Atopic Dermatitis: topicals & biologics

The therapeutic revolution is underway

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Conflicts of Interest Disclosure

Amgen, Eli Lilly, Abbvie, Pfizer, National Psoriasis Foundation, LEO, Regeneron, Sanofi, Arcutis, Dermavant, Novartis

Goals:

1. Review the diagnosis of atopic dermatitis
2. Incorporate new therapeutics in your treatment algorithm for atopic dermatitis
3. Learn best practices

What exactly is eczema?

maculopapularrash
atopicdermatitis dermatitisnos
eczema
atopiceczema
reaction
contactdermatitis hypersensitivity prurigo
lichensimplexchronicus
drugreaction urticaria

AAD Diagnostic Criteria for Atopic Dermatitis

Essential Features: *must be present for diagnosis*

Chronic or relapsing history

Eczema (acute, subacute, chronic)

Pruritus

Typical morphology:

infants/children–face, neck, extensors

Any age group–flexural lesions, sparing groin/axilla

Important Features: support dx

Atopy (personal or family history)

Early age at onset

IgE reactivity

Xerosis

Associated features: nonspecific

Facial pallor/dermographism

Keratosis pilaris, P. Alba,

Hyperlinear palms, ichthyosis

Ocular/periorbital changes

Perifollicular accentuation

LIchenification

Prurigo lesions

Key recommendations for practice

1. Emollients should be used as 1° therapy for flares/maintenance.
2. Once daily bathing in lukewarm water for 5-10 min.
3. Antibiotics should be used to treat secondary bacterial infections, not for tx of AD.
4. Skin prick tests or RAST blood test are NOT recommended for routine evaluation of AD.
5. Avoid long-term term tx with oral or IM systemic steroids.
6. Oral antihistamines are not routinely recommended.

Emollients are the foundation of AD skin care routine

Do you apply medication or emollient first?

The National Eczema Society states "There are no standard rules on whether to apply a topical steroid before or after using an emollient. Some people are happiest using an emollient first to prepare the skin, followed by the topical steroid. Whichever order of care you choose, it is important that you leave a gap of at least 10 minutes (and if possible 20-30 minutes). This is intended to avoid diluting the strength of the topical steroid preparation, and to prevent the spread of topical steroids to areas not affected by eczema.

Does Order of Application of Emollient and Topical Corticosteroids Make a Difference in the Severity of Atopic Eczema in Children?

-46 patients 4mo-5yo with moderate to severe AD

Group A: emollient then TCS 15 min. later twice daily x 2 weeks

Group B: TCS then emollient 15 min later twice daily x 2 weeks

No difference in EASI score or improvement in BSA or itch scores

Conclusion: This study suggests that the ***order of application of emollient and TCS does not matter*** in the treatment of AE in children and that parents can apply topical medications in whichever order they prefer.

Ng SY, Begum S, Chong SY. Does Order of Application of Emollient and Topical Corticosteroids Make a Difference in the Severity of Atopic Eczema in Children? Pediatr Dermatol. 2016 Mar-Apr;33(2):160-4. doi: 10.1111/pde.12758. Epub 2016 Feb 9. PMID: 26856694.

Topical Corticosteroids (TCS)

Acute treatment: QD or BID application
Maintenance: Intermittent application–twice weekly

Low-potent

Delicate skin–face, axilla, genitals

Mid-potent

work-horse of management

Super-potent

Refractory lesion, touch-to-treat areas

Hydrocortisone

Aclometasone

Desonide

Fluocinonide

Triamcinolone

Mometasone

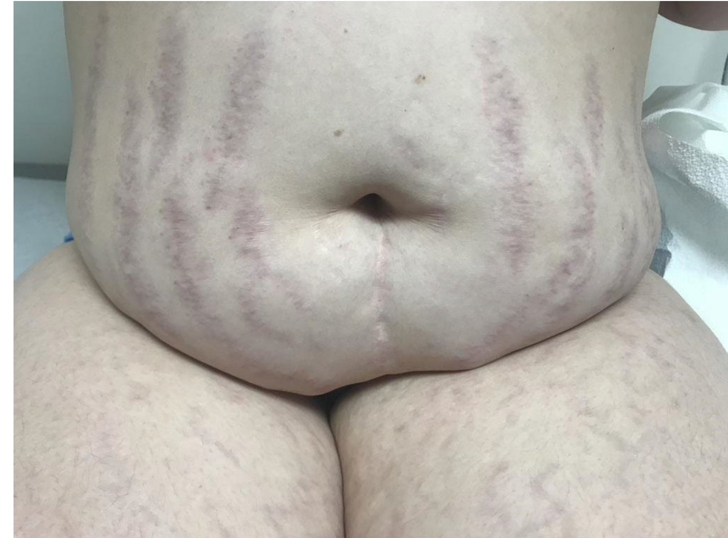
Clobetasol

Topical Corticosteroids: adverse events

Atrophy: hypopigmentation, thinning/increased skin fragility, poor wound healing, striae

