Apogee
CLINICAL IMMERSION

Understanding Atopic Dermatitis Treatments

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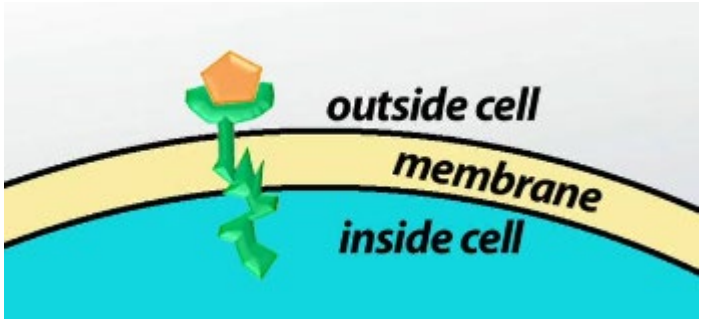
Overview

- What are the different mechanisms of actions of drugs?
  - Antagonists, agonists, and aryl hydrocarbon receptor (AHR)
- What is the difference between topical and systemic medications?
- The Allergist’s approach
- Current & Emerging treatments in atopic dermatitis (AD)
- Q&A

How drugs work

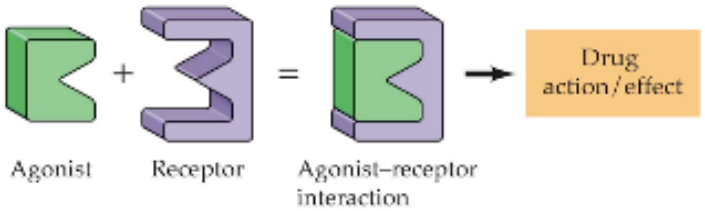
- Mechanism of action: Describes how a drug/substance produces an effect on the body
  - Acting on receptors on the cell membranes
  - Acting in synapses
  - Blocking enzymes
  - Blocking cell transport
  - Etc…

General mechanisms of drug action via receptors



Agonist

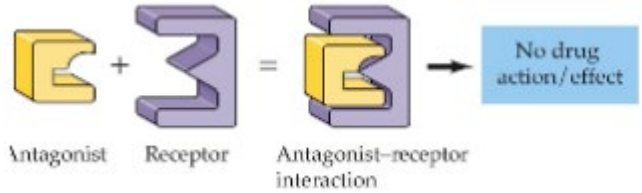
- Drug/substance activates the receptor



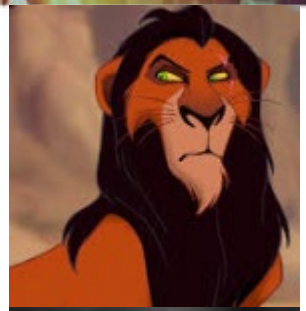
- Examples:
  - Morphine – mimics endorphins at the opioid receptors
  - Isoproterenol – mimics adrenaline at the beta adrenoreceptors

Antagonist

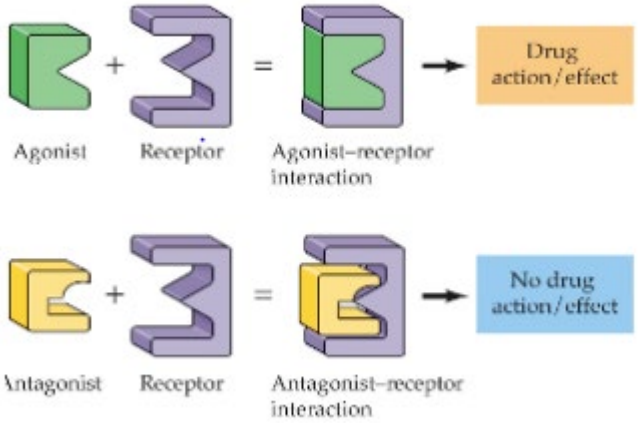
- Drug/substance blocks or dampens a response when it binds to the receptor
- Sometimes called “blockers”



- Examples:
  - Naloxone – binds opioid receptors and blocks the effect of opioids
  - Metoprolol – Beta-blocker used to treat high blood pressure and blocks the beta adrenoreceptors



Examples



Receptor Type	Agonist	Antagonist
Adrenoceptors	Adrenaline	Labetalol
Opioid receptors	Morphine	Naloxone
Histamine receptors	Histamine	Antihistamine (i.e. Benadryl)

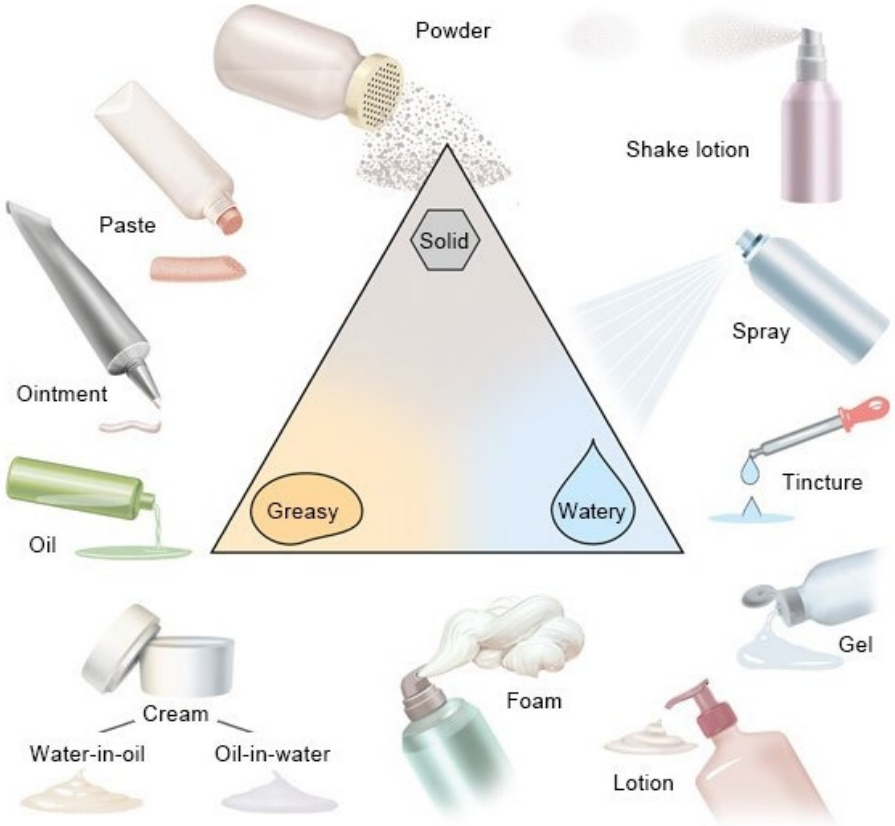
https://resources.time.leeds.ac.uk/pills/pb_12.html

What’s the difference between topical and systemic medications?

Topical medications

- Medication that is applied to a specific part of the body

Topical formulations for the skin



Using medication: Learn More – Topical medications. InformedHealth.org. https://www.ncbi.nlm.nih.gov/books/NBK361003/

Systemic medications

- Drugs that are given by mouth, by injection, or infusion
- When absorbed, they reach the bloodstream and can affect the whole body
- Enteral (gut absorption) or Parenteral (injection/infusion/etc)

The Allergist's Approach

+

Classes of AD Drugs

New & emerging therapies

Approach to AD

Is AD severe?

No

- Identification and elimination of exacerbating factors (irritants, *proven* allergens)
- Addressing psychosocial aspects/quality of life issues
- Education
- Hydration
- Moisturizers
- Topical corticosteroids (low to mid potency)
- Topical calcineurin inhibitors*
- Topical PDE4 inhibitor
- Antiinfective therapy
- Antipruritic therapy
- Written care plan

**Per boxed warning:* second-line, intermittent therapy for patients ≥2 years of age.

Middleton's Allergy: Principles and Practice. 10th edition (unpublished)

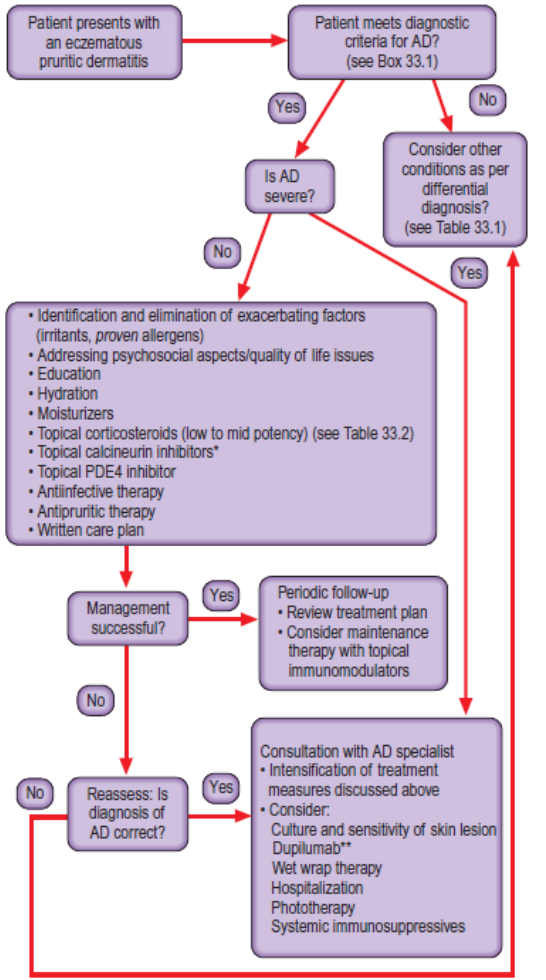


Fig. 33.6 Approach to the patient with atopic dermatitis *(AD)*. **Per boxed warning:* second-line, intermittent therapy for patients ≥2 years of age. ***Approved for patients ≥12 years of age with moderate to severe AD.

