UBC Dermatology
Care • Teaching • Research

Novel Topical Therapies for the Treatment Atopic Dermatitis

Faculty/Presenter Disclosure

- Faculty/Presenter: Chih-ho Hong
- Relationships with financial sponsors:
  - Advisory Board: Abbvie, Amgen, Arcutis, Bausch Health, Boehringer-Ingelheim, Bristol Meyers Squibb, Celgene, Dermavant, Eli-Lilly, Galderma, GSK, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, Sun Pharma, UCB
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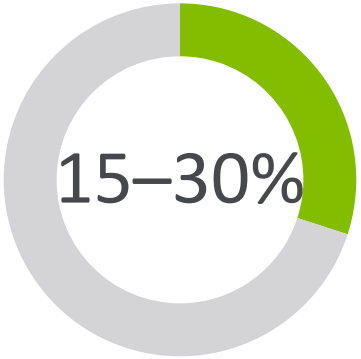
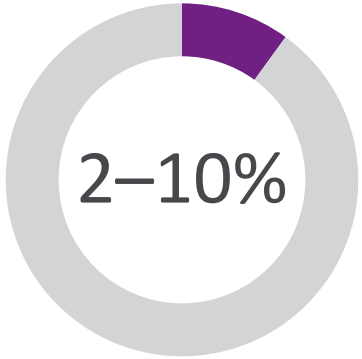
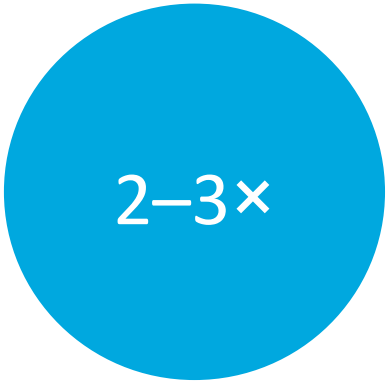
AD is a common chronic inflammatory skin disease[1–3]



Lifetime prevalence in **children**[1,2]



Lifetime prevalence in **adults**[2,3]



Increase in **incidence** since the 1970s[4]

Dermatitis[a] accounts for the **largest skin disease** burden globally (Global burden of disease 2013 study)[5]

[a]Including atopic, seborrheic, and contact dermatitis
AD, atopic dermatitis

1. Bieber T. Ann Dermatol 2010;22:125–37; 2. Nutten S. Ann Nutr Metab 2015;66(Suppl. 1):8–16;
3. Abuabara K, et al. Ann Intern Med 2019;170:354–6; 4. Avena-Woods C. Am J Manag Care 2017;23:S115–S23;
5. Karimkhani C, et al. JAMA Dermatol 2017;153:406–12