Steroid Phobia: discontinuous use or poor adherence resulting in “lack of efficacy”

Consider Vehicle–the secret sauce matters!



Topical Calcineurin Inhibitors

Recommended as a steroid sparing agent for *acute and chronic* AD, especially sensitive skin areas

Pimecrolimus 1% cream: comparable to low-potency TCS

Tacrolimus 0.03% oint: superior to pimecrolimus & low potency TCS

Tacrolimus 0.1% oint: superior to 0.03%, pimecrolimus & low potency TCS; equivocal to mid-potency TCS

Slower onset of action than TCS

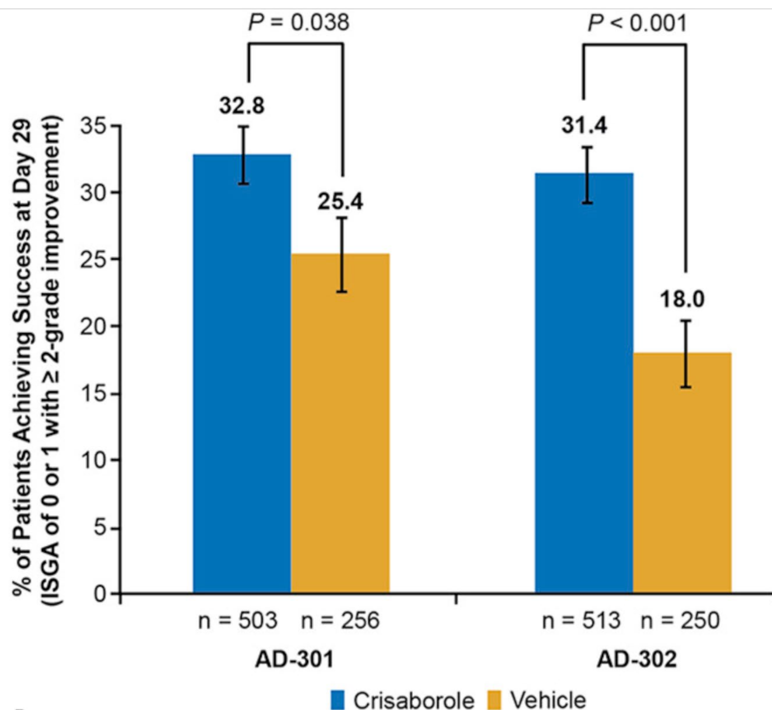
Local skin reactions: burning, stinging & pruritus

Eichenfield LF, et al. J Am Acad Dermatol. 2014;71(1):116-132; Cury Martins J, et al. Cochrane Database Syst Rev. 2015;(7):CD009864.

Topical PDE4 inhibitor: *Eucrisa* (crisaborole)

FDA approved since 2016

Recommended as a steroid sparing agent for ***acute and chronic* AD** for **mild-moderate AD > 3 months of age**



Local adverse reactions: stinging & burning

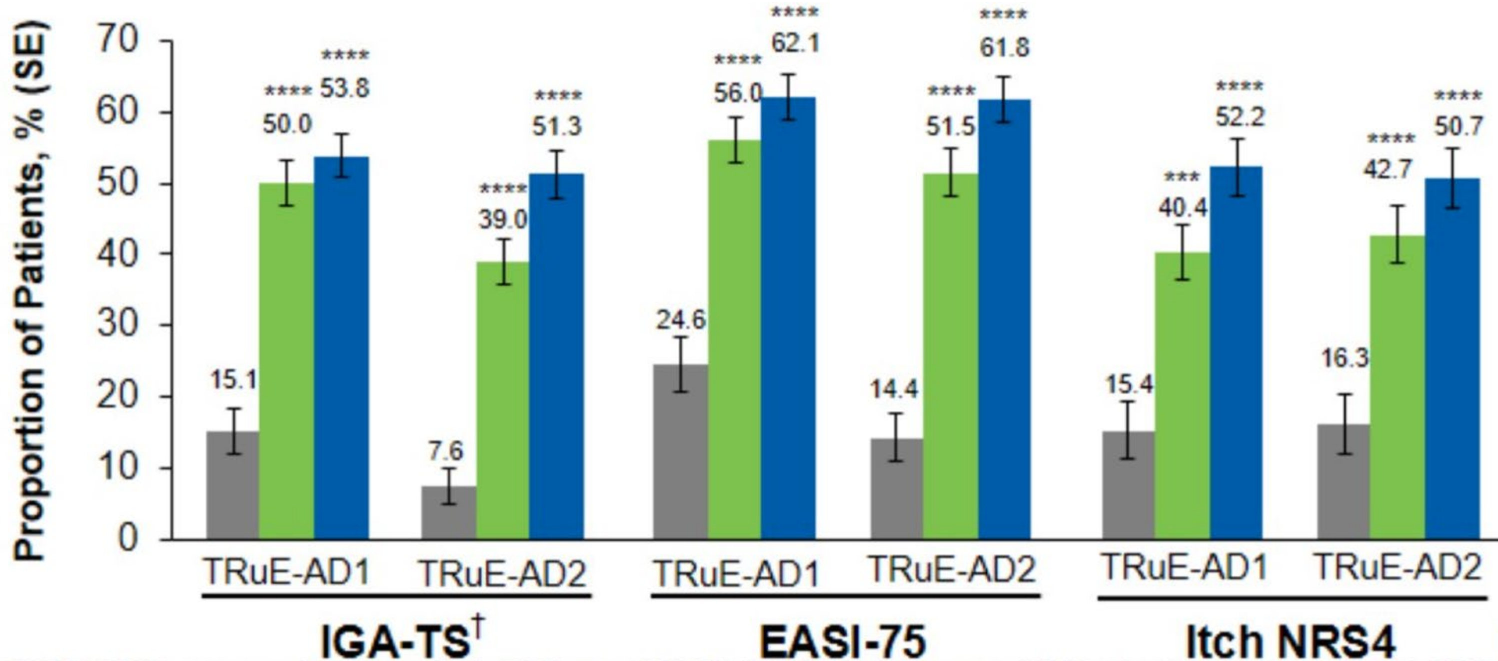
Slow onset of efficacy → use as steroid sparing topical for maintenance.

1st Topical JAKi (1,2): *Opzelura* (ruxolitinib)

- FDA approved in Sep 2021
- Twice daily application
- 60 gram tube

for the topical short-term and non-continuous chronic treatment of *mild to moderate atopic dermatitis* (AD) in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable.

Opzelura (ruxolitinib) 1.5%: results at 8 weeks



Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Leung DYM, Forman SB, Venturanza ME, Sun K, Kuligowski ME, Simpson EL. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol. 2021 Oct;85(4):863-872. doi: 10.1016/j.jaad.2021.04.085. Epub 2021 May 4. PMID: 33957195.

Pooled safety data from TRuE-AD1 and TRuE-AD2 during the 8-week vehicle-controlled period

	OPZELURA (N = 499) n (%)	Vehicle (N = 250) n (%)
Subjects with any TEAE	*132 (27)*	*83 (33)*
Nasopharyngitis	13 (3)	2 (1)
Bronchitis	4 (1)	0 (0)
Ear infection	4 (1)	0 (0)
Eosinophil count increased	4 (1)	0 (0)
Urticaria	4 (1)	0 (0)
Diarrhea	3 (1)	1 (< 1)
Folliculitis	3 (1)	0 (0)
Tonsillitis	3 (1)	0 (0)
Rhinorrhea	3 (1)	1 (< 1)
Burning	0.8%	4.4%
Pruritus	0%	2.4%

Low rates of application site reactions

Rare events occurring <1%: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis

Opzelura (ruxolitinib): black box warning

Mortality

Major Cardiovascular Events

Thrombosis

Malignancy

These warnings were based on data from a long-term, randomized, post-marketing study (Phase IV) assessing safety of tofacitinib versus tumor necrosis factor alpha (TNFa) inhibitors in patients with rheumatoid arthritis.

