Tennessee Society of Allergy, Asthma & Immunology
Annual Meeting 2023

Update on Current and Emerging Therapies for Atopic Dermatitis

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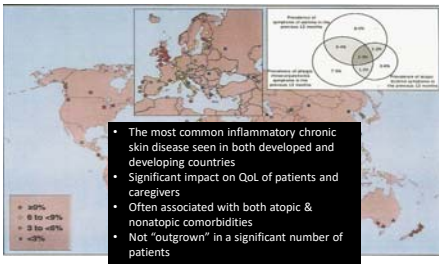
Learning Objectives

Upon completion of this learning activity, participants should be able to:

1. Apply knowledge of the pathophysiology of atopic dermatitis to the selection of treatment for patients with atopic dermatitis
2. Recognize indications for new therapies for atopic dermatitis and appropriate monitoring for potential adverse events
3. Discuss emerging therapies for atopic dermatitis

2

Global variations in prevalence of eczema symptoms in children from ISAAC Phase

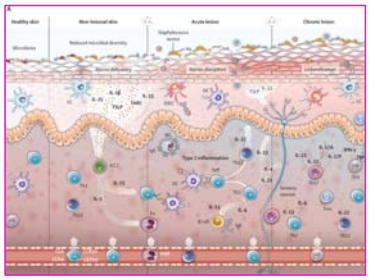


- The most common inflammatory chronic skin disease seen in both developed and developing countries
- Significant impact on QoL of patients and caregivers
- Often associated with both atopic & nonatopic comorbidities
- Not "outgrown" in a significant number of patients

Lancet 1998;351:1225; Odhiambo JA, et al. J Allergy Clin Immunol 2009;124:1251

3

Insights into pathophysiology of atopic dermatitis: Implications for narrow vs broad targeting approach



Lancet 2020;396:345-60

4

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Type 2 cytokines & AD…

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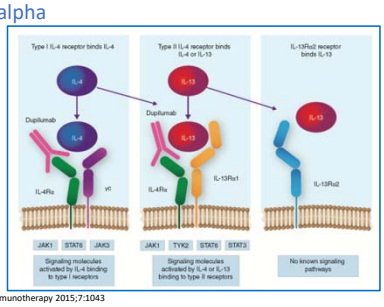
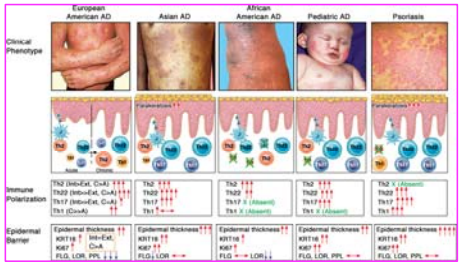
Dupilumab, a fully human monoclonal antibody targeting IL-4 receptor-alpha



Hamilton JD, et al. Immunotherapy 2015;7:1043

7

AD phenotypes and related endotypes



Czarnowicki T, et al. J Allergy Clin Immunol 2019;143:1

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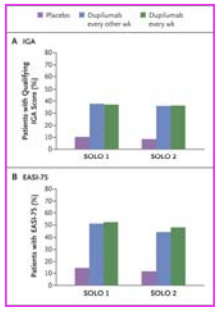
Two phase 3 trials of dupilumab vs placebo in atopic dermatitis



P<0.001 for all dupilumab vs placebo

N Engl J Med 2016;375:2335-48

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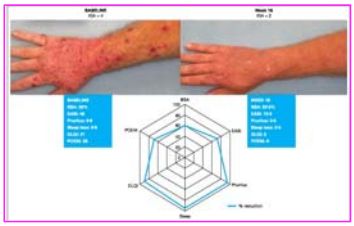
Dupilumab provides important clinical benefits to patients with atopic dermatitis who do not achieve clear or almost clear skin according to the Investigator's Global Assessment: a pooled analysis of data from two phase III trials



Among patients with IGA > 1 at wk 16, dupilumab significantly improved several outcome measures compared with placebo:
- EASI (-48·9% vs. -11·3%, P < 0·001)
- pruritus NRS (-35·2% vs. -9·1%, P < 0·001)
- affected BSA (-23·1% vs. -4·5%, P < 0·001)
- POEM score ≥ 4-point improvement (57·4% vs. 21·0%, P < 0·001)
- DLQI score ≥ 4-point improvement (59·3% vs. 24·4%, P < 0·001)

Silverberg JI, et al. Br J Dermatol 2019;181:80-87

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Adolescent, pediatric and infant AD trials with dupilumab

JAMA Dermatology | Original Investigation
Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis A Phase 3 Randomized Clinical Trial

CONCLUSIONS AND RELEVANCE In this study, dupilumab significantly improved AD signs, symptoms, and quality of life in adolescents with moderate to severe AD, with an acceptable safety profile. Placebo-corrected efficacy and safety of dupilumab were similar in adolescents and adults. (JAMA Dermatol 2020;156:44-56)

Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial

Conclusion: Dupilumab + TCS is efficacious and well tolerated in children with severe AD, significantly improving signs, symptoms, and QOL. (J Am Acad Dermatol 2020;83:1282-93.)