Clinical presentation of AD ranges in severity*

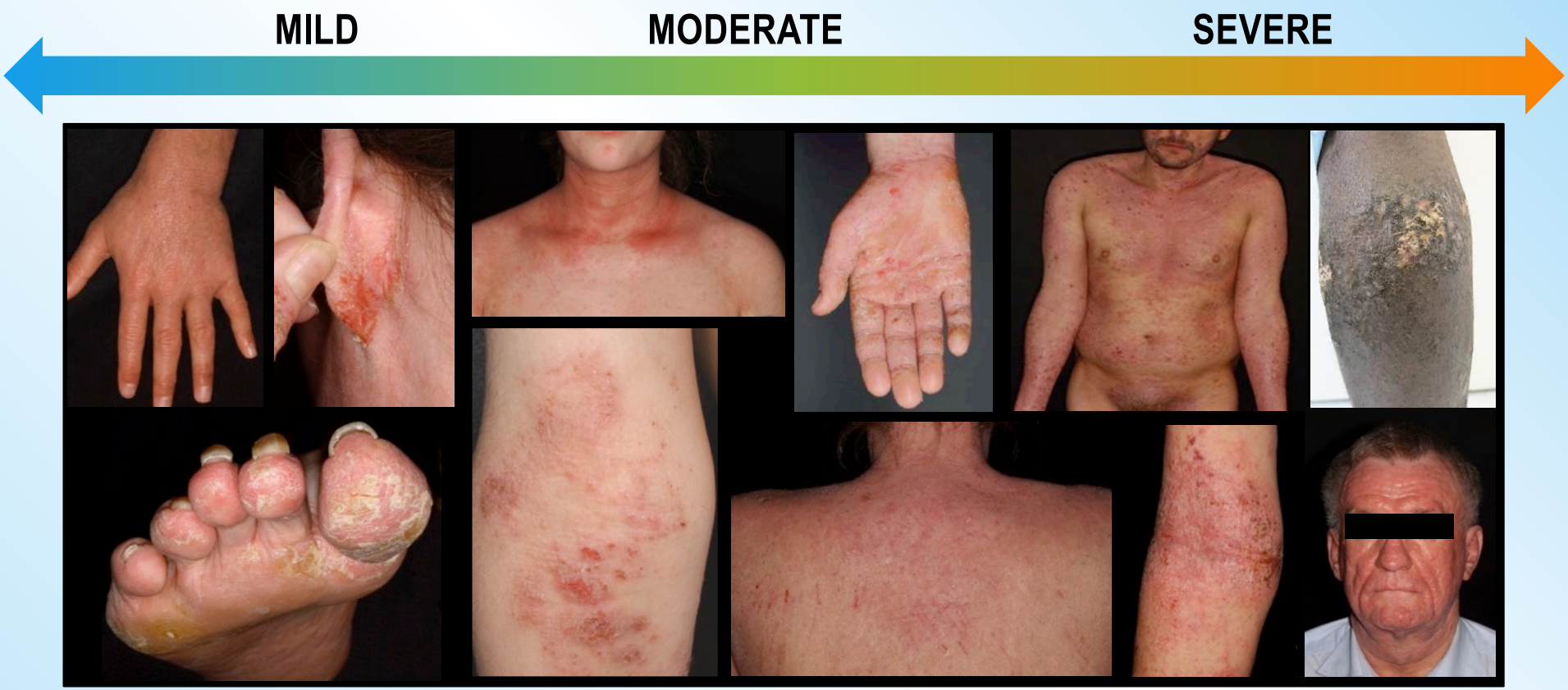
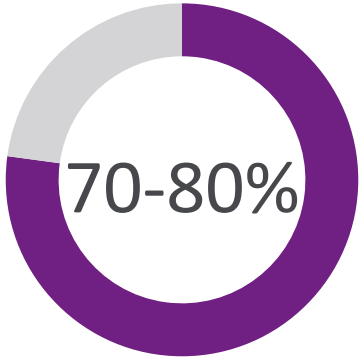


*Figure adapted from Bieber T, Nestle F, eds. *Personalized Treatment Options in Dermatology*. DOI: 10.1007/978-3-662-45840-2_5; Berlin Heidelberg: Springer-Verlag; 2015, with images courtesy of Dr Thomas Bieber; and from Leung DYM et al.

About 70% of Atopic Dermatitis is mild to moderate disease[1,2]



AD rated as mild to moderate

Majority of AD cases are suitable for topical treatment

1. . Esaki H, et al. *J Allergy Clin Immunol*. 2016;138(6):1639-1651.
2. Arkwright PD, et al. *J Allergy Clin Immunol Pract*. 2013;1(2):142-151.

Definition

- What is “mild”, “moderate”, “severe”, or“moderate to severe”?
- Overlapping, inconsistent, and confusing nomenclature
- Changing definition of patients in the “moderate to severe” category over time

Definition

- Currently:
  - IGA: 3-4 on 5 point scale
  - EASI: ≥ 16
  - BSA: ≥ 10
  - SCORAD: > 25 moderate; ≥ 50 severe

Protopic for M2S?