Opzelura (ruxolitinib): safety summary

No new safety signals in the long term safety period up to 52 weeks

No clinically significant changes or trends in hematologic tests during 52 weeks period

No adverse events suggestive of a relationship to systemic exposure

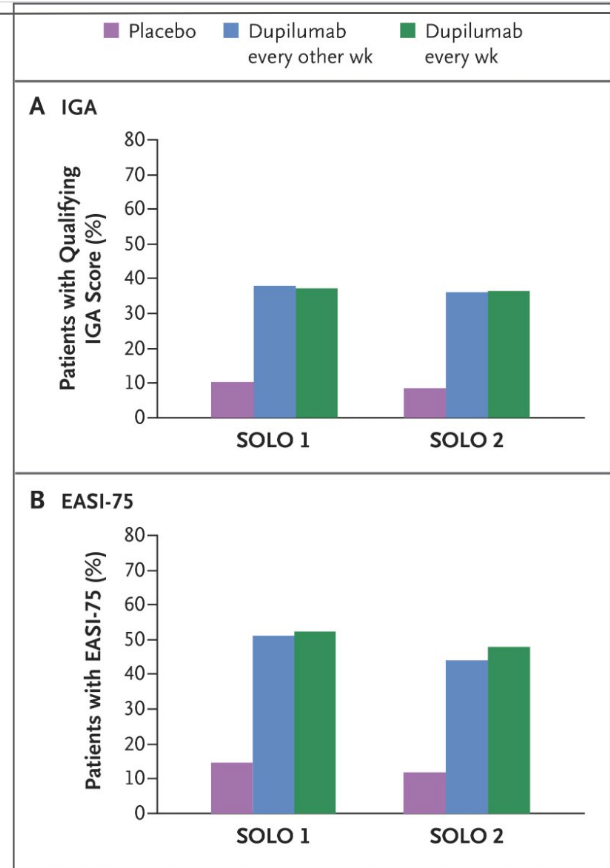
Dupilumab (Dupixent) FDA approved since 2017

Now approved for >6 months age

MOA: monoclonal Ab that binds to IL-4**α** Receptor thereby inhibiting IL4 & 13

Not an immunosuppressant

Given by SQ injection



Dupilumab-associated Conjunctivitis (DAC)

Associated with worse atopic dermatitis severity

disproportionally higher incidence of conjunctivitis in AD patients on dupilumab compared with those with asthma, chronic rhinosinusitis, or eosinophilic esophagitis.

Clinical presentation: bilateral conjunctival hyperemia most prominent finding.
Other: Ocular symptoms included pruritus, tearing, irritation, foreign body sensation, and decreased visual acuity.
Onset: 2-8 weeks
Overall incidence in 6 RCTs: 8.6–22.1%

Akinlade BO, Guttman-Yassky EM, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol.* 2019 doi: 10.1111/bjd.17869.

Dupilumab-associated Conjunctivitis treatment algorithm

First Step:

Artificial tears, ophthalmic/oral antihistamines (olopatadine, systane)

If not responding or moderate-severe conjunctivitis → co-management with ophthalmology is necessary if treatment requires steroid, tacrolimus, or cyclosporine eyedrops or eye ointment.

Head and Neck associated dermatitis

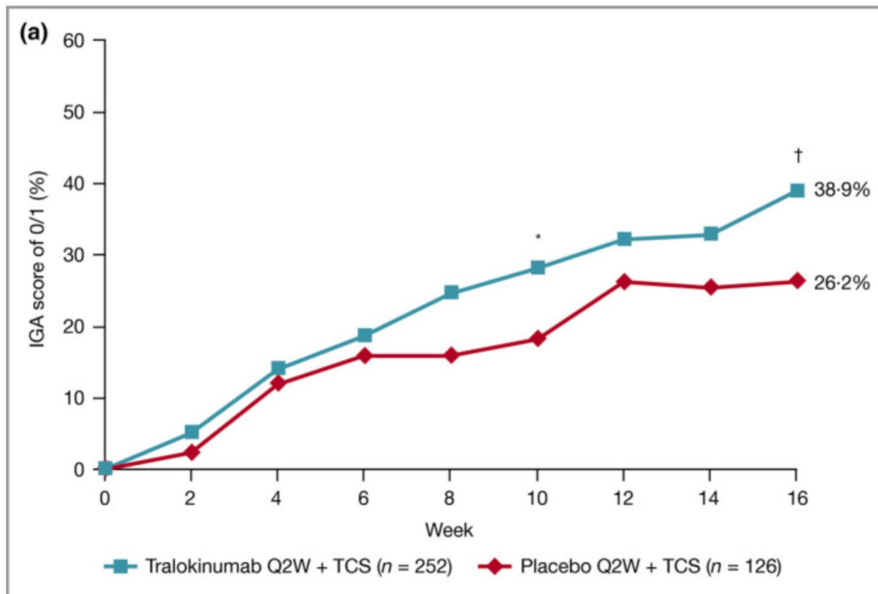
Tx (*without dupilumab interruption*):

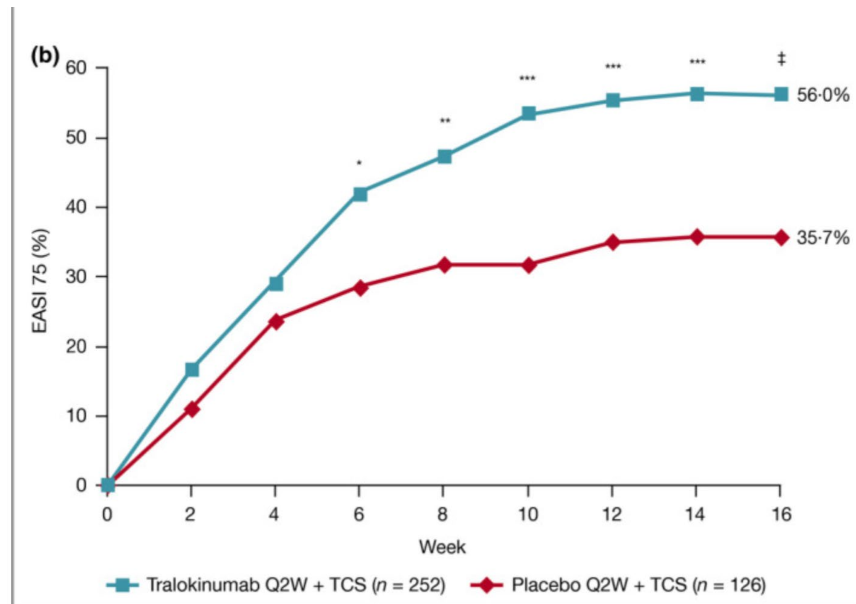
short courses of low- to mid-potency topical steroids, topical calcineurin inhibitors and/or topical ketoconazole

A short course of itraconazole or adjunct systemic therapy has provided benefit in some patients not responding to topical therapy.

Tralokinumab (*Adbury*): immunoglobulin G4 monoclonal antibody that inhibits IL-13 (FDA approved in Dec 2021)

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





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.

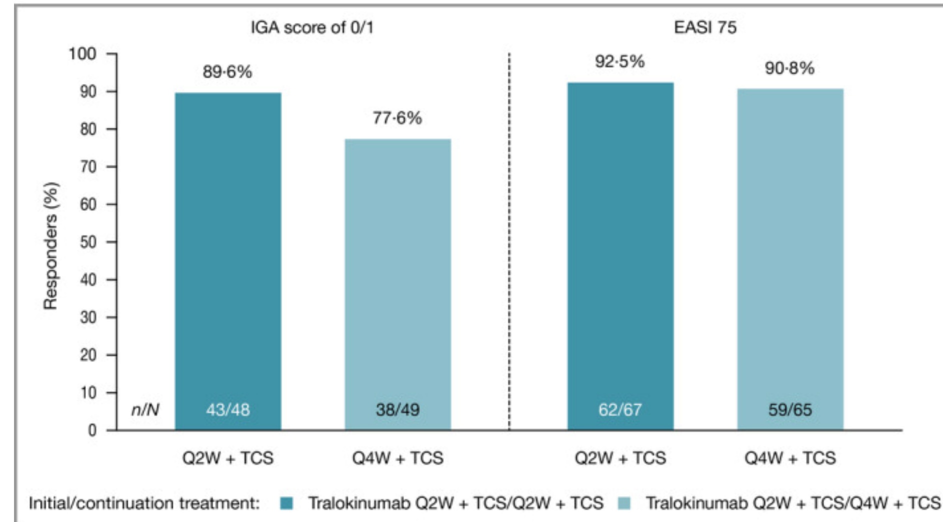
Tralokinumab (*Adbury*): safety & maintenance

tralokinumab may offer the possibility of dosing Q4W

overall frequency and severity of AEs comparable with placebo over 32 weeks.

SAEs was low, with most events not being related to treatment

Mild-to-moderate conjunctivitis: 11 vs 1% was seen in the patients treated with tralokinumab plus TCS



A high % of patients maintain 0/1 at week 32.

Coming soon…AD treatment evolution

Lebrikizumab

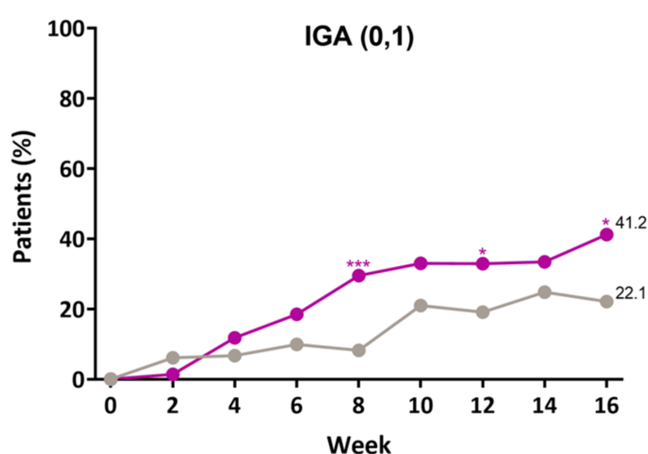
Tapinarof

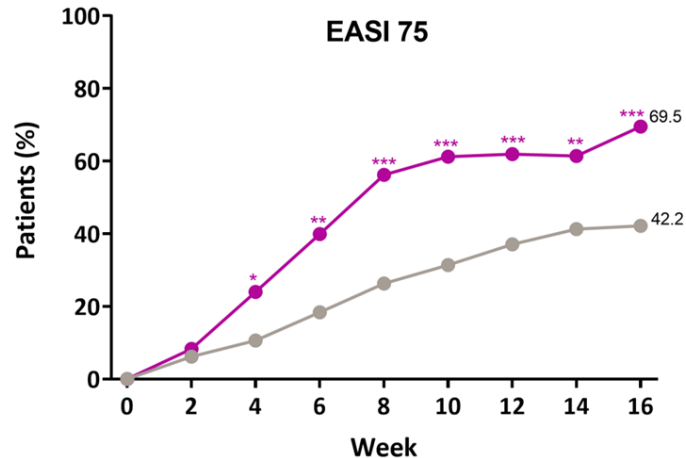
Roflumilast

Lebrikizumab: high-affinity immunoglobulin G4 monoclonal antibody targeting interleukin (IL)-13

Lebrikizumab selectively prevents IL-13 signaling via the receptor

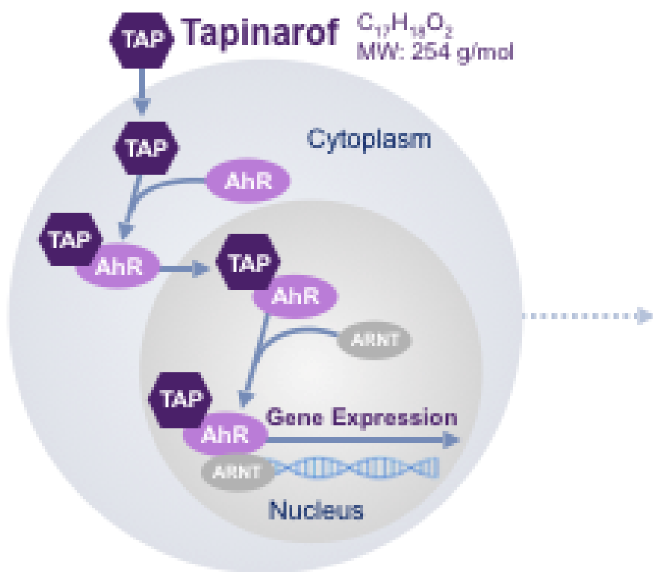
Efficacy and Safety of Lebrikizumab in Combination with Topical Corticosteroids in Patients with Moderate-to-Severe Atopic Dermatitis: A Phase 3, Randomized, Placebo-Controlled Trial (ADhere)





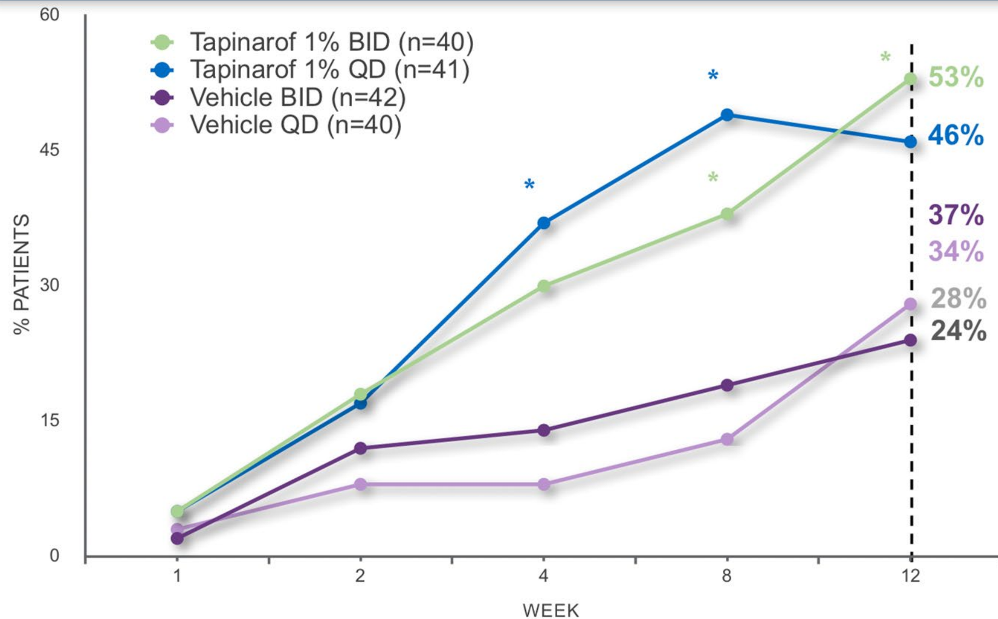
Placebo+TCS/MCMC LEB 250mg+TCS/MCMC

Investigational topical: Tapinarof cream is a small-molecule topical aryl hydrocarbon receptor (AhR) agonist



Gene Regulation effects	Possible Effects in the skin
↓TH17 cytyokines	Improves psoriasis plaques
↓TH2 cytokines	Decrease AD inflammation: IL4, 5, 13
↑Antioxidant Activity	Decrease oxidative stress
↑Filaggrin, loricrin & involucrin	Normalize skin barrier

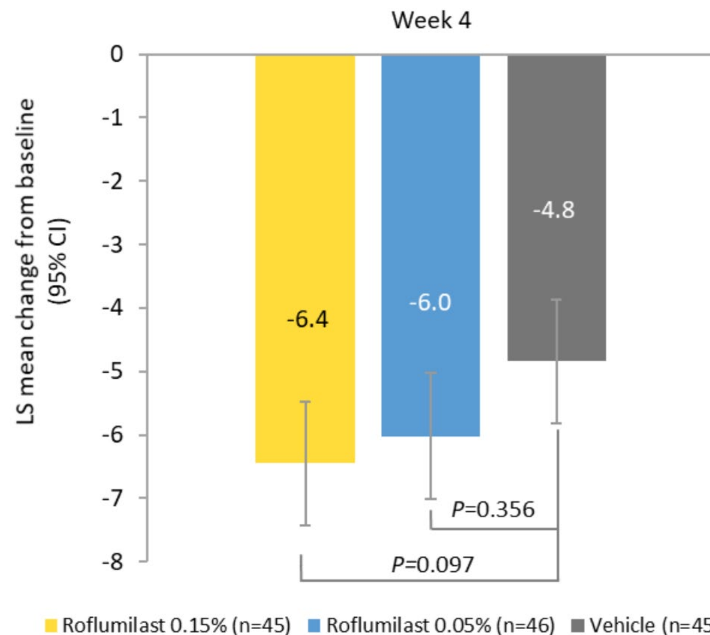
A phase 2b, double-blind, vehicle-controlled study randomly assigned adolescents and adults with AD to receive tapinarof cream 0.5%, 1%, or vehicle, once or twice daily, for 12 weeks with a 4-week follow-up



FDA approved for psoriasis at this time, not atopic dermatitis.

Investigational topical: Roflumilast cream is a highly potent PDE-4 inhibitor with ~25- to >300-fold higher potency than other approved PDE-4 inhibitors

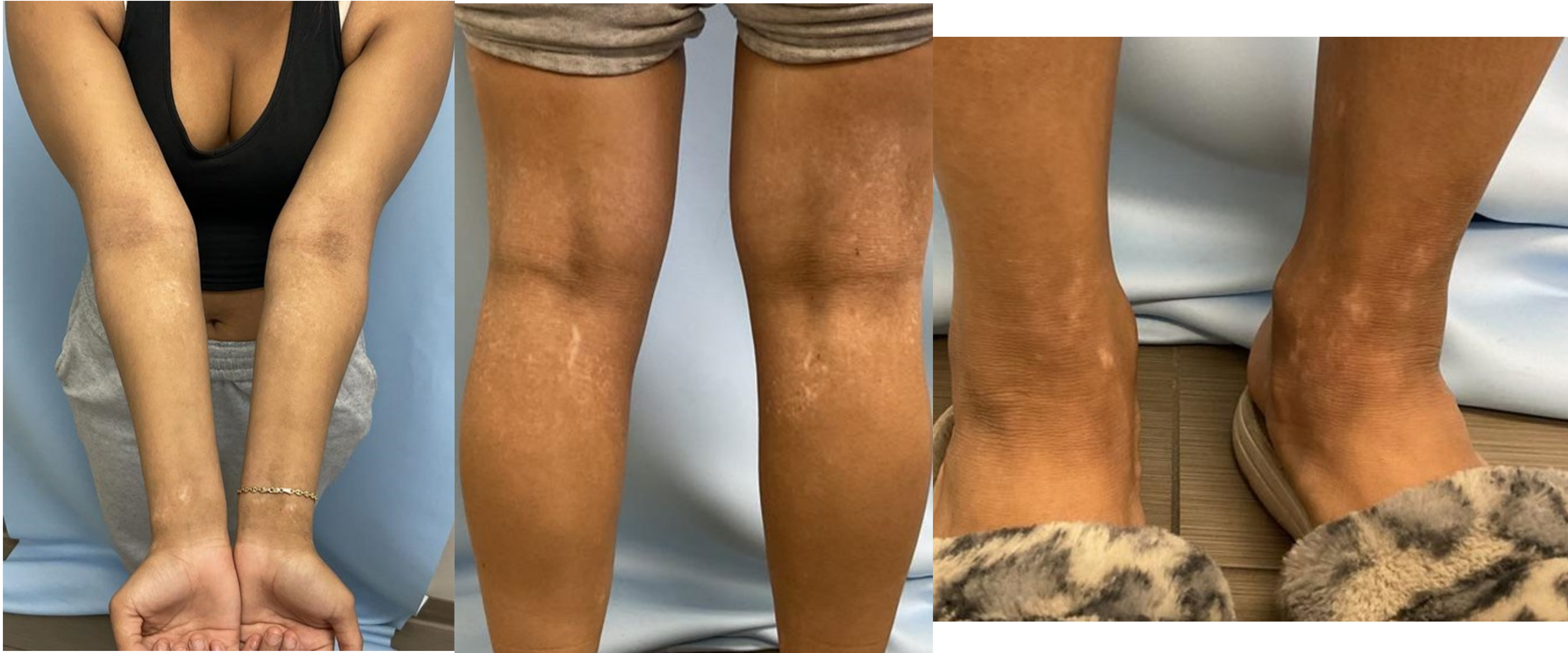
The Safety and Efficacy of Roflumilast Cream 0.15% and 0.05% in Atopic Dermatitis: Phase 2 Proof-of-Concept Study



- At this early time point of 4 weeks, there was improvement in atopic dermatitis severity, yet not statistically significant for the primary endpoint
- A robust response to vehicle was observed

Gooderham, M. J., Kircik, L. H., Zirwas, M., Lee, M., Kempers, S. E., Draelos, Z. D., Ferris, L., Jones, T. M., Sain l., Merritt, C., Elias, M., Navale, L., Higham, R. C., Droege, M., & Berk, D. R. (2020). The Safety and Efficacy of Ro Study. *SKIN The Journal of Cutaneous Medicine*, *4*(6), s93. https://doi.org/10.25251/skin.4.supp.93

Post treatment dyspigmentation in skin of color….



Thank you