with slightly better scores than dupilumab, and upadacitinib, 15 mg daily, was associated with similar scores to dupilumab. Abrocitinib, 100 mg daily, baricitinib, 4 mg and 2 mg daily, and tralokinumab, 300 mg, every 2 weeks were associated with slightly worse scores.

Upadacitinib 30mg/Abrocitinib 200mg > Dupilumab = Upadacitinib 15mg > Abrocitinib 100mg/Tralokinumab 300mg

Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, Di Giorgio S, Arents BWM, Burton T, Spuls PI, Schmitt J, Flohr C. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol. 2022 May 1;158(5):523-532. doi: 10.1001/jamadermatol.2022.0455. PMID: 35293977; PMCID: PMC8928094.

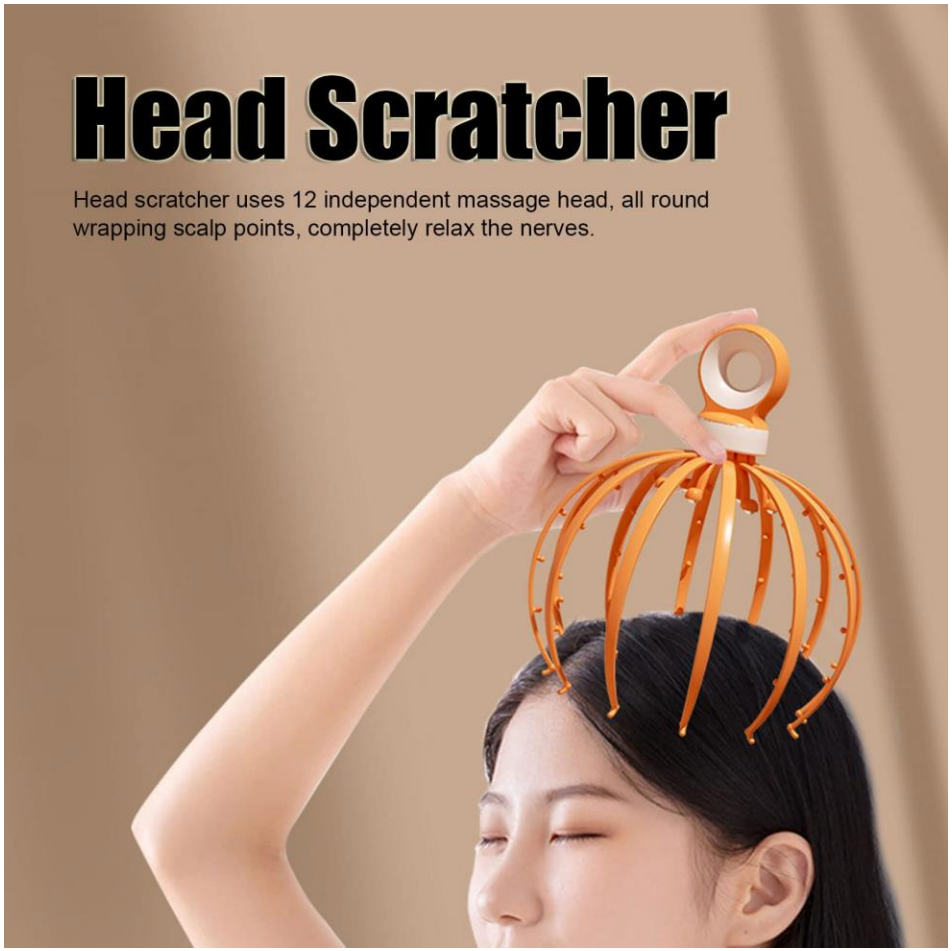
Greener the better

	EASI	POEM	ITCH
Dupilumab 300mg Q2W (Standard Dose)	-10.72 (-12.30 to -9.19)	-7.05 (-7.64 to -6.50)	-2.14 (-2.38 to -1.90)
[redacted]	-4.98 (-13.97 to 4.02)		
[redacted]	-3.82 (-11.33 to 3.68)		-1.30 (-2.74 to 0.13)
Leb[redacted]2W (Standard Dose)	-9.10 (-12.36 to -5.84)	-6.10 (-9.40 to -2.76)	-1.77 (-2.32 to -1.24)
[redacted]	-3.48 (-9.89 to 2.93)	-4.21 (-7.30 to -1.13)	-1.30 (-3.03 to 0.41)
[redacted]	-3.40 (-7.36 to 0.52)	-4.77 (-7.24 to -2.35)	-2.16 (-2.88 to -1.44)
Omalizumab	0.17 (-6.81 to 7.23)	-0.51 (-3.59 to 2.51)	
[redacted]	-2.13 (-6.98 to 2.68)		-0.57 (-1.95 to 0.81)
Tralokinumab 300mg Q2W (Standard Dose)	-6.45 (-8.67 to -4.27)	-4.47 (-5.37 to -3.58)	-1.08 (-1.51 to -0.65)
[redacted]	1.58 (-5.01 to 8.27)		0.03 (-1.69 to 1.76)
Oral JAK Inhibitors			
Abrocitinib 200mg (High Dose)	-9.44 (-11.90 to -6.98)	-7.38 (-8.23 to -6.51)	-2.22 (-2.62 to -1.83)
Abrocitinib 100mg (Low Dose)	-6.89 (-9.49 to -4.28)	-4.69 (-5.62 to -3.74)	-1.40 (-1.82 to -0.99)
[redacted] (High Dose)	-5.99 (-8.78 to -3.22)	-4.51 (-5.61 to -3.39)	-1.24 (-1.71 to -0.77)
[redacted] (Low Dose)	-3.47 (-6.81 to -0.12)	-2.21 (-3.60 to -0.80)	-0.69 (-1.27 to -0.11)
Upadacitinib 30mg (High Dose)	-13.99 (-16.62 to -11.37)	-8.26 (-9.41 to -7.20)	-2.91 (-3.35 to -2.49)
Upadacitinib 15mg (Low Dose)	-11.43 (-14.25 to -8.64)	-6.54 (-7.64 to -5.45)	-1.90 (-2.35 to -1.45)

Chu AWL, Wong MM, Rayner DG, Guyatt GH, Díaz Martinez JP, Ceccacci R, Zhao IX, McMullen E, Srivastava A, Wang J, Wen A, Wang FC, Brignardello-Petersen R, Izcovich A, Oykhman P, Wheeler KE, Wang J, Spergel JM, Singh JA, Silverberg JI, Ong PY, O'Brien M, Martin SA, Lio PA, Lind ML, LeBovidge J, Kim E, Huynh J, Greenhawt M, Gardner DD, Frazier WT, Ellison K, Chen L, Capozza K, De Benedetto A, Boguniewicz M, Smith Begolka W, Asiniwasis RN, Schneider LC, Chu DK. Systemic treatments for atopic dermatitis (eczema): Systematic review and network meta-analysis of randomized trials. J Allergy Clin Immunol. 2023 Dec;152(6):1470-1492. doi: 10.1016/j.jaci.2023.08.029. Epub 2023 Sep 9. PMID: 37678577.

How do you choose???

- All FDA approved systemic medications work REALLY well with marginal differences
- Safety first (risk tolerance)
- Method of administration (PO vs SQ)
- Convenience (frequency of admin, refrigeration?, start/stop?)
- Efficacy if tried and failed other meds



My Personal Preference

- 1st line- Dupilumab
  - Strong efficacy and safety
  - Easiest to get insurance coverage

----------IF OVER 12----------

- 2nd line- Tralokinumab
  - Strong efficacy and safety (though not as good as dupilumab)

- 3rd line- Upadacitinib 15mg or 30mg OR Abrocitinib 100mg or 200mg
  - Best efficacy but ??safety

Conclusion

- Atopic dermatitis is common in children
- Moisturizing + gentle skin care is the cornerstone to all treatment regimens
- MANY choices when it comes to treatment for atopic dermatitis
- MANY MORE choices are coming down the pipeline

- **Lebrikizumab Phase 3 Randomized Controlled Clinical Trial**

- 6 **months** – 18 years of age

- Failed standard treatments of atopic dermatitis

- Injectable every 4 weeks

- 16 weeks with 52 week extension study afterwards

Enrolling

A Study of Lebrikizumab (LY3650150) in Participants 6 Months to <18 Years of Age With Moderate-to-Severe Atopic Dermatitis (ADorable-1)

J2T-MC-KGBI - ClinicalTrials.gov - NCT05559359

The main purpose of this study is to measure the effect, safety and how well the body absorbs Lebrikizumab in pediatric participants 6 months to <18 years of age with moderate-to-severe atopic dermatitis (AD).

Jiade.yu@mgh.Harvard.edu