—

Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: Part I, Efficacy

Jon M. Hanifin, MD,[a] Mark R. Ling, MD,[b*] Richard Langley, MD,[c] Debra Breneman, MD,[d] Elyse Rafal, MD,[e] and the Tacrolimus Ointment Study Group[**] *Portland, Oregon; Atlanta, Georgia; Boston, Massachusetts; Cincinnati, Ohio; and Stony Brook, New York*

doi:10.1067/mjd.2001.109810

Acta Derm Venereol (Stockh) 1989; Suppl 144: 13–14

Grading of the Severity of Atopic Dermatitis

G. RAJKA and T. LANGELAND

Department of Dermatology, the National Hospital, Rikshospitalet, Oslo, Norway

Table I. *Grading (severity) of atopic dermatitis*

I. *Extent*	
(*a*) Childhood and adult phase	
Less than approx. 9% of the body area	1
Involvement evaluated to be more than score 1, less than score 3	2
More than approx. 36% of the body area involved	3
(*b*) Infantile phase	
Less than approx. 18% of the skin involved	1
Involvement evaluated to be more than score 1, less than score 3	2
More than 54% of the skin involved	3
II. *Course*	
More than three months of remission during a year[a]	1
Less than 3 months remission during a year[a]	2
Continuous course	3
III. *Intensity*	
Mild itch, only exceptionally disturbing night's sleep	1
Itch, evaluated to be more than score 1, less than score 3	2
Severe itch, usually disturbing night's sleep	3
Score summation	
3–4 = mild	
4.5–7.5 = moderate	
8–9 = severe	

When doubt, score 1.5 or 2.5, may also be used.

[a] May be adjusted in infants or if onset was less than 1 year before grading.

Other topicals

- FYI
  - pimecrolimus (2002 JAAD) used IGA 2/3 (mild to moderate)
  - Crisaborole (2016 JAAD) used sIGA 2/3 (mild to moderate)

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

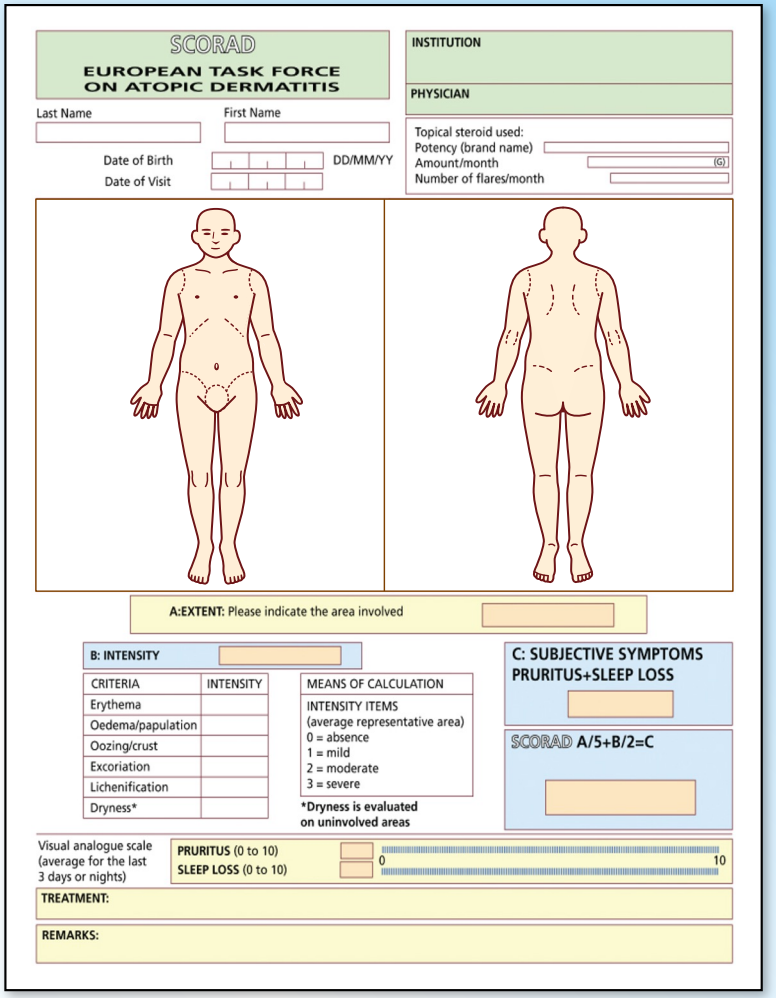
Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

Disease severity scale: SCORAD

- Validated score that includes:
  - Objective physician estimates (extent, severity)
  - Subjective patient assessment (itch, sleep loss)
- App available at:
  - http://scorad.org/



SCORAD: Scoring Atopic Dermatitis.