Dupilumab in children aged 6 months to younger than 6 years with uncontrolled atopic dermatitis: a randomised, double-blind, placebo-controlled, phase 3 trial

Dupilumab significantly improved AD signs & symptoms vs placebo in children < 6 y. Dupilumab was well tolerated and showed an acceptable safety profile ~ older children and adults. (Lancet 2022;400:908)

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Select baseline demographics

- 69% White, 19% Black, 6% Asian
- 77% IGA 4 (severe); EASI 34 (severe); SCORAD 72 (severe)
- Concurrent atopic diseases (self-reported): FA 68%, AR 44%, asthma 41%, AC 4%
- Previous systemic treatments for AD: steroids 19%, CsA 11%, MTX 7%, MMF 1%, Aza 1%
- 11 pts total < 2 yrs (7% of study population) *
- 6 pts < 2 yrs treated with dupilumab , youngest 10 months old

Paller AS, et al. Lancet 2022;400:908

*In phase 2 trial, 20 pts < 2 y treated with dupi (10 with 3mg/kg, 10 with 6 mg/kg, as single dose

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Current dupilumab approval in the United States

- Dupilumab approved in
  - Patients aged ≥ 6 ~~years~~ months with moderate-to-severe AD uncontrolled by topical prescription medicines or when those medications are not advised
  - As add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥ 6 years with an eosinophilic phenotype or with oral steroid dependent asthma
  - As add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis
  - In patients ≥ 12 years weighing at least 40 kg with EoE
  - In adults with prurigo nodularis

No laboratory monitoring required

- Dupilumab pediatric dosing in AD (subcutaneous injection)
  - ≥ 60 kg — 600 mg x 1, 300 mg Q2W
  - 30 kg - < 60 kg — 400 mg x 1, 200 mg Q2W
  - 15 kg - < 30 kg — 600 mg x1, 300 mg Q4W
  - 15 kg - < 30 kg* — 300 mg Q4W (no loading dose)
  - 5 kg - < 15 kg* — 200 mg Q4W (no loading dose)

  (* ≥6 mo to <6 yrs)

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Conjunctivitis in dupilumab clinical trials

- Evaluation of randomized placebo-controlled trials of dupilumab in AD (n = 2629), asthma (n = 2876), CRSwNP (n = 60) and EoE (n = 47)
- Conjunctivitis more frequent with dupilumab treatment in most AD trials
- In dupilumab trials in other type 2 diseases, incidence of conjunctivitis overall very low and similar for dupilumab and placebo
- In AD, incidence of conjunctivitis associated with AD severity and prior history of conjunctivitis
- Etiology and treatment of conjunctivitis in dupilumab-treated patients require further study

Akinlade B, et al. Br J Dermatol 2019;181:459-473

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Adolescent study pt on dupilumab, eczema well controlled but significant ocular irritation, tearing, photophobia x 1 month despite nedocromil gtt & artificial tears

- Evaluated and treated by Ophthalmology with topical steroid gtt (FML QID x1 wk, taper over next 4 wks)
- Continued on dupilumab, nedocromil gtt & artificial tears
- Considering changing dupilumab dosing to Q3-4 wks

Bilateral conjunctivitis

Periocular dermatitis

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Dupilumab facial redness: Positive effect of itraconazole

- Case reports describe ACD, *Malassezia* hypersensitivity, rosacea and psoriasis

Adult with DFR & elevated serum *Malassezia*-specific IgE, responsive to itraconazole while continuing on dupilumab

JAAD Case Rep 2019;5: 888

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Atopic Dermatitis Yardstick Update

- Biologics: dupilumab, tralokinumab
- JAK inhibitors: ruxolitinib, abrocitinib, upadacitinib

Boguniewicz M, et al. Ann Allergy Asthma Immunol 2023 (June); 130:811-20

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Atopic Dermatitis Yardstick Update: Expert Commentary

- Case reports of psoriasiform eruptions in patients treated with dupilumab have led to questions related to blocking type 2 immune responses with shift to a type 1 response.
- …it is important for clinicians to establish a diagnosis of AD, as patients with other inflammatory diseases including psoriasis have been erroneously treated with dupilumab.
- …the Asian AD phenotype … combines features of atopic dermatitis and psoriasis with increased T_H17 polarization.

Boguniewicz M, et al. Ann Allergy Asthma Immunol 2023 (June); 130:811-20

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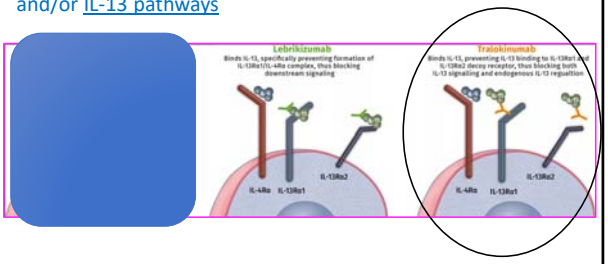
Mechanism of action for biologics targeting the IL-4 and/or IL-13 pathways



Exp Dermatol 2019;28:756

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Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2)

- Adults with moderate-to-severe AD randomized (3 : 1) to subQ tralokinumab 300 mg Q2W or placebo
- Primary endpoints were IGA 0 /1 at wk 16 and EASI 75 at wk 16; Pts with IGA 0/1 and/or EASI 75 with tralokinumab at wk 16 re-randomized to tralokinumab Q2W or Q4W or placebo for 36 wks
- At wk 16, more pts on tralokinumab vs placebo achieved IGA 0/1: 15.8% vs 7.1% in ECZTRA 1 [$P = 0{\cdot}002$] and 22.2% vs 10.9% in ECZTRA 2 [$P < 0{\cdot}001$] and EASI 75: 25% vs 12.7% [$P < 0{\cdot}001$] and 33.2% vs 11·4% [$P < 0{\cdot}001$]
- AEs reported in 76.4% and 61.5% of pts on tralokinumab and in 77.0% and 66% of pts on placebo in 16-wk initial period (conjunctivitis 7%/3%)
- Tralokinumab monotherapy was superior to placebo at 16 wks of treatment and was well tolerated up to 52 wks of treatment

Br J Dermatol 2021;184:437-49

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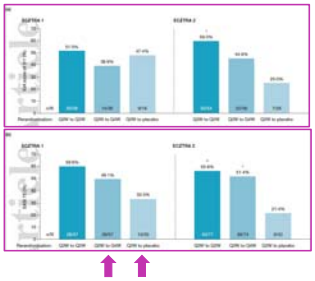
Maintenance of (a) IGA score of 0/1* and (b) EASI 75* clinical response at week 52 in ECZTRA 1 and ECZTRA 2



*Assessed in pts achieving W16 primary outcome of IGA or EASI75 score without use of rescue medication after initial randomization to tralokinumab

Br J Dermatol 2021;184:437-49

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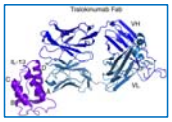
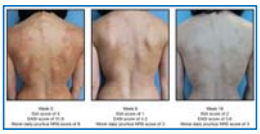
Tralokinumab: direct targeting of IL-13





- Approved by FDA 12/2021 for adults 18 yrs and older* with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
  - 600 mg loading dose, followed by 300 mg QOW by subcutaneous injection (150 mg/ml prefilled syringe) +/- TCS (or TCIs)
  - Pts < 100 kg treated for 16 W who are clear/almost, consider 300 mg Q4W dosing

*Approved in EU and Canada down to 12 yrs (< 18 y under review by FDA)

J Mol Biol 2017;429:208; Br J Dermatol 2021;184:437

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Efficacy and safety of tralokinumab in adolescents with moderate to severe atopic dermatitis

- 52-week, randomized, DBPC P3 ECZTRA 6 trial conducted at 72 centers in 10 countries in North America, Europe, Asia, and Australia
- Pts 12 to 17 yrs old with moderate to severe AD (IGA score ≥3; EASI ≥16) randomized (1:1:1) to tralokinumab (150 or 300 mg) or placebo Q2W for 16 weeks
- Pts with IGA 0 (clear) or 1 (almost clear) and/or EASI 75 at week 16 without rescue medication received maintenance treatment; other patients switched to open-label tralokinumab 300 mg Q2W
- Primary end points at week 16 were IGA score of 0 or 1 and/or achieving EASI 75
- Key secondary end points were reduction of Adolescent WPNRS of 4 or more, change in SCORAD and change in CDLQI from baseline to week 16; safety end points were number of AEs and serious AEs
- Of 301 pts randomized, 289 comprised full analysis set (median [IQR] age, 15.0 [13.0-16.0] years; 149 [51.6%] male)
- More patients receiving tralokinumab 150 mg (n = 98) and tralokinumab 300 mg (n = 97) achieved IGA score of 0 or 1 without rescue medication at week 16 (21 [21.4%] and 17 [17.5%], respectively) vs placebo (n = 94; 4 [4.3%]), P < .001 and 13.8% [95% CI, 5.3%-22.3%]; P = .002, respectively)

Paller AS, et al. JAMA Dermatol 2023 (June):159:596

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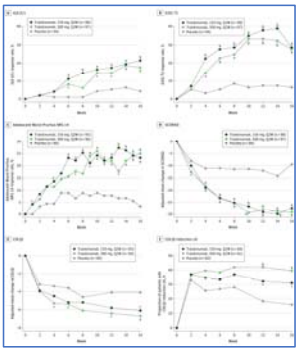
Tralokinumab efficacy vs placebo across primary and key secondary end points up to week 16 (initial treatment period), full analysis set



Paller AS, et al. JAMA Dermatol 2023 (June):159:596

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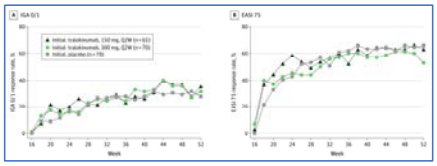
Tralokinumab efficacy during weeks 16-52 of the open-label phase



Paller AS, et al. JAMA Dermatol 2023 (June):159:596

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Conjunctivitis in adult patients with moderate-to-severe atopic dermatitis: Results from five tralokinumab clinical trials

- 2285 adults with AD studied up to 16 wks
- Incidence of conjunctivitis higher (7.5%) with tralokinumab compared to placebo (3.2%)
- Most events were mild or moderate in severity and 78.6% and 73.9% of events resolved during the trial in the tralokinumab and placebo groups, respectively
- Two (1.4%) events led to permanent discontinuation of tralokinumab
- Increased incidence of conjunctivitis, regardless of treatment group, associated with more severe baseline AD, history of allergic conjunctivitis/atopic keratoconjunctivitis, as well as the number of atopic comorbidities

Br J Dermatol 2022;186:453

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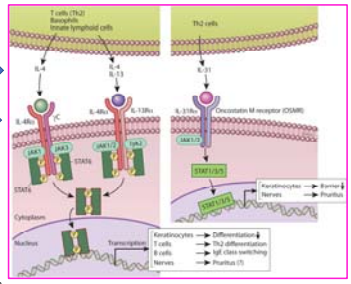
From biologics to small molecules…JAK-STAT signaling as a therapeutic target

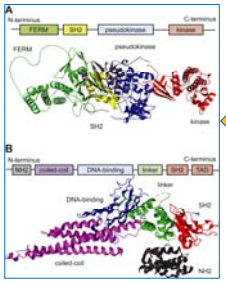


The JAK-STAT pathway is a master regulator
of immune function, implicated in the downstream signaling of inflammatory cytokines, including ILs, IFNs, and multiple growth factors

Paller AS, et al. J Allergy Clin Immunol 2017;140:633

27

JAK & STAT proteins



Jakinibs

Luo Y, et al. J Allergy Clin Immunol 2021; 148:911

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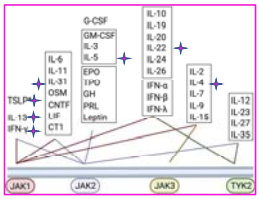
Cytokine signaling via distinct JAK proteins

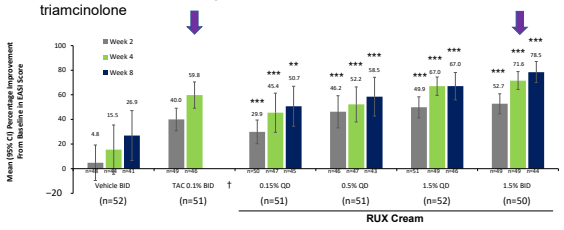


Damsky W, et al. J Allergy Clin Immunol 2021;147:814-26

29

Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream

- RUX 1.5% BID resulted in greater improvement in EASI scores versus triamcinolone

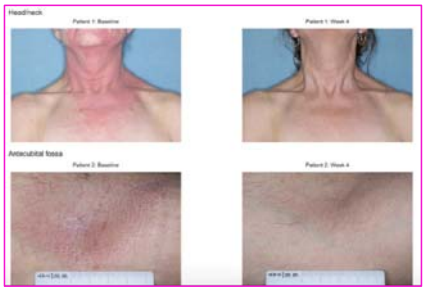


Kim BS, et al. J Allergy Clin Immunol 2020;145:572

*** P<0.001 vs vehicle; ** P<0.01 vs vehicle

30

Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream



Kim BS, et al. J Allergy Clin Immunol 2020;145:572

31

A maximum-use trial of ruxolitinib cream in adolescents and adults with atopic dermatitis

- Pts ≥ 12-65 yrs with AD, IGA ≥ 2 and ≥ 25% BSA enrolled in an open-label, maximum-use phase I study
- Pts applied 1.5% ruxolitinib cream BID to lesions identified at baseline for 28 days and continued use only on active lesions for additional 28 days (extension period)
- 41 pts enrolled and 37 (90.2%) entered extension period, all of whom completed the study. TEAEs reported in 13 pts (31.7%); treatment-related AEs reported in 4 pts (9.8%)
- Mean (SD) steady-state plasma concentration was 104 (309) nM during the first 28 days, well below half-maximal inhibitory concentration of JAK-mediated myelosuppression in bone marrow (281 nM), and decreased further during the extension period (higher concentrations detected in a few pts treated for a high affected BSA)
- At day 56, 94.6% of pts achieved EASI75

Bissonnette R, et al. Am J Clin Dermatol 2022; 23:355-64

32

Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial

- Multicentre, double-blind, randomised P3 trial (JADE MONO-1), pts ≥12 years (≥ 40 kg) with moderate-to-severe AD (IGA ≥3, EASI ≥16, BSA ≥10%, and PP-NRS score ≥4 enrolled at 69 sites in Australia, Canada, Europe, and USA
- Pts randomly assigned (2:2:1) to oral abrocitinib 100 mg, abrocitinib 200 mg or placebo once daily for 12 wks

Lancet 2020;396:255-66

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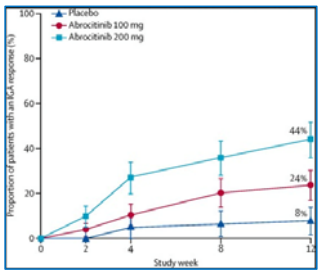
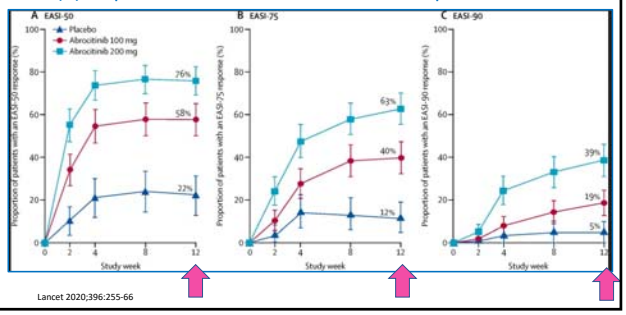
Proportion of patients who achieved an IGA response over the 12-week treatment period



Lancet 2020;396:255-66

34

Proportion of patients who achieved an EASI-50 (A), EASI-75 (B), and EASI-90 (C) response over the 12-week treatment period



Lancet 2020;396:255-66

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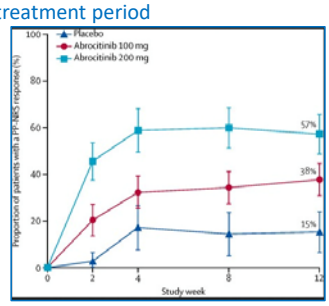
Proportion of patients who achieved a PP-NRS response* over the 12-week treatment period



Lancet 2020;396:255-66

*Defined as a ≥4-point improvement from baseline in PP-NRS score

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Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials

	Measure Up 1			Measure Up 2		
	Upadacitinib 15 mg (n=281)	Upadacitinib 30 mg (n=285)	Placebo (n=281)	Upadacitinib 15 mg (n=276)	Upadacitinib 30 mg (n=282)	Placebo (n=278)
Disease duration since diagnosis, years	20·5 (15·9)	20·4 (14·3)	21·3 (15·3)	18·8 (13·3)	20·8 (14·3)	21·1 (13·6)
Body surface area affected, %	48·5 (22·2)	47·0 (22·0)	45·7 (21·6)	45·1 (22·4)	47·0 (23·2)	47·6 (22·7)
vIGA-AD score						
3 (moderate)	154 (54·8)	154 (54·0)	156 (55·5)	126 (45·7)	126 (44·7)	125 (45·0)
4 (severe)	127 (45·2)	131 (46·0)	125 (44·5)	150 (54·3)	156 (55·3)	153 (55·0)
EASI score	30·6 (12·8)	29·0 (11·1)	28·8 (12·6)	28·6 (11·7)	29·7 (12·2)	29·1 (12·1)
Weekly WP-NRS score	7·2 (1·6)	7·3 (1·5)	7·3 (1·7)	7·2 (1·6)	7·3 (1·6)	7·3 (1·6)

Guttman-Yassky E, et al. Lancet 2021;397:2151

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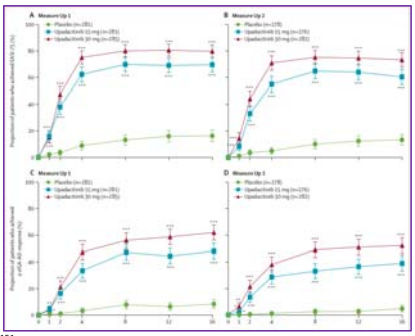
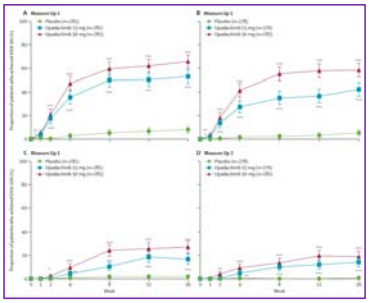
Proportion of patients who achieved EASI-75 and vIGA-AD improvement from baseline over 16-week treatment period in the intention-to-treat population



Guttman-Yassky E, et al. Lancet 2021;397:2151

38

Proportion of patients who achieved an EASI-90 response and EASI-100 response over the 16-week treatment period in the intention-to-treat population



Guttman-Yassky E, et al. Lancet 2021;397:2151

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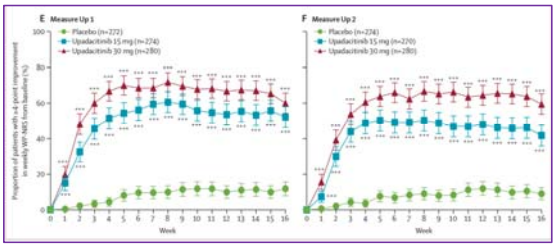
Proportion of patients who achieved ≥4-point improvement from baseline in WP-NRS over 16-week treatment period in the intention-to-treat population



Guttman-Yassky E, et al. Lancet 2021;397:2151

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Efficacy and Safety of Upadacitinib Treatment in Adolescents With Moderate-to-Severe Atopic Dermatitis: Analysis of the Measure Up 1, Measure Up 2, and AD Up Randomized Clinical Trials

- 552 adolescents (mean age ~ 15 y) randomized to once-daily oral upadacitinib 15 mg, upadacitinib 30 mg, or placebo alone (Measure Up 1 and Measure Up 2) or with topical corticosteroids (AD Up)
- In Measure Up 1, Measure Up 2, and AD Up, respectively, a greater proportion of adolescents (% [95% CI]) achieved at least 75% improvement in the EASI at week 16 with upadacitinib 15 mg (73% [63%-84%], 69% [57%-81%], 63% [51%-76%]), and upadacitinib 30 mg (78% [68%-88%], 73% [62%-85%], 84% [75%-94%]), than with placebo (12% [4%-20%], 13% [5%-22%], 30% [19%-42%]; nominal P < .001 for all comparisons vs placebo)
- Acne was the most common adverse event, and all acne events were mild or moderate

JAMA Dermatol 2023;159:526

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Topical and oral JAK inhibitors

- Ruxolitinib (topical JAK1/2 inhibitor) approved in 09/2021
  - For short term and non-continuous chronic treatment of mild to moderate AD in non-immunocompromised patients 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies not advisable
  - Twice daily up to 20% BSA involved areas, no more than 60g/week
  - Lab monitoring optional

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- Abrocitinib (oral JAK 1 inhibitor) approved 01/2022
  - For adults and pediatric patients 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable
  - Recommended dose 100 mg QD and 200 mg QD if inadequate response after 12W
  - 50 mg dose approved to treat moderate-to-severe AD specifically in pts with moderate renal impairment, certain patients receiving treatment with inhibitors of cytochrome P450 (CYP) 2C19 or poor metabolizers of CYP2C19
- Upadacitinib (oral JAK 1 inhibitor) approved 01/2022
  - Indicated for treatment of moderate to severe AD in adults and children 12 yrs and older whose disease did not respond to previous treatment and is not well controlled with other pills or injections, including biologic medicines, or when use of other pills or injections is not recommended
  - 15 mg once daily can be initiated in adults and children 12 yrs of age and older weighing at least 40 kg
  - In children and adults < 65 yrs of age who do not achieve an adequate response, dose may be increased to 30 mg once daily

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JAK inhibitor Boxed Warnings

- **Serious infections. ...** including TB and infections caused by bacteria, fungi, or viruses that can spread throughout the body. HCP should test you for TB before starting [JAK inhibitor] and check you closely for signs and symptoms of TB during treatment.... You may be at higher risk of developing shingles (herpes zoster).
- **Increased risk of death in people ≥ 50 years who have at least 1 cardiovascular risk factor**
- **Cancer and immune system problems.** Follow HCP's advice about having your skin checked for skin cancer during treatment with [JAK inhibitor] . Limit the amount of time you spend in sunlight. Wear protective clothing when you are in the sun and use sunscreen.
- **Increased risk of major cardiovascular (CV) events, such as heart attack, stroke, or death, in people ≥ 50 years who have at least 1 CV risk factor, especially if a current or past smoker.**
- **Blood clots. ...** more often in people who are ≥ 50 years and older and with at least 1 CV risk factor.
- **Allergic reactions. ...**seen in people taking [JAK inhibitor].
- **Tears in the stomach or intestines and changes in certain laboratory tests.** Your HCP should do blood tests before you start taking [JAK inhibitor] and while you take it.

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My JAK inhibitor checklist for the Atopic Dermatitis Yardstick Update

- **ASK:**
  - CV risks factors, smoking, blood clots
  - skin cancer
  - TB
  - vaccine status (H zoster*, Varicella)
  - pregnancy
- **SCREEN:**
  - for TB before starting JAK inhibitor and check for signs and symptoms of TB during treatment
  - monitor for shingles (H zoster)
  - skin checks for skin cancer during treatment & limit amount of time in sunlight (protective clothing and sunscreen)
- **TEST:**
  - CBC w/diff before starting & after ~ 4W on treatment & after increasing dose; LFTs & baseline hepatitis B & C serology; lipid profile after ~ 4 (12)W treatment

* Per CDC, recommended for ≥ 19 yrs with weakened immune systems because of disease or therapy

Boguniewicz M, et al. Ann Allergy Asthma Immunol 2023 (June); 130:811-20

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Atopic Dermatitis Yardstick Update: Expert Commentary

- While JAK inhibitors have a box warning and their use needs to be monitored, there is a benefit to their use in patients that do not want an injectable therapy, and want an oral medication that allows flexibility of dosing, as well as in patients that failed or could not sustain response on dupilumab or other biologics, including those patients that have side effects on dupilumab (e.g. conjunctivitis, occurrence or exacerbation of facial rashes, or arthralgias).
- Also, patients with more moderate disease that do not want to be on a systemic medication continuously may be able to take an oral JAK inhibitor intermittently, rather than stop and restart a biologic, which could be problematic (e.g. development of ADA).
- Since JAK 1 inhibition with abrocitinib targets more than one cytokine pathway, one can also postulate that JAK inhibitors may likely be able to control the majority of AD subtypes, that show skewing of more than just the Th2 pathway. However, careful monitoring needs to be instituted and particular caution should be exercised in patients over 65 years of age (see Table 2).

Boguniewicz M, et al. Ann Allergy Asthma Immunol 2023 (June); 130:811-20

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JAK inhibitors vs biologics ...any head-to-head comparisons?

- JAK inhibitors have several advantages compared with biologics
  - orally bioavailable
  - rapid efficacy
  - predictable pharmacokinetics
  - elicit no immunogenicity [can be stopped and re-started]
  - may allow flexible dosing regimens according to disease activity
  - could be used as induction regimen in acute phases
- Biologics have advantages compared to JAK inhibitors
  - established safety including in children and adolescents (dupilumab)
  - no laboratory monitoring requirement
  - less frequent dosing
  - additional indications for atopic co-morbidities (dupilumab)

Lancet 2020;396:215

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Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis

- 24-wk head-to-head, P3b multicenter, randomized, double-blinded, double-dummy, active-controlled clinical trial comparing safety and efficacy of upadacitinib with dupilumab among 692 adults with moderate-to-severe AD who were candidates for systemic therapy
- Pts randomized 1:1 to oral upadacitinib 30mg QD or subQ dupilumab 300mg QOW
- At wk 16, 247 pts receiving upadacitinib (71.0%) and 210 pts receiving dupilumab (61.1%) achieved EASI75 ($P = .006$)
- All ranked secondary end points also demonstrated superiority of upadacitinib vs dupilumab including improvement in Worst Pruritus NRS as early as wk 1 (mean [SE], 31.4%[1.7%] vs 8.8% [1.8%]; $P < .001$), achievement of EASI75 as early as wk 2 (152 [43.7%] vs 60 [17.4%];$P < .001$), and achievement of EASI100 at wk 16 (97 [27.9%] vs 26 [7.6%]; $P < .001$)
- Rates of serious infection, EH, H zoster, and lab-related AEs higher for pts who received upadacitinib with rates of conjunctivitis and injection-site reactions higher for pts who received dupilumab

Blauvelt A, et al. JAMA Dermatol 2021;157:1047

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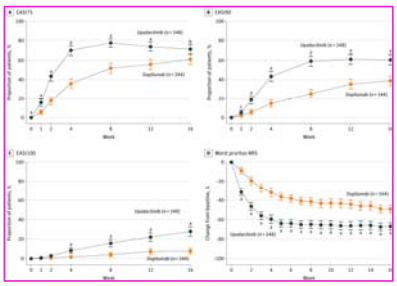
Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis



Blauvelt A, et al. JAMA Dermatol 2021;157:1047

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Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial

- 362 patients randomized to oral abrocitinib (200 mg per day) vs 365 to subcutaneous dupilumab (300 mg Q2WK) for 26 WK
  - Participants required to apply topical steroids (medium or low potency), TCIs or topical PDE4 inhibitor to active lesion areas
  - Primary endpoints: ≥PP-NRS4 at WK 2 and EASI-90 at WK 4
- Larger proportion of pts treated with abrocitinib reached primary outcomes, PP-NRS4 at WK 2 (48% vs 26%, p<0·0001) and EASI-90 at WK 4 (29% vs 15%, p<0·0001)
- TEAEs reported by 74% of abrocitinib pts and by 65% of dupilumab pts
- Abrocitinib 200 mg per day was more efficacious than dupilumab in adults with moderate-to-severe AD on background topical therapy in inducing early reductions of itch and AD disease signs

Reich K, et al. Lancet 2022; 400:273-82

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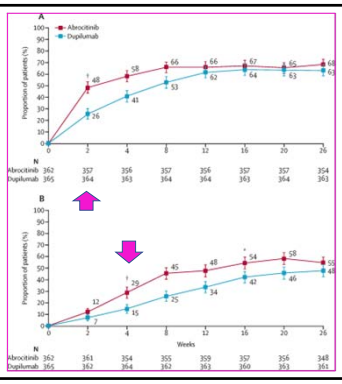
Proportion of patients reaching a clinically meaningful improvement in PP-NRS* and EASI**

*4 point or higher improvement from baseline in PP-NRS (A)
**90% or higher improvement from baseline in EASI (B)



Reich K, et al. Lancet 2022; 400:273-82

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Atopic Dermatitis Yardstick Update: Expert Commentary

- In a systematic review and meta-analysis of randomized clinical trials of 12-16 week duration for systemic or biologic monotherapy (no concomitant prescription topical therapy allowed) in moderate-to-severe AD, upadacitinib 30 mg followed by abrocitinib 200 mg led to highest clinical responses (IGA clear or almost clear, EASI-75, and 4-point improvement in PPNRS).
- Upadacitinib 15 mg daily was associated with considerably higher clinical responses than dupilumab at week 16 while abrocitinib 100 mg daily was associated with similar clinical responses to dupilumab 600 mg loading dose and 300 mg every other week.
- …tralokinumab 300mg every 2 weeks … associated with lower rates of clinical response than dupilumab in this network meta-analysis, though head-to-head trials are lacking for these agents.
- …oral JAK-inhibitors … were associated with higher rates of clinical response than dupilumab at week 2.

Boguniewicz M, et al. Ann Allergy Asthma Immunol 2023 (June); 130:811-20

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Dupilumab Improves Clinical Scores in Children and Adolescents With Moderate to Severe Atopic Dermatitis: A Real-World, Single-Center Study

- All patients (n = 23) who received dupilumab for 1 year or more achieved EASI 75 and IGA 0/1, and 60.8% achieved EASI 90
- 12 patients had AEs (13.5%), of which conjunctivitis (5.6%) and joint pain (2.2%) were most common
  - There were no serious AEs
- Dupilumab was well-tolerated and effective in treating pediatric and adolescent AD regardless of age, sex, race, or ethnicity

Pagan AD, et al. J Allergy Clin Immunol Pract 2022;10:2378

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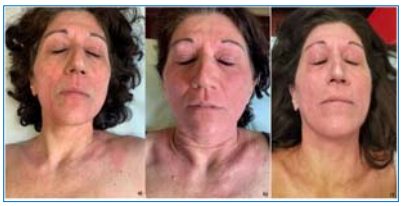
Efficacy of tralokinumab after failure with upadacitinib and dupilumab in a patient affected by atopic dermatitis



- (a) At end of dupilumab therapy: extensive erythematous involvement of the face and neck
- (b) At end of upadacitinib therapy: erythema and lichenification of the face, neck, and neckline
- (c) First follow-up after initiation of tralokinumab: initial reduction in the extent of erythematous lesions and reduction in lichenification at the face

Mastorino L, et al. J Dermatol Treat 2023;34:1

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Moving from "one size fits all" to a precision medicine approach

health.ucdavis.edu

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A · D · R · N
Atopic Dermatitis Research Network

NIAID

LEADS: Longitudinal Endotyping of Atopic Dermatitis Through Transcriptomic Skin Analysis

Primary Objective
To determine if the type 2-high non-lesional skin (skin tape) endotype is associated with current mild versus moderate-to-severe AD disease

Secondary Objectives
1. To determine how gene expression in the skin (skin tape) differs between non-AD participants and those with current mild or moderate-to-severe AD disease
2. To determine how gene expression in the skin (skin tape) changes over time among the study outcome groups: (1) steroid responders, (2) dupilumab responders, (3) dupilumab non-responders, (4) non-AD, and (5) long-term dupilumab participants

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Emerging therapies for AD...An embarrassment of riches

- Topical
  - Tapinarof (aryl hydrocarbon receptor agonist) cream
  - Roflumilast (PDE4 inhibitor) cream
  - Brepocitinib (TYK2/JAK1 inhibitor)
- Systemic
  - Lebrikizumab (anti-IL-13)
  - Nemolizumab (anti-IL-31 RA)
  - Rocatinlimab (anti-OX40)
  - Amlitelimab (anti-OX40L)
- 1286 clinical trials for atopic dermatitis registered with ClinicalTrials.gov
  - 237 phase 3 trials (06/20/23)

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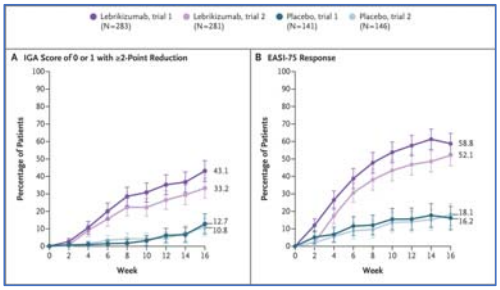
2 Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis



Silverberg JI et al. N Engl J Med 2023;388:1080

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Trial of nemolizumab and topical agents for AD with pruritus

- Nemolizumab is a subcutaneously administered humanized monoclonal antibody against interleukin-31 receptor A
- 16 wk, double-blind, phase 3 trial in Japanese patients with AD and moderate-to-severe pruritus and inadequate response to topical agents 2:1 to subcut nemolizumab (60 mg) or placebo Q 4 wks with concomitant topical agents
  - 143 patients randomly assigned to nemolizumab and 72 to placebo
- Primary end point was mean % change in VAS score for pruritus (0 to 100) from baseline to wk 16
  - Median VAS score for pruritus at baseline was 75
- At wk 16 mean % change in VAS score was -42.8% in nemolizumab group and -21.4% in placebo group (P<0.001)
- Mean % change in EASI score was -45.9% with nemolizumab and -33.2% with placebo

Kabashima K, et al. N Engl J Med 2020 383:141

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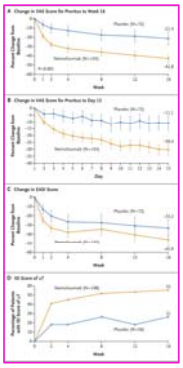
Trial of nemolizumab and topical agents for AD with pruritus

- Subcutaneous nemolizumab in addition to topical agents for AD resulted in a greater reduction in pruritus than placebo plus topical agents
- Incidence of injection-site reactions was greater with nemolizumab than with placebo



Kabashima K, et al. N Engl J Med 2020 383:141

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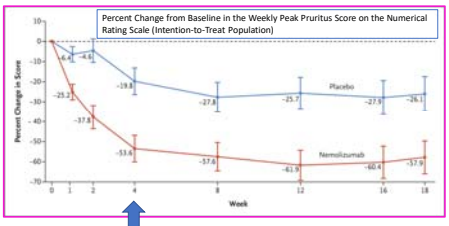
Trial of nemolizumab in moderate-to-severe prurigo nodularis



Primary efficacy

0 (no itch) to 10 (worst itch imaginable)

Stander S, et al. N Engl J Med 2020;382:706

More instances of abdominal symptoms, including abdominal pain and diarrhea, and musculoskeletal symptoms (nonspecific bodily pains) in nemolizumab group than in placebo group

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Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: A randomized phase 2a clinical trial

- 113 patients randomized 1:1 to subcut tezepelumab 280 mg or placebo Q2W plus TCS
- Primary endpoint: Wk12 response rate for ≥50% reduction in EASI (EASI50)
- Secondary endpoints including EASI75, IGA, SCORAD 50, SCORAD 75, PNR and 5-D itch scales assessed at wks 12 and 16 (post hoc)
- Numerically greater percentage of tezepelumab plus TCS-treated patients achieved EASI50 (64.7%) vs placebo plus TCS (48.2%; P = .091)
- Although not statistically significant, numerical improvements over placebo for all wk 12 endpoints demonstrated with greater wk 16 responses

Simpson EL, et al. J Am Acad Dermatol 2019;80:1013

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New Therapies Take Home Messages

- Patients with AD often have a relapsing highly pruritic disease impacting QOL with pathophysiology that is complex and involves immune dysregulation, skin barrier abnormalities and microbial dysbiosis with Type 2 inflammation seen across the spectrum of clinical phenotypes
- Currently approved biologics block either the receptor for 2 key type 2 cytokines IL-4 & -13 (dupilumab) or bind directly to IL-13 (tralokinumab)
  - Dupilumab approved down to 6 months of age for moderate-to-severe AD (also approved for asthma & CRSwNP & EoE & PN)
  - Tralokinumab currently approved for adults with moderate-to-severe AD
- Approved JAK inhibitors target multiple cytokines and have been shown to be rapidly effective and relatively safe in short term trials with long term data emerging
  - Topical ruxolitinib for mild-moderate AD 12 y and older (limit use to up to 20% BSA)
  - Oral abrocitinib and upadacitinib (both, 12 y and older) for moderate-to-severe AD not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable with recommended safety monitoring

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