Is AD severe?

Yes

Consultation with AD specialist
- Intensification of treatment measures discussed above
- Consider:
  - Culture and sensitivity of skin lesion
  - Wet wrap therapy
  - Dupilumab**
  - Tralokinumab***
  - Oral JAK inhibitor****
  - Phototherapy
  - Hospitalization
  - Systemic immunosuppressives

Approach to the patient with atopic dermatitis (AD). **Approved for patients ≥6 months of age for moderate to severe AD. ***Approved for patients ≥12 years of age for moderate to severe AD. ****Approved for patients ≥12 years of age for moderate to severe AD in the US, with baricitinib approved for patients ≥2 years of age in Europe.

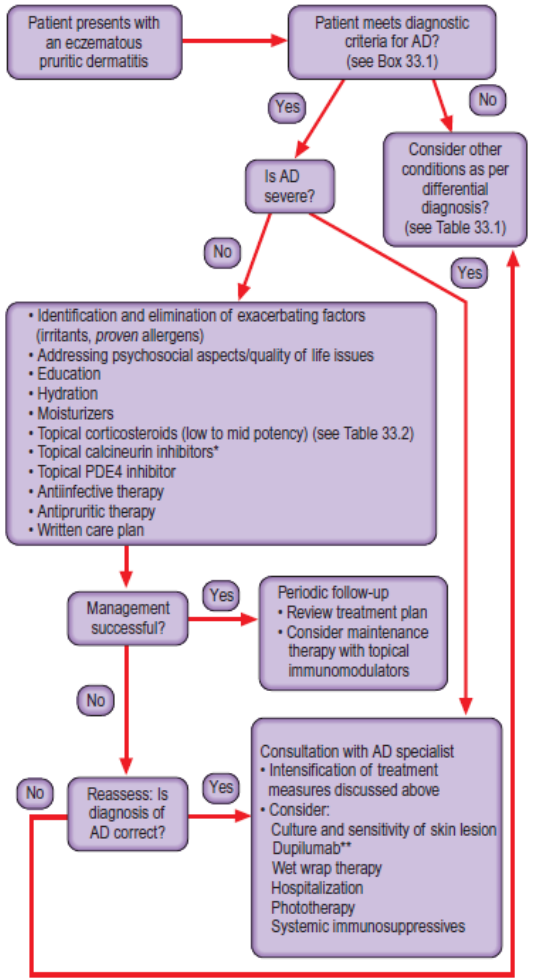


Fig. 33.6 Approach to the patient with atopic dermatitis *(AD)*. **Per boxed warning:* second-line, intermittent therapy for patients ≥2 years of age. ***Approved for patients ≥12 years of age with moderate to severe AD.

Periodic follow-up
- Review treatment plan
- Consider maintenance therapy with topical immunomodulators

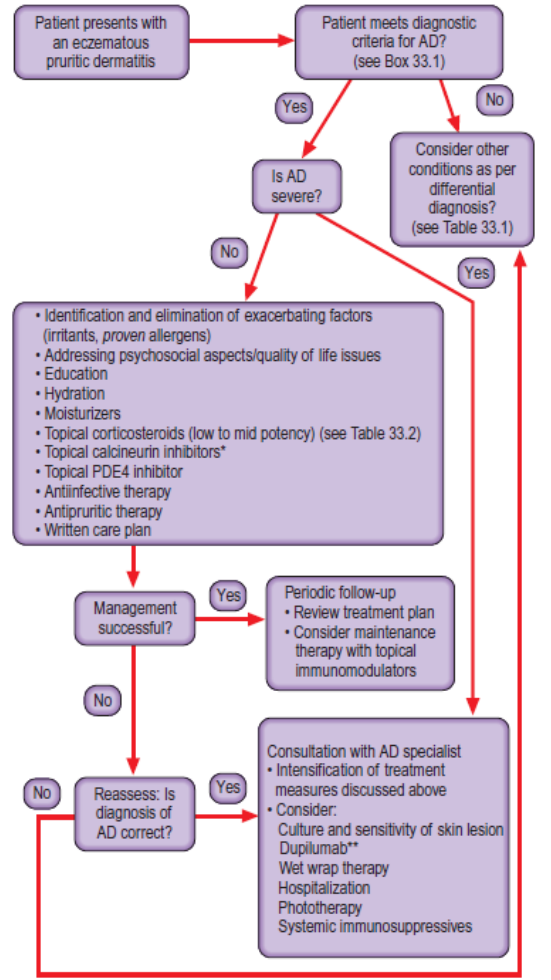


Fig. 33.6 Approach to the patient with atopic dermatitis *(AD)*. **Per boxed warning:* second-line, intermittent therapy for patients ≥2 years of age. ***Approved for patients ≥12 years of age with moderate to severe AD.

The approach in EVERY patient

- Hydration! Moisturization!

Topical Treatments

Current therapies

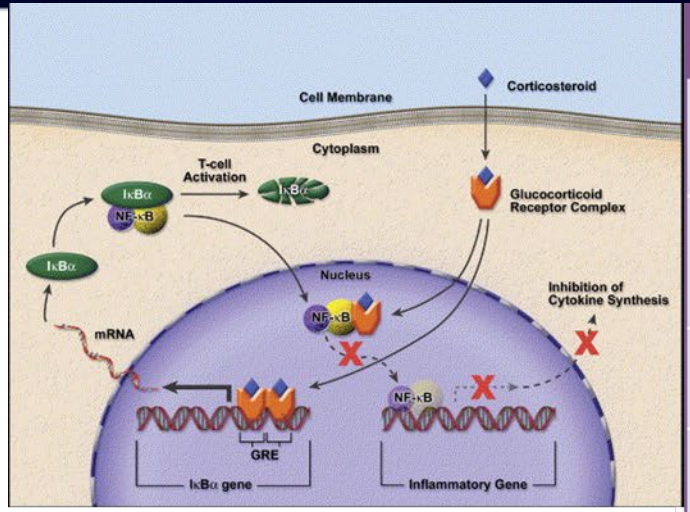
New & emerging therapies

Topical Treatments

Step-up therapy: start with the lowest potency topical medication

- Topical steroids
  - Group 7 is least potent
  - Group 1 is most potent
- Topical calcineurin inhibitors (TCIs)
  - Tacrolimus (Protopic) 0.03% and 0.1% ointment
  - Pimecrolimus (Elidel) 1% cream
- Topical phosphodiesterase-4 (PDE-4) inhibitor
  - Crisaborole (Eucrisa) 2% ointment
  - Roflumilast (Zoryve) 0.15% cream
- Topical AHR agonist
  - Tapinarof (VTAMA) 1% cream
- Topical JAK inhibitor
  - Ruxolitinib
  - Delgocitinib 2% cream
- Can use a mix of the above

Topical Corticosteroids



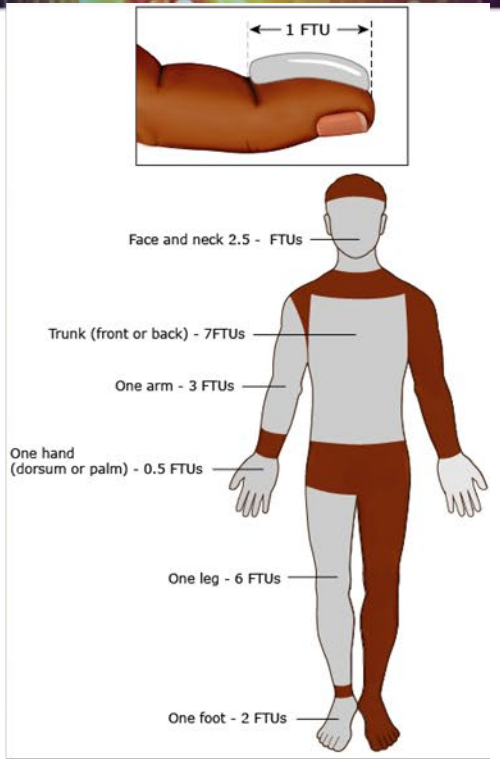
Adverse Effects:

- Skin thinning
- Striae
- Telangiectasia
- Acne
- Withdrawal

Safe when used appropriately

TABLE 33.2 Select Topical Corticosteroid Preparations[a]

Group	Preparations
1	Clobetasol propionate (Temovate) 0.05% ointment/cream Betamethasone dipropionate (Diprolene) 0.05% ointment/cream
2	Mometasone furoate (Elocon) 0.1% ointment Halcinonide (Halog) 0.1% cream Fluocinonide (Lidex) 0.05% ointment/cream Desoximetasone (Topicort) 0.25% ointment/cream
3	Fluticasone propionate (Cutivate) 0.005% ointment Halcinonide (Halog) 0.1% ointment Betamethasone valerate (Valisone) 0.1% ointment
4	Mometasone furoate (Elocon) 0.1% cream Triamcinolone acetonide (Kenalog) 0.1% ointment/cream Fluocinolone acetonide (Synalar) 0.025% ointment
5	Fluocinolone acetonide (Synalar) 0.025% cream Hydrocortisone valerate (Westcort) 0.2% ointment
6	Desonide (DesOwen) 0.05% ointment/cream/lotion/gel Alclometasone dipropionate (Aclovate) 0.05% ointment/cream
7	Hydrocortisone (Hytone) 2.5% and 1% ointment/cream



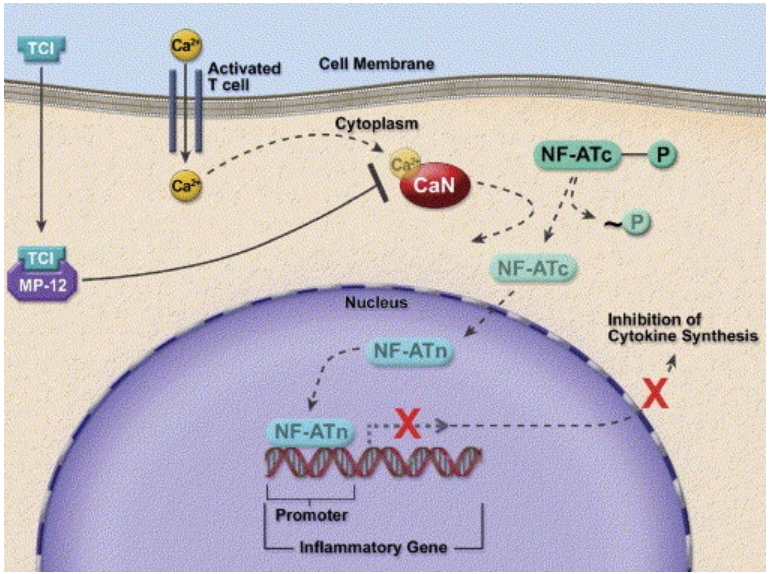
Middleton's Allergy: Principles and Practice. 9th edition

Topical Calcineurin Inhibitors (TCI)

- Tacrolimus (Protopic) 0.03% and 0.1% ointment
  - 0.03% for ≥ 2 years
  - 0.1% for ≥ 16 years
- Pimecrolimus (Elidel) 1% cream
  - for ≥ 2 years

- Once to twice daily
- Commonly used down to 3 months old

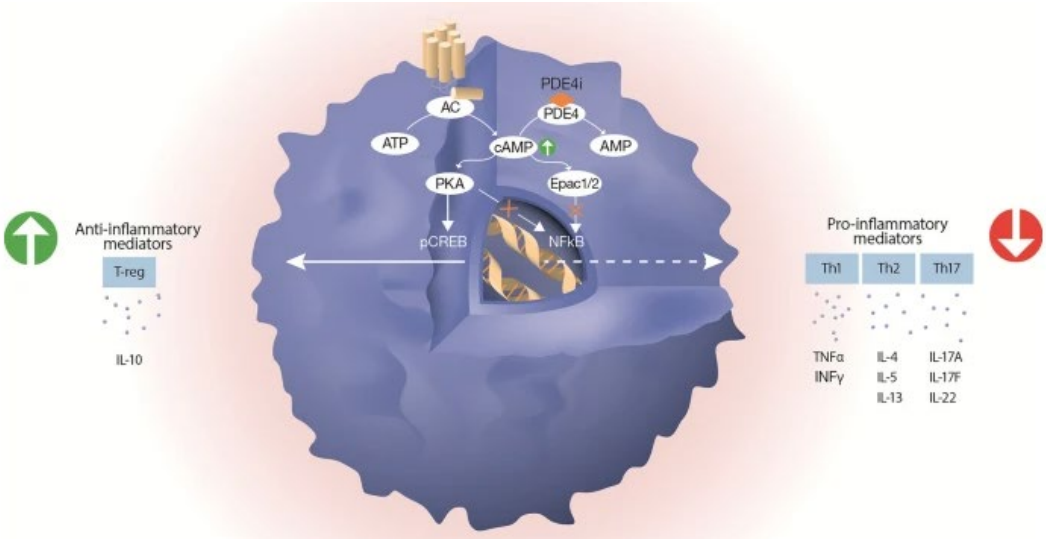
- TCIs have a black box warning – rare cases of malignancy (skin cancer, lymphoma)
  - Updated studies: no credible increase in cancer across all ages[1]



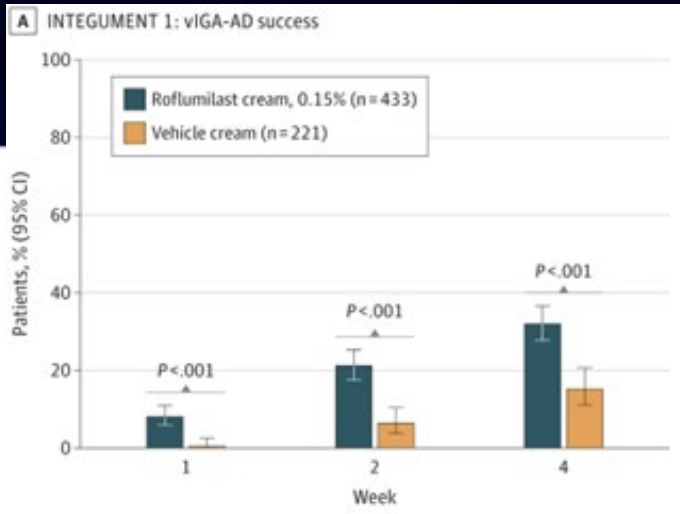
The Lancet Child Adolesc Health. 2023; **7**:13-25
Norris DA. J Am Acad Dermatol. 2005 Jul;53(1 Suppl 1):S17-25.

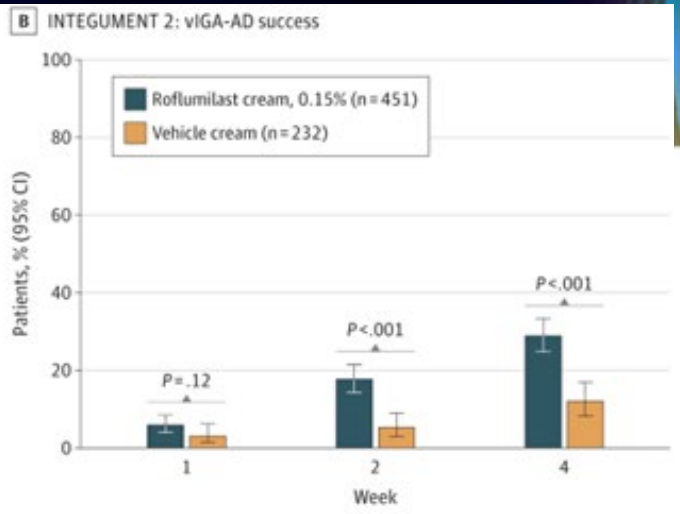
Topical Phosphodiesterase-4 (PDE-4) inhibitors

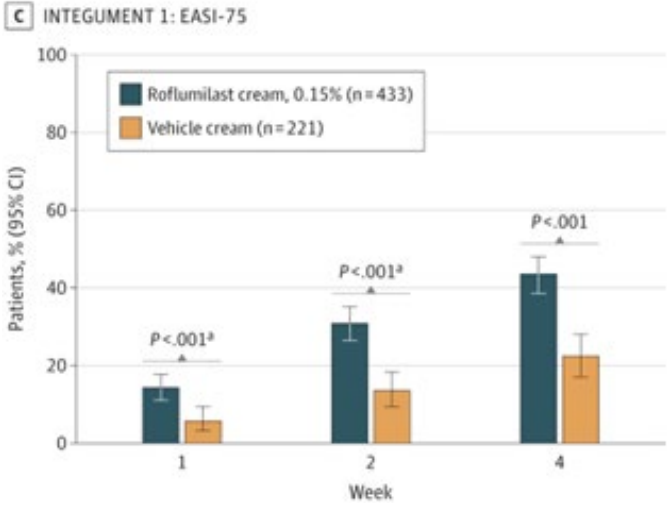
- Crisaborole (Eucrisa) 2% ointment
  - ≥ 3 months
  - Twice daily
  - Adverse effects: stinging, burning
- Roflumilast (Zoryve) 0.15% cream
  - ≥ 6 years
  - Once daily
  - Less application site reactions
  - Adverse effects: headache, GI symptoms
  - *Two Phase 3 trials (INTEGUMENT-1 and 2)[1]: 1337 patients randomized 2:1*
    - *Primary endpoint: vIGA-AD score of 0 or 1, plus ≥ 2-grade improvement at week 4*
- Mild to moderate AD

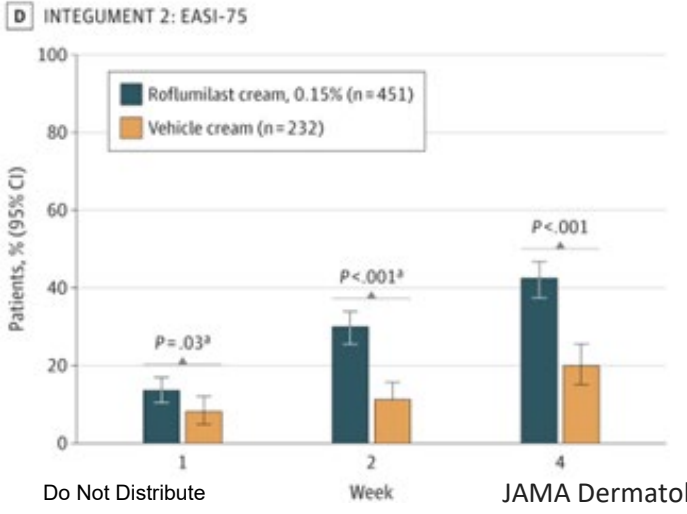


[1]JAMA Dermatol. 2024 Nov 1;160(11):1161-1170.
Blauvelt A et al. Dermatol Ther (Heidelb). 2023 Dec;13(12):3031-3042. Dermatitis. 2025 Jan 10. doi: 10.1089/derm.2024.0418









JAMA Dermatol. 2024 Nov 1;160(11):1161-1170.

Table. Adverse Event Profiles for Roflumilast and Vehicle Groups in INTEGUMENT-1 and INTEGUMENT-2[a]

Event	No. of patients (%)			
	INTEGUMENT-1		INTEGUMENT-2	
	Roflumilast cream, 0.15% (n = 433)	Vehicle cream (n = 221)	Roflumilast cream, 0.15% (n = 452)	Vehicle cream (n = 230)
Patients with any TEAE	92 (21.2)	35 (15.8)	102 (22.6)	30 (13.0)
Patients with any treatment-related TEAE[b]	27 (6.2)	4 (1.8)	26 (5.8)	8 (3.5)
Patients with any serious TEAE[c]	4 (0.9)	0	4 (0.9)	0
Patients with any TEAE leading to discontinuation	6 (1.4)	3 (1.4)	8 (1.8)	2 (0.9)
Most common TEAEs by preferred term, ≥1% in any group				
Headache	10 (2.3)	3 (1.4)	16 (3.5)	1 (0.4)
Nausea	8 (1.8)	2 (0.9)	9 (2.0)	0
Application-site pain	9 (2.1)	1 (0.5)	4 (0.9)	2 (0.9)
Nasopharyngitis	8 (1.8)	2 (0.9)	0	1 (0.4)
COVID-19	4 (0.9)	5 (2.3)	4 (0.9)	3 (1.3)
Diarrhea	6 (1.4)	0	7 (1.5)	2 (0.9)
Vomiting	5 (1.2)	0	8 (1.8)	2 (0.9)
Upper respiratory tract infection	0	1 (0.5)	5 (1.1)	1 (0.4)

Abbreviations: INTEGUMENT, Interventional Trial Evaluating Roflumilast Cream for the Treatment of Atopic Dermatitis; TEAE, treatment-emergent adverse event.

[a] Adverse events are for the safety population, defined as all patients who were enrolled and received at least 1 confirmed dose of trial medication.

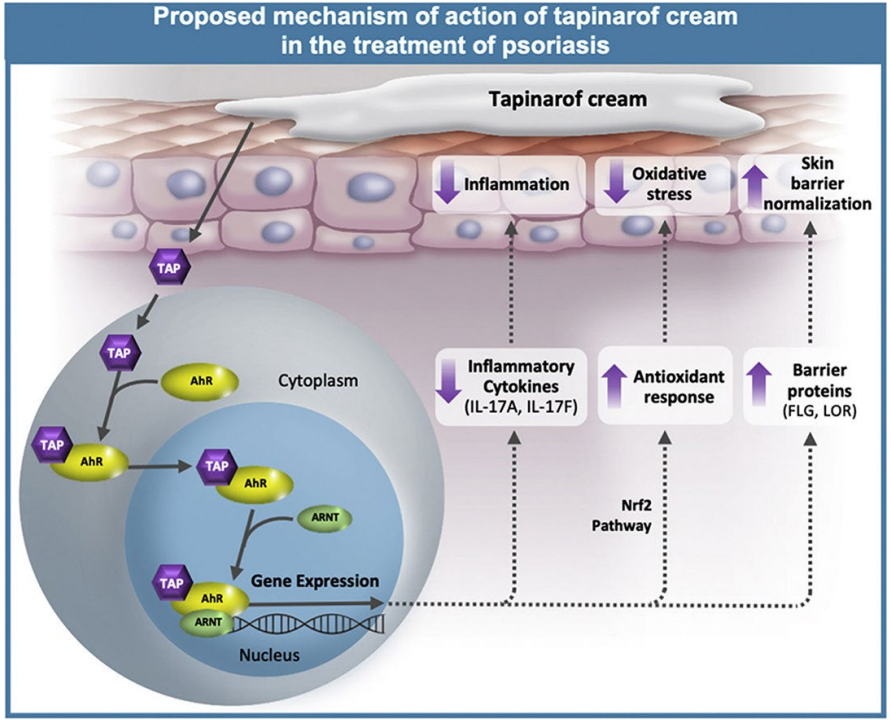
[b] Investigators reviewed each event and assessed its relationship to the investigational product. A treatment-related TEAE is defined as any TEAE that is assessed by the investigator as likely, probably, or possibly related to study treatment.

[c] In INTEGUMENT-1, serious adverse events were depression (unlikely related to the investigational product), diverticulitis (unrelated to the investigational product), pulmonary embolism (unrelated to the investigational product), and suicidal ideation (unrelated to the investigational product). In INTEGUMENT-2, serious adverse events were cutaneous nerve entrapment (unrelated to the investigational product), general physical health deterioration (possibly related to the investigational product), progression of atopic dermatitis that was disproportionately greater than the natural history of atopic dermatitis (probably related to the investigational product), and staphylococcal scalded skin syndrome (unlikely related to the investigational product).

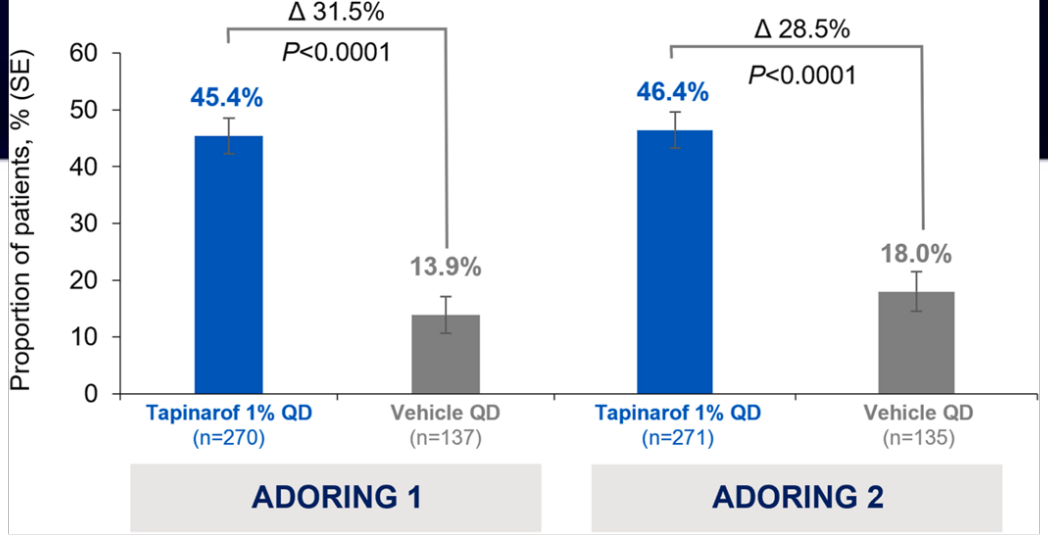
JAMA Dermatol. 2024 Nov 1;160(11):1161-1170.

Topical AHR Agonist

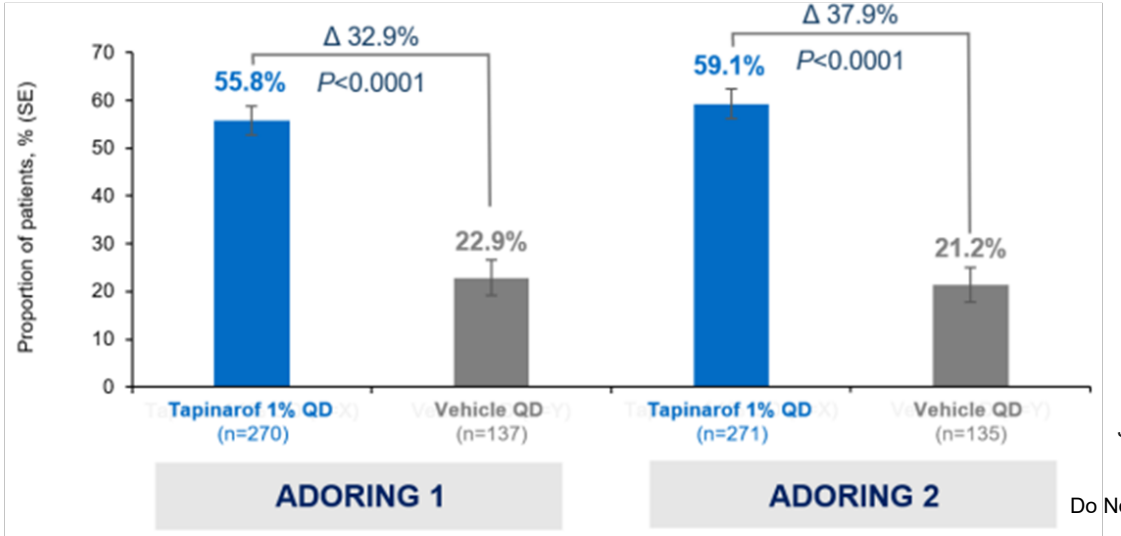
- Tapinarof (VTAMA) 1% cream
  - ≥ 2 years
  - Once daily
  - *Two Phase 3 trials (ADORING 1 and 2)[1]: 813 patients randomized 2:1*
    - *Primary endpoint: vIGA-AD score of 0 or 1, plus ≥ 2-grade improvement at week 8*
  - Adverse effects: Folliculitis, headache, nasopharyngitis
- Moderate to severe AD



V-IGA



EASI-75



J Am Acad Dermatol. 2024 Sep;91(3):457-465.

Table II. Adverse events (safety population)*

Characteristic	ADORING 1		ADORING 2	
Patients, *n* (%)	Tapinarof 1% QD (*n* = 270)	Vehicle QD (*n* = 137)	Tapinarof 1% QD (*n* = 271)	Vehicle QD (*n* = 133)
Any adverse event	123 (45.6)	35 (25.5)	100 (36.9)	28 (21.1)
Serious adverse event†	3 (1.1)	0	2 (0.7)	0
TEAE leading to trial discontinuation	5 (1.9)	5 (3.6)	4 (1.5)	4 (3.0)
Treatment-related TEAEs				
Any	34 (12.6)	9 (6.6)	32 (11.8)	9 (6.8)
Serious	0	0	0	0
Adverse events of special interest‡				
Contact dermatitis	4 (1.5)	3 (2.2)	3 (1.1)	2 (1.5)
Grade 3	0	0	0	0
Led to trial discontinuation	2 (0.7)	2 (1.5)	0	1 (0.8)
Follicular event§	27 (10.0)	1 (0.7)	24 (8.9)	2 (1.5)
Grade 3	0	0	0	0
Led to trial discontinuation	1 (0.4)	0	0	0
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Grade 3	1 (0.4)	0	0	0
Led to trial discontinuation	1 (0.4)	1 (0.7)	0	0
Any TEAE (≥5%)				
Folliculitis	22 (8.1)	1 (0.7)	22 (8.1)	2 (1.5)
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Nasopharyngitis	13 (4.8)	7 (5.1)	4 (1.5)	1 (0.8)

MedDRA, Medical Dictionary for Regulatory Activities; *QD*, once daily; *TEAE*, treatment-emergent adverse event.

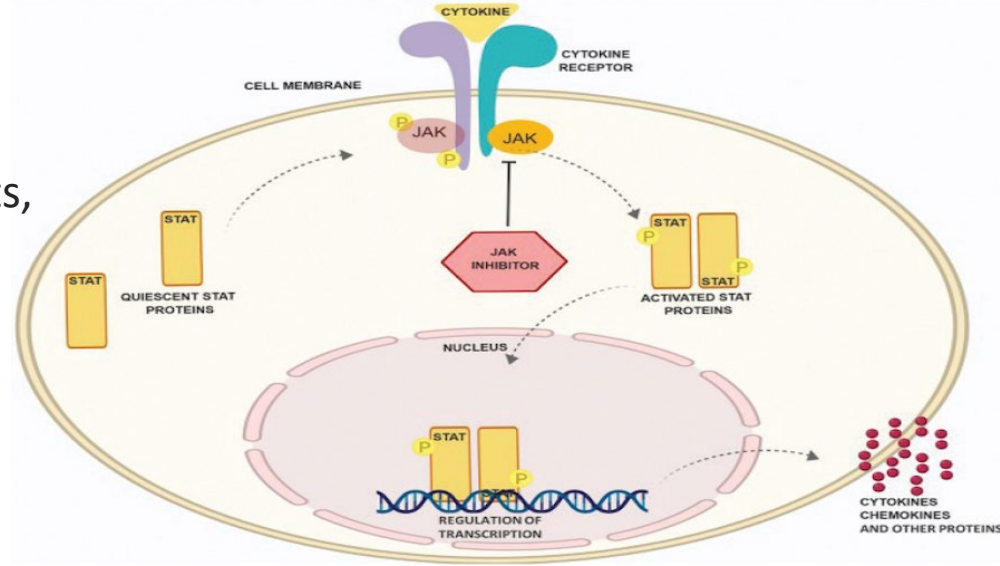
*Each patient with an adverse event was counted only once for each MedDRA preferred term. Severity was based on the Common Terminology Criteria for Adverse Events (version 5.0), where Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe or medically significant but not immediately life-threatening; Grade 4 = Life-threatening consequences; Grade 5 = Death related to adverse event.

†No serious adverse events were considered by the investigators to be related to tapinarof 1% cream.

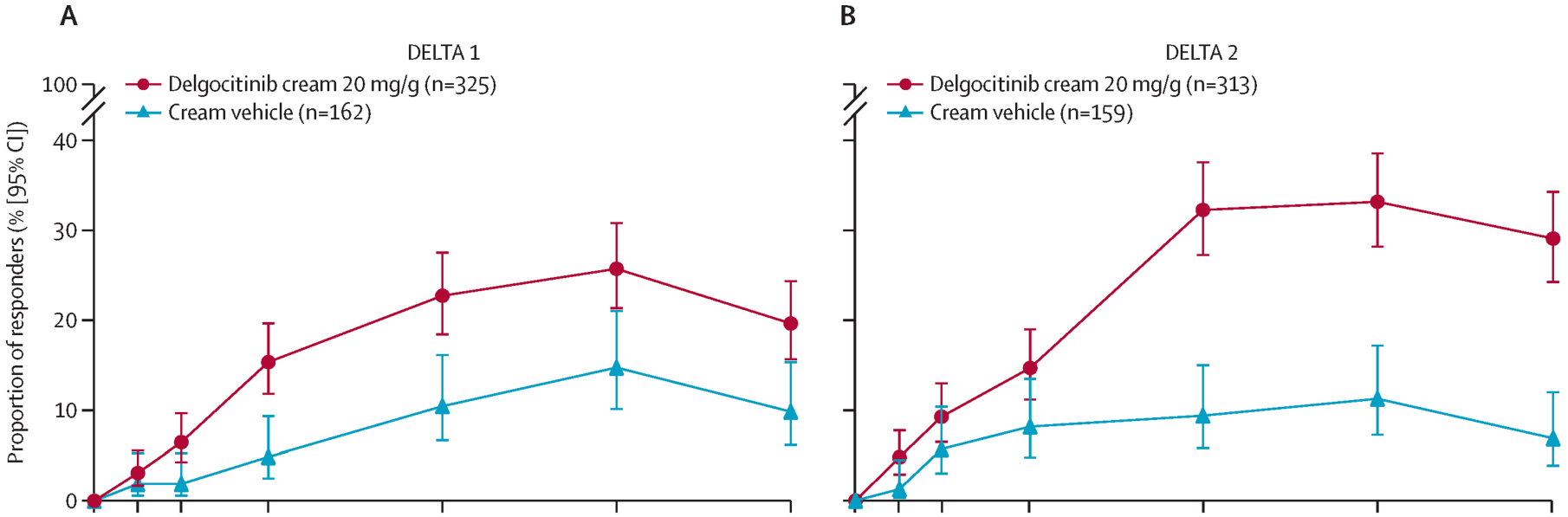
‡No adverse events of special interest were graded 4 or 5 (considered either life-threatening or related to death).

§Events of folliculitis, follicular eczema, keratosis pilaris, and application site folliculitis were categorized as follicular events (adverse events of special interest).

- Ruxolitinib (Opzelura) 1.5% cream
  - ≥ 12 years
  - Twice daily
  - Mild to moderate AD
  - Black box warning: cancer, blood clots, infections
- Delgocitinib 2% cream
  - FDA filing for NDA
  - Severe chronic hand eczema
  - *Phase 3 studies (DELTA 1, 2)[1]: adults randomized 2:1*
    - *Primary endpoint: IGA-CHE score of 0 or 1 at 16 weeks*
  - Adverse effects: skin irritation, naropharyngitis



[1]Lancet. 2024 Aug 3;404(10451):461-473.



Lancet. 2024 Aug 3;404(10451):461-473.

Other therapies that we use

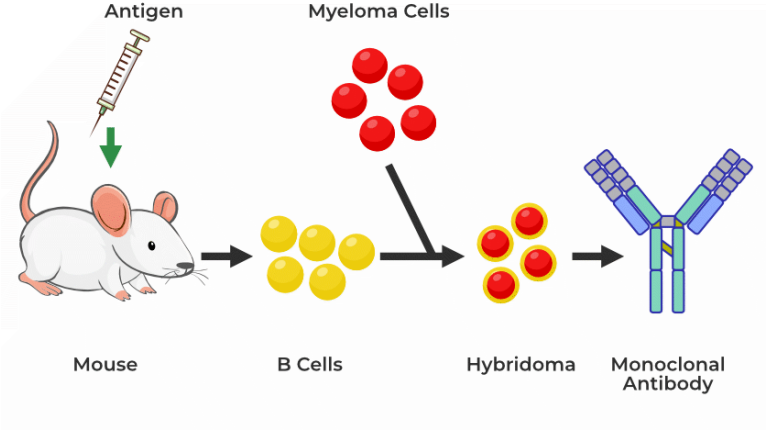
- Bleach baths
- Wet wrap therapy

Systemic Treatments

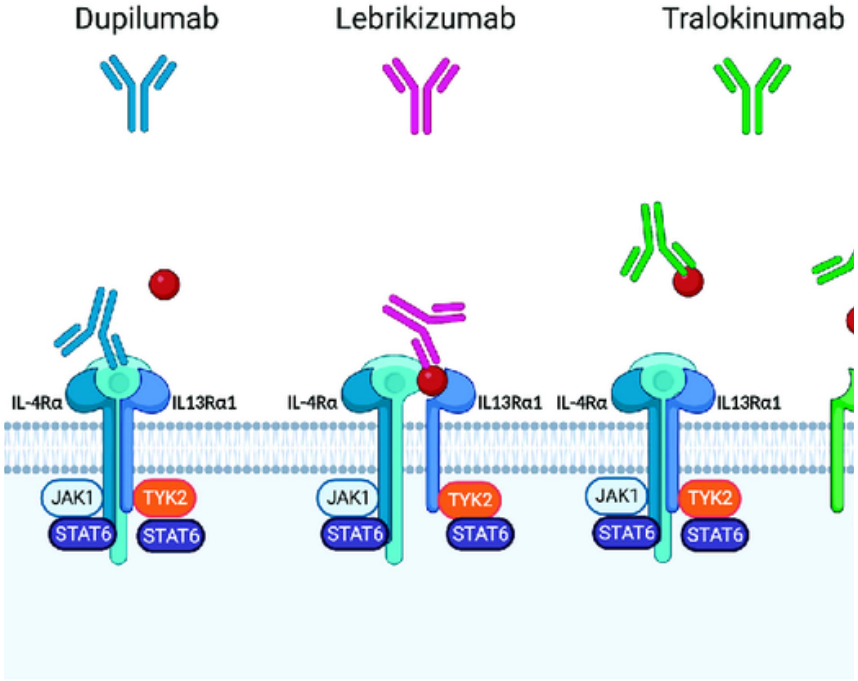
Current therapies

New & emerging therapies

Monoclonal antibody production & nomenclature



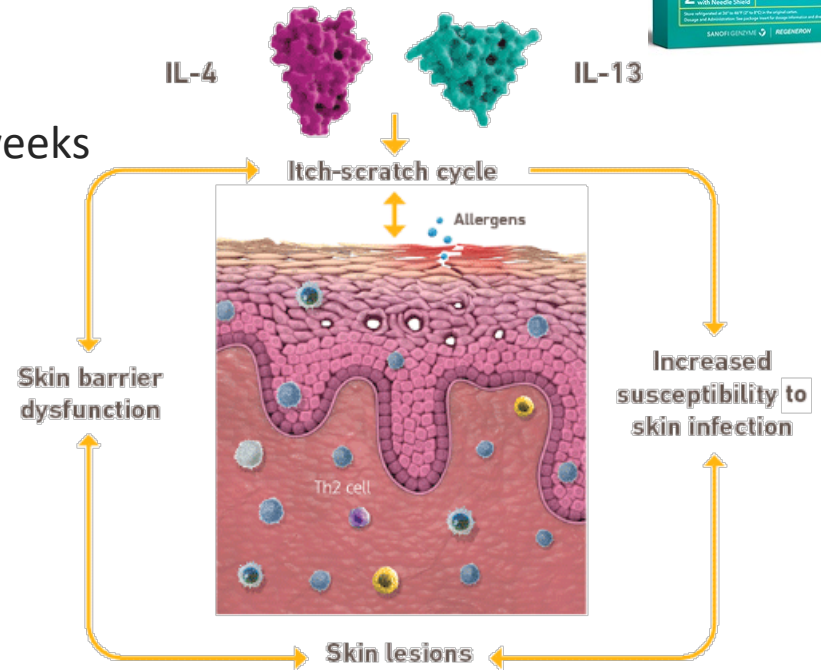
https://www.geeksforgeeks.org/monoclonal-antibody/



https://www.researchgate.net/figure/Mechanisms-of-IL-13-inhibition-by-dupilumab-lebrikizumab-tralokinumab-and-eblasakimab_fig1_368379847

Dupilumab (Dupixent)

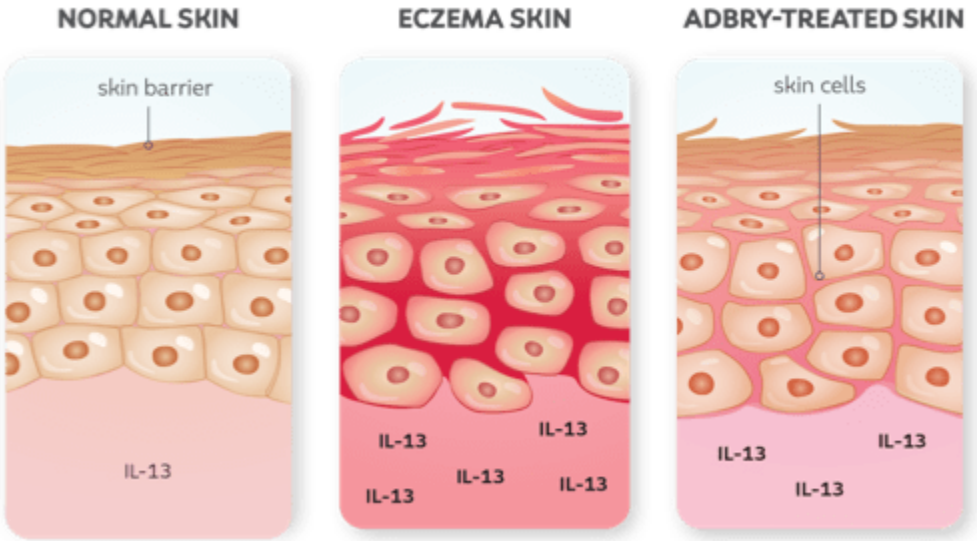
- Dupilumab (Dupixent)
  - Blocks IL-4/IL-13
- 6 months & older
  - Loading dose (6 years & older)
  - Maintenance dose every 2 or 4 weeks
- Safety profile
  - Favorable
  - Injection site reactions
  - Ocular surface disease
  - Facial redness



https://www.dupixent.com/atopicdermatitis/about-dupixent/how-dupixent-works

Tralokinumab (Adbry)

- Tralokinumab (Adbry)
  - Inhibits IL-13
- 12 years old & older
  - Loading dose
  - Maintenance dose every 2 or 4 weeks
- Safety profile
  - Upper respiratory tract infections (colds, nose/throat)
  - Injection site reactions
  - Ocular surface disease

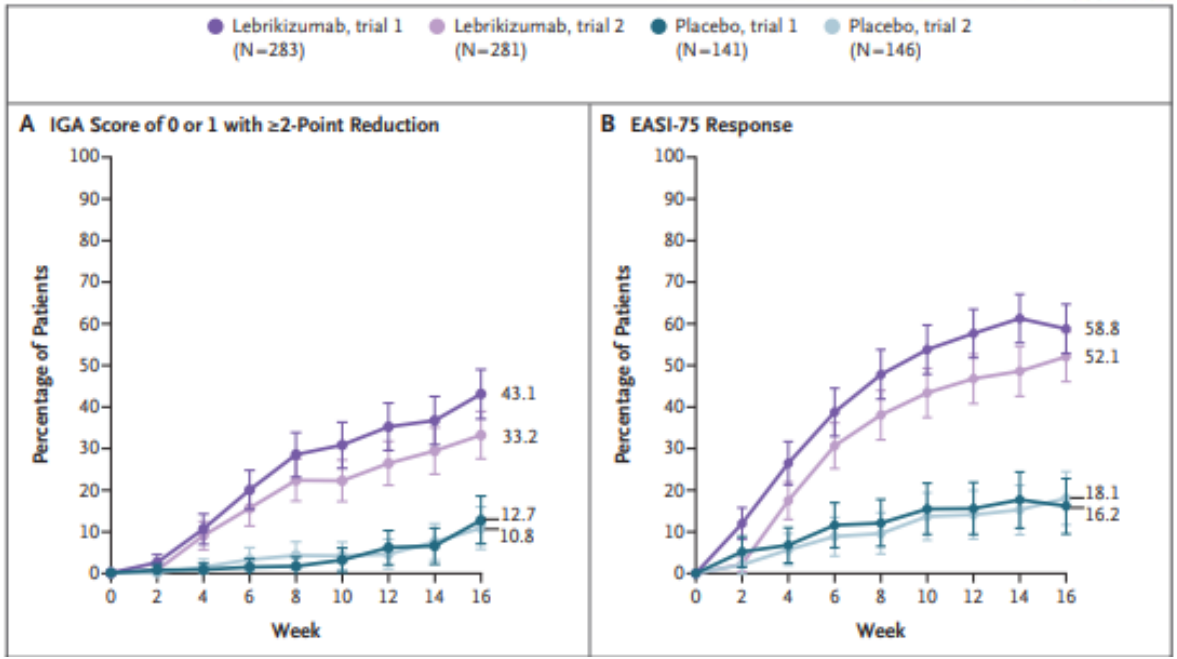


https://www.adbry.com/about-adbry/how-adbry-works

Lebrikizumab

- Lebrikizumab (Ebglyss)
  - Inhibits IL-13
- 12 years & older
  - 500 mg at week 0 and 2, followed by 250 mg every other week until week 16
  - Reduce to 250 mg every 4 weeks when clinical response is achieved
- *Phase 3 studies (ADvocate1 and Advocate 2)*[1]
  - *16 week induction, 36 week maintenance, 2:1 randomized*
  - *Primary endpoint: IGA score of 0 or 1, at least 2 points from baseline at 16 weeks*
- Safety profile
  - Injection site reactions
  - Upper respiratory tract infections
  - Conjunctivitis

[1]N Engl J Med. 2023 Mar 23;388(12):1080-1091.

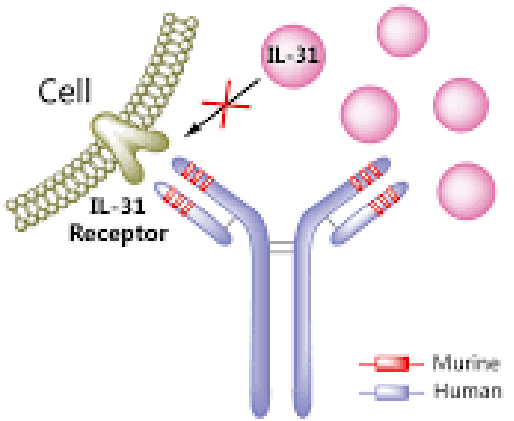


P<0.001 for all outcomes

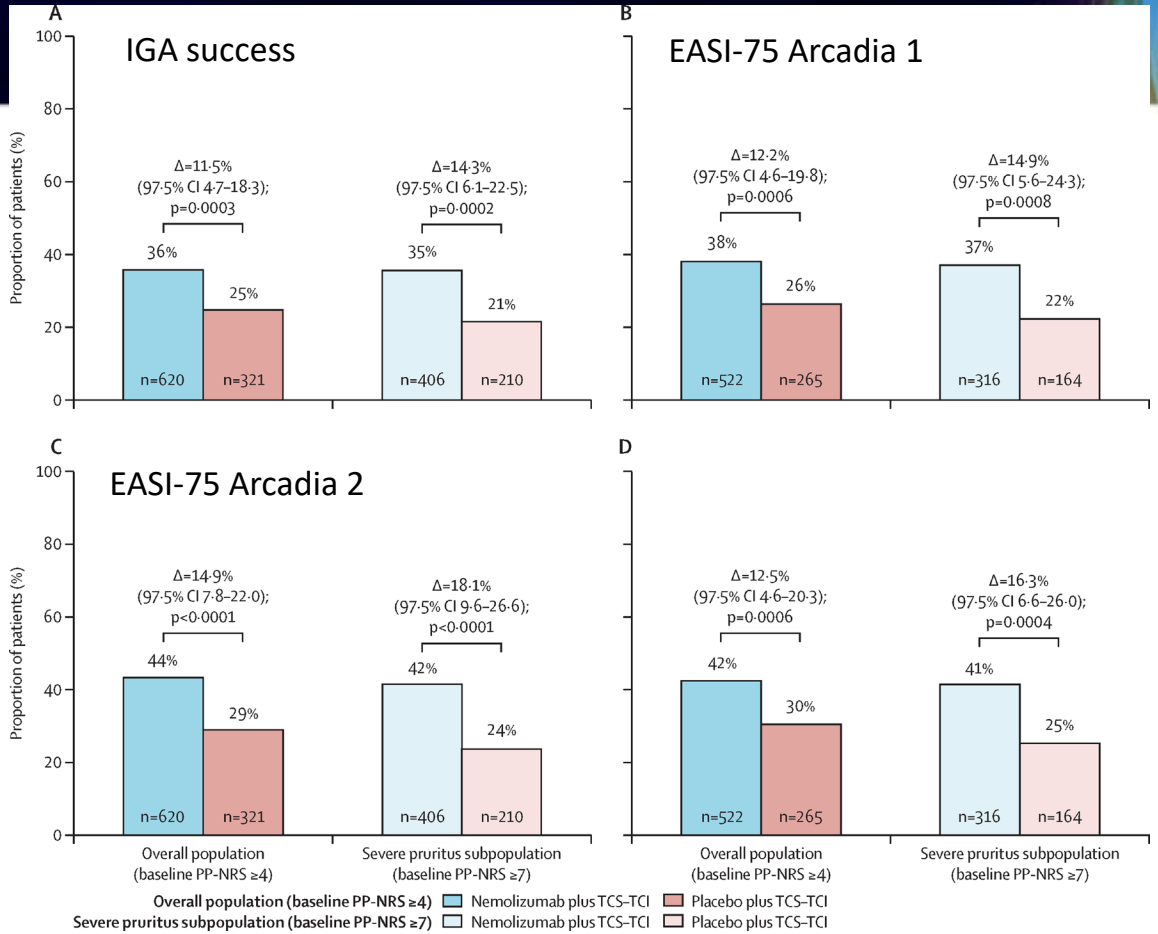
N Engl J Med. 2023 Mar 23;388(12):1080-1091.

Nemolizumab

- Nemolizumab (Nemluvio)
  - Inhibits IL-31
- 12 years & older
  - 60 mg, followed by 30 mg every 4 weeks
  - 30 mg every 8 weeks if achieve clear/almost clear skin after 16 weeks
- *Phase 3 studies (ARCADIA 1 and 2)*[1]
  - *Randomized 2:1, TCS run-in, allowed background TCS with or without TCI*
  - *Primary endpoints at week 16:*
    - *IGA of 0 or 1 with at least 2-point improvement*
    - *At least 75% improvement in EASI*
- Safety profile:
  - Headache
  - Arthralgia
  - Myalgias
  - Peripheral edema
  - ?Worsening of asthma



[1]Lancet. 2024 Aug 3;404(10451):445-460.

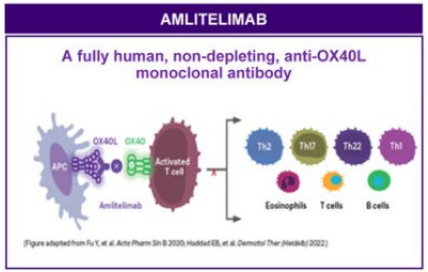


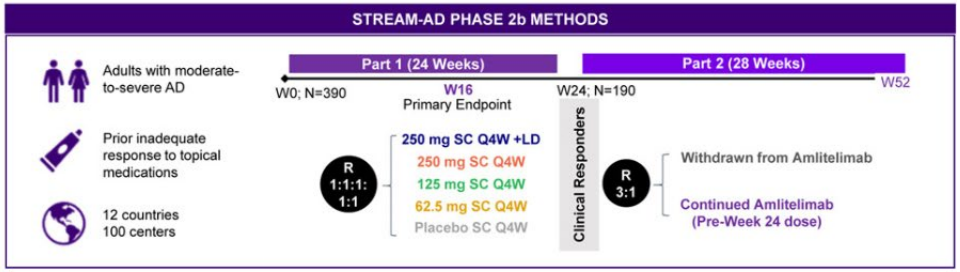
Ox40 Inhibitors (in phase 3)

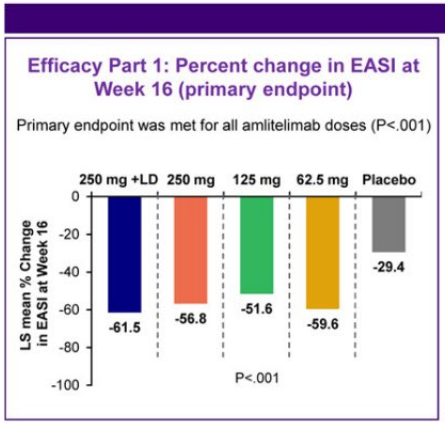
- Amlitelimab

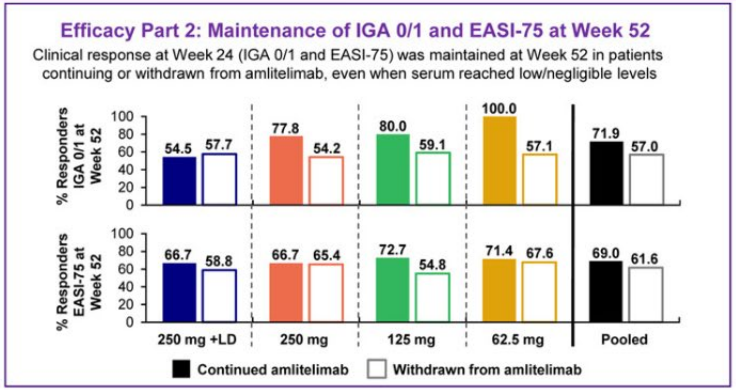
J Allergy Clin Immunol. 2024 Nov 8:S0091-6749(24)01175-8.

Phase 2b randomized clinical trial of amlitelimab, an anti-OX40 Ligand antibody, in patients with moderate-to-severe atopic dermatitis





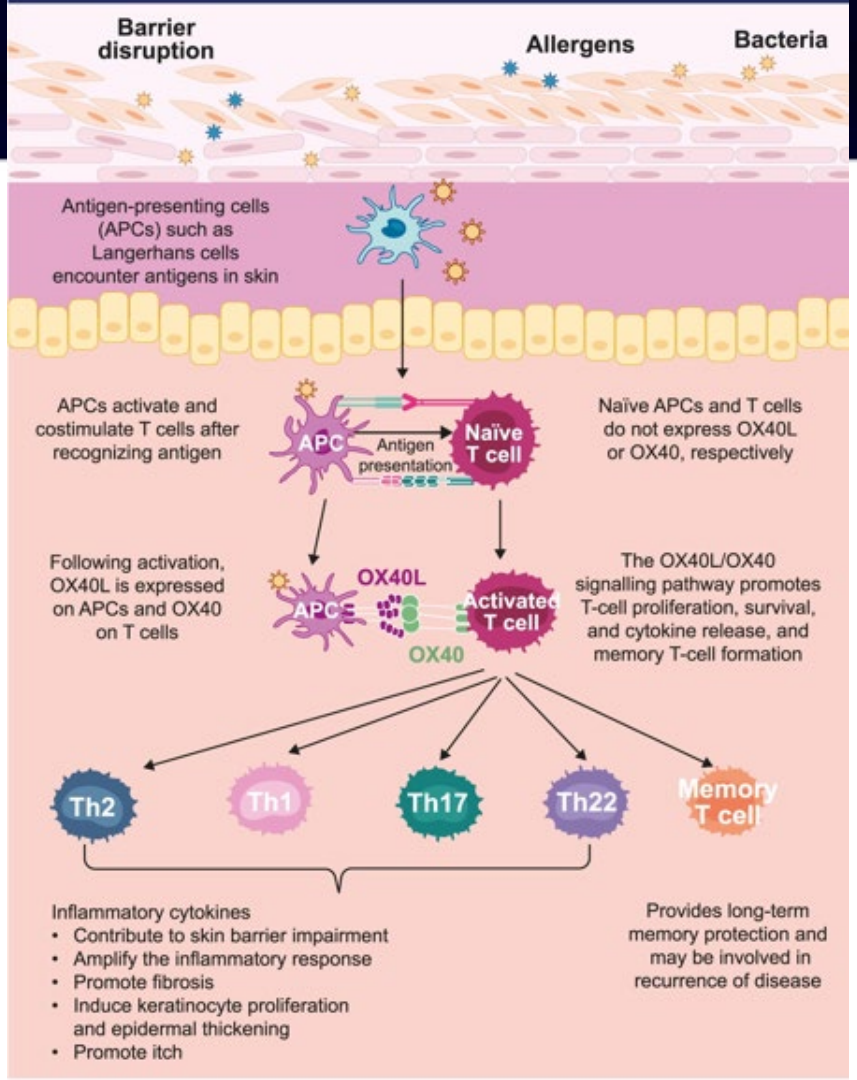




Safety:

- Amlitelimab was well tolerated over 52 weeks
- No dose effect on TEAE incidence

APC: antigen-presenting cells; EASI: eczema area and severity index; IGA: investigator's global assessment; LD: loading dose; OX40L: OX40 Ligand; Q4W: every four weeks; SC: subcutaneous; Th: T helper; TEAE: treatment emergent adverse events

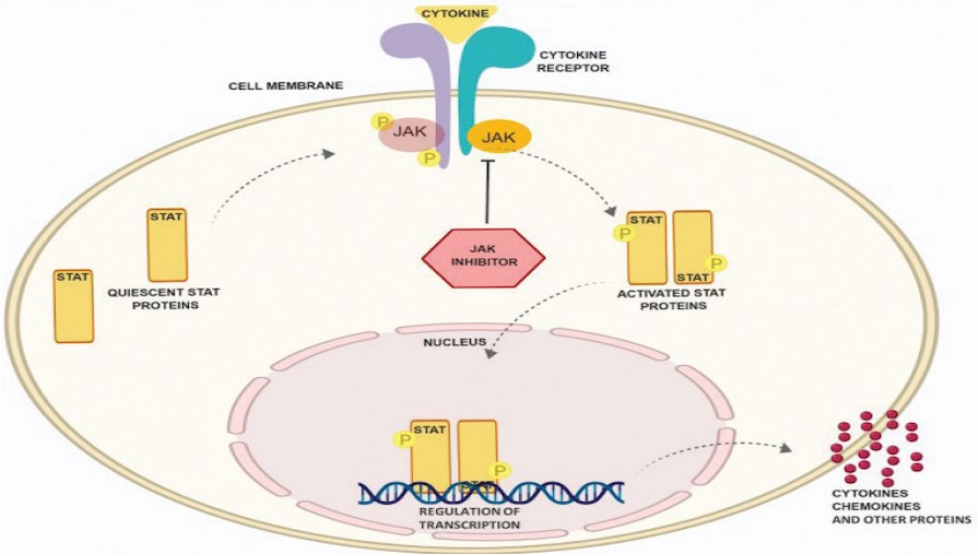


Therapies targeting the OX40L/OX40 pathway	
Amlitelimab	Nondepleting anti-OX40L monoclonal antibody Phase III studies ongoing
Rocatinlimab	Anti-OX40 monoclonal antibody Phase III studies ongoing
Telazorlimab	Anti-OX40 monoclonal antibody Phase IIb study completed
IMG-007	Anti-OX40 monoclonal antibody Phase IIa study ongoing

Br J Dermatol. 2024 Sep 18;191(4):488-496.

Oral JAK Inhibitors

- Oral JAK inhibitors:
  - Suppress immune pathways
  - Rapid improvement in AD
  - Upadacitinib (Rinvoq) daily
    - 12 years & older
  - Abrocitinib (Cibinqo) daily
    - 12 years & older
  - Baricitinib (Olumiant) (Europe only)
    - 18 years & older
  - Safety:
    - Risk of eczema herpeticum, herpes zoster
    - Nasopharyngitis, nausea, acne, headaches
    - [Black box warning: Blood clots, CV events, malignancy – low rates in AD studies / short duration]
    - *Screening and monitoring:*
      - *Baseline TB, CBC, CMP, hepatitis B and C, pregnancy test*
      - *Follow CBC, lipid panel 4 weeks after*
      - *Contraindicated in pregnancy and breastfeeding*

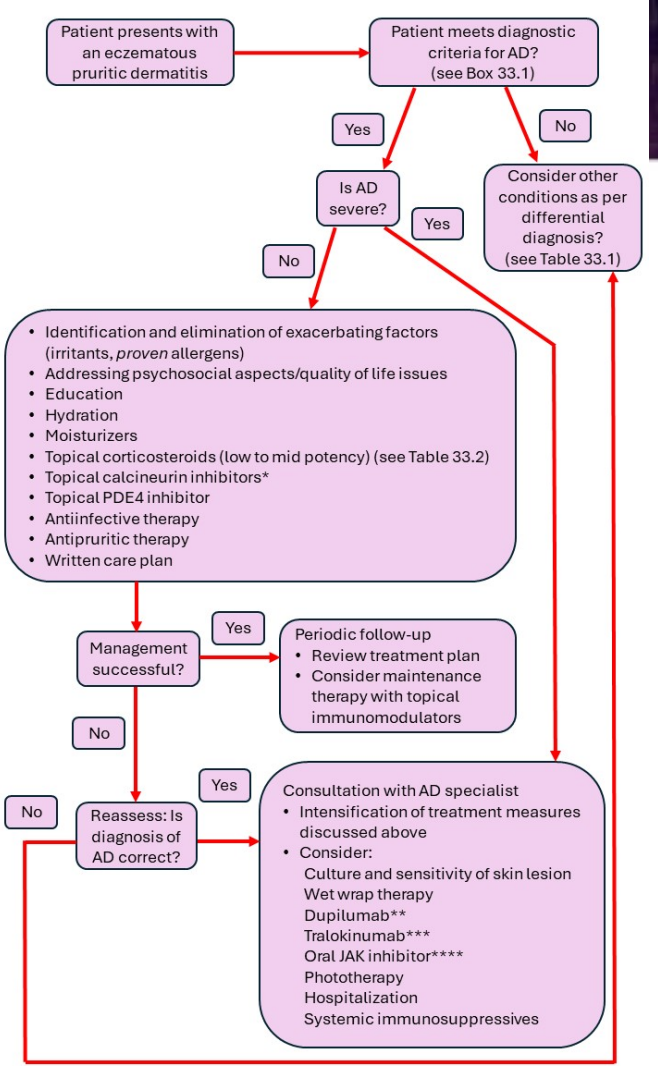


Difficult to manage AD (moderate to severe)

- Phototherapy

How do we put all of this information together?

- Each patient is unique
- There will be situations where one medication is preferred over another
- Treatment is not static – there is room for stepping up and stepping down
- Shared decision making between the provider and patient/family



Thank you! Questions?