European Task Force on Atopic Dermatitis. *Dermatology* 1993;186:23-31.

Disease severity scale: EASI

- Based on objective physician estimates of disease extent, severity[1]
- One of the best-validated instruments for AD assessment[2]
- App available at: http://www.homeforeczema.org/resources.aspx

EASI[1]

0 — 72

Mild < 8	Moderate 8–15	Severe > 15

Example of EASI for patients aged ≥ 8 years.

EASI: Eczema Area and Severity Index.

Area of Involvement: Each body area has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points may be used e.g. 2.5.

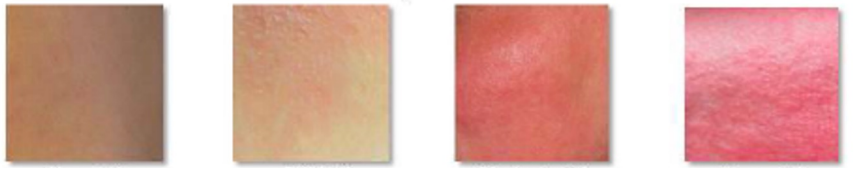
Scoring table:

Body region	Erythema (0-3)		Edema/ Papulation (0-3)		Excoriation (0-3)		Lichenification(0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(	+	+	+	+	)		x	X 0.1	
Trunk	(	+	+	+	+	)		x	X 0.3	
Upper extremities	(	+	+	+	+	)		x	X 0.2	
Lower extremities	(	+	+	+	+	)		x	X 0.4	
The final EASI score is the sum of the 4 region scores:										_____ (0-72)

1. Hanifin JM, et al. *Exp Dermatol* 2001;10:11-18. 2. Lesham YA, et al. *Br J Dermatol* 2015;172:1353-1357.

EASI atlas of disease severity

Erythema



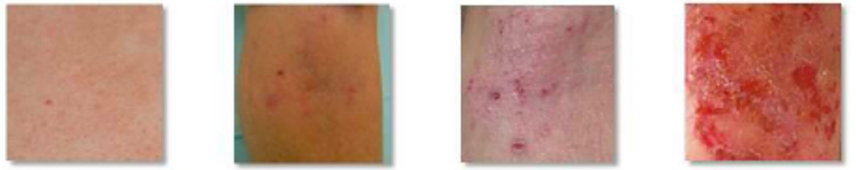
None = 0

Mild = 1
Faintly detectable, pink

Moderate = 2
Clearly distinguishable dull red

Severe = 3
Deep dark or fiery bright red

Excoriation



None = 0

Mild = 1
Scant, superficial excoriations

Moderate = 2
Many superficial and/or some deeper excoriations

Severe = 3
Diffuse extensive superficial and/or many deep excoriations

Edema / Papulation

None = 0

Mild = 1
Barely perceptible elevation

Moderate = 2
Clearly perceptible elevation but not prominent

Severe = 3
Prominent elevation

Lichenification

None = 0

Mild = 1
Slight thickening of the skin with skin markings minimally exaggerated

Moderate = 2
Clearly thickened skin with exaggerated skin markings and/or some prurigo nodules

Severe = 3
Prominent skin thickening with exaggerated skin markings creating deep furrows and/or many prurigo nodules

EASI: Eczema Area and Severity Index.

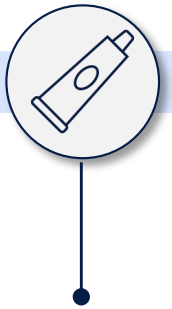
HOME: Harmonising Outcome Measures for Eczema; University of Nottingham Website: http://www.homeforeczema.org/documents/easi-user-guide-dec-2016-v2.pdf

Ok – so how do we treat it?

Treatment options for AD[a]

Non-pharmacologic interventions
- Topical moisturizers

Topical corticosteroids



Topical calcineurin inhibitors
- Pimecrolimus
- Tacrolimus

Topical PDE-4 inhibitors
- Crisaborole

Topical antimicrobials and antiseptics
- Bleach baths
- Intranasal mupirocin

Wet wrap therapy

Phototherapy

Systemic therapies
- Cyclosporin
- Azathioprine
- Methotrexate
- IL-4/-13 biologics
- JAK inhibitors

[a]Not all of these treatments are licensed by any or all health authorities for the treatment of AD
AD, atopic dermatitis; IL, interleukin; JAK, Janus kinase; PDE, phosphodiesterase

Wollenberg A, et al. J Eur Acad Dermatol Venereol 2020;34:2717–44

Topical treatments used in moderate-to-severe AD[1]

Topical corticosteroids

- Used to control acute flares and reduce relapses
- Treatment success measured by reduction in itch

Limitations

- Can lead to skin changes and needs to be limited in sensitive areas
- Patient fear of side effects needs to be considered and managed

Topical calcineurin inhibitors (tacrolimus, pimecrolimus)

- Licensed in the EU for flare and maintenance treatment[2]
- May be used in sensitive skin areas

Limitations

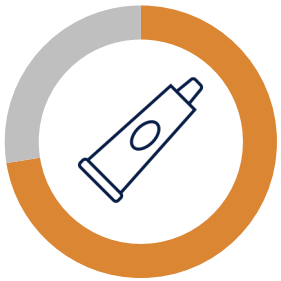
- Not recommended for acute flares
- Stinging, burning, flushing
- Sunscreen advised in patients

AD, atopic dermatitis

1. Wollenberg A, et al. J Eur Acad Dermatol Venereol 2018;32:657–82; 2. Protopic SmPC, 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/protopic-epar-product-information_en.pdf (last accessed September 2021)

Although many patients benefit from topical therapies, concerns about safety and inconvenience of topical treatments means that AD may be undertreated

Patient concerns about TCS can lead to treatment non-compliance[1]



72.5%
of people are worried about using TCS on their own or their child's skin

Perceived risk of skin thinning
34.5%

Systemic absorption leading to effects on growth and development
9.5%

n=200

24.0%
of people admitted to having been non-compliant with TCS treatment because of these worries

Adherence rates are typically highest at the start of treatment and decrease with extended treatment duration[2]

3-day
93%
n=20

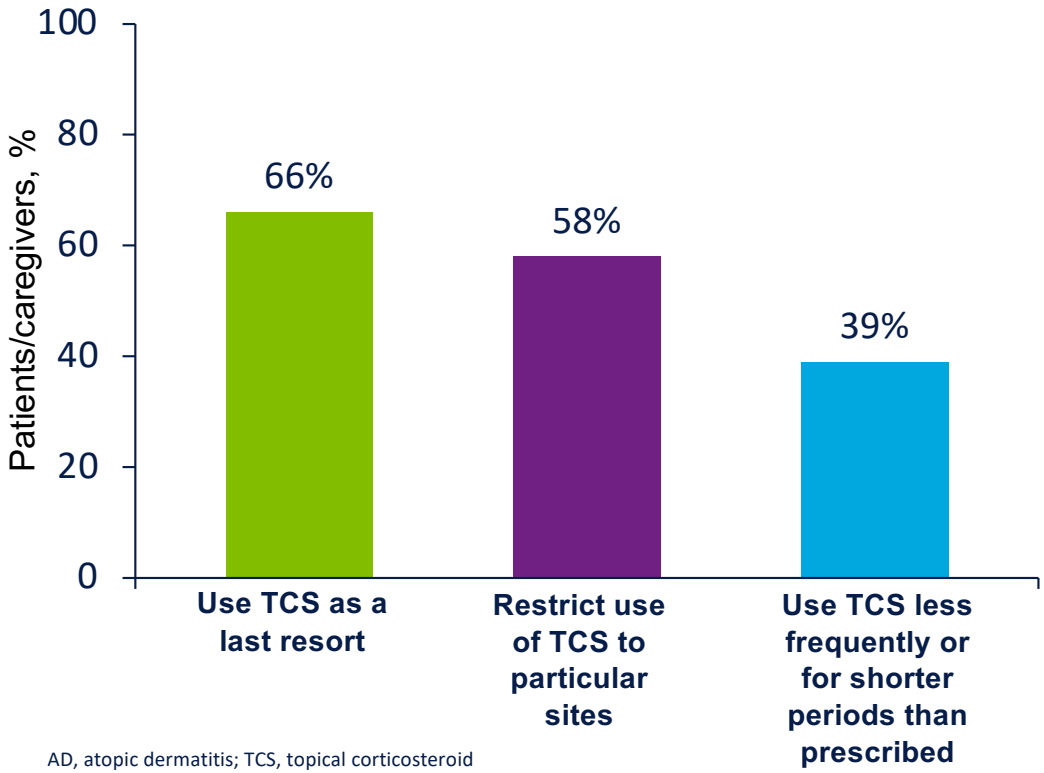
8-day
32%
n=37

AD, atopic dermatitis; TCS, topical corticosteroid; TSW, topical steroid withdrawal

1. Charman CE, et al. Br J Dermatol 2000;142:931–6;
2. Snyder A, et al. Cutis 2015;96:397–401

Patients with AD often delay treating flares with topical prescription medications, resulting in untreated disease for a period of the time they are in flare

Among a population of patients aged >13 years (60%) and caregivers (40%)



"The fear of topical corticosteroid side effects might also, at least partly, explain why patients delay initiating treatment when the disease flares"

Average 6.1-day delay before treatment

AD, atopic dermatitis; TCS, topical corticosteroid

Zuberbier T, et al. J Allergy Clin Immunol 2006;118:226–32

Tips to improve counselling of topical therapy

1) Make it simple
2) Write it down – use an eczema care plan
3) Demonstrate proper application
4) Get patient input
   - What is realistic for applying – once/twice daily
   - Ointments vs creams vs other
   - Cost consideration

5) Disease will flare in the future – address proactive therapy (2x weekly application to “hot spots”)

Eczema Care Plan

Written Eczema Care Plans

Health Care Provider Tool — Tear-Off Pad



WHAT IS A WRITTEN ECZEMA CARE PLAN?

A written eczema care plan is a recommended tool to improve therapeutic outcomes. Patients and caregivers may benefit from having a written plan in order to carry out the multi-step plan of caring for eczema (atopic dermatitis). This often includes specific bathing and moisturizing recommendations and instructions for using anti-inflammatory medications.

This pad provides a sample written eczema care plan, which may be helpful for patients, and may be customised as the health care provider wishes. Note that this is not a validated tool. This sample written eczema care plan was developed by Canadian dermatologists and is from the health care provider resource ***Atopic Dermatitis: A Practical Guide to Management, Third Edition***. To view or order a copy of this document contact Eczema Society of Canada by telephone at 1-855-ECZEMA-1, by email at info@eczemahelp.ca, or online at www.eczemahelp.ca.

The dissemination of this resource was supported in part by funding from Pfizer Canada.

* *Also available in French*

eczemahelp.ca

HEALTH CARE PROVIDER TOOL — SAMPLE WRITTEN ECZEMA CARE PLAN

WRITTEN ECZEMA CARE PLAN

Patient Name: _____

Date: _____

Physician Name: _____

STEP 1

Every day, take a 5- to 10-minute bath or shower. If this is not enjoyable or is uncomfortable, take a shower or bath every second day. You can use a gentle cleanser if you wish. Gently towel dry.

STEP 2

Apply prescription medications to any areas of eczema that are red, rough, and/or itchy.

Apply _____ to the affected areas of the face, neck, armpits, and groin _____ times per day.

Apply _____ to the scalp _____ times per day.

Apply _____ to other affected areas of the body _____ times per day.

STEP 3

Apply a moisturizer to the unaffected areas of the body, within a few minutes of exiting the bath or shower.

ADDITIONAL INSTRUCTIONS

- Moisturizer may be applied throughout the day, whenever the skin feels dry or itchy, or after any contact with water (e.g. bathing, swimming, etc).
- Continue using the prescription medications until the skin is clear, smooth, and the redness and itchiness is gone. If after two weeks of regular medication use, your skin has not cleared, speak with your physician.
- After the rash has cleared, continue applying moisturizer at least two times a day to the entire body.
- Restart the prescription medications, as described in **Step 2**, when the eczema flares again.
- Oozing fluid, yellow crusts, blisters, and/or red swelling need to be reported to your doctor immediately. This could be an infection or other concern.

NOTES

IMPORTANT NOTE:

Should you have any questions about this care plan or any concerns related to your eczema treatment, contact the prescribing doctor.

For more information on Eczema Society of Canada visit **www.eczemahelp.ca**

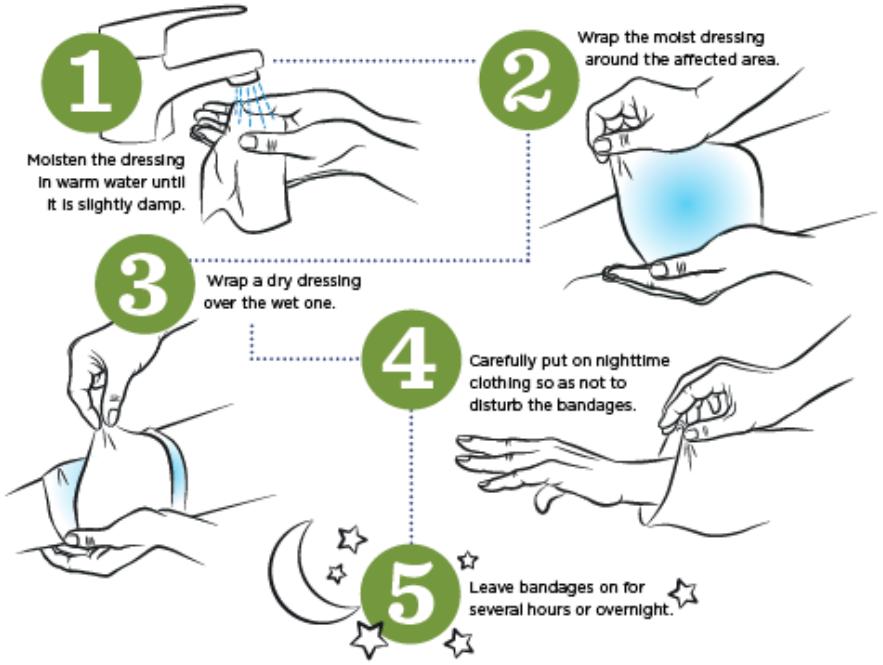
Wet wrap therapy

National Eczema Association

Wet Wrap Step-By-Step

During particularly intense eczema flare-ups with severe itch or pain, wet wrap therapy can work wonders to rehydrate and calm the skin and help topical medications work better.

Wet wraps are best done in the evening after bathing, moisturizing and applying medication. You can use clean, cotton clothing as a dressing and pajamas or a onesie on top if the eczema is widespread, cotton gloves or socks if it is not.



Localized disease

- Intralesional Kenalog helpful for thick, lichenified areas, particularly if localized
- Kenalog 2.5mg/ml to 5mg/ml very helpful particularly if localized areas of LSC
- May be a preferred form of therapy for certain patient groups

Canadian Working Group: Simple classification of patients based on response to first-line topical therapies for AD

Patients with disease adequately controlled by topical therapies

Patients with moderate to severe AD with disease that is not adequately controlled by topical therapies*

*Disease not adequately controlled by topical therapies or in whom topical treatments are not appropriate (e.g., contraindicated or not tolerated). Inadequate disease control defined as absence of meaningful improvement, judged by clinician and patient, within 4 to 8 weeks of initiating topical therapy with moderate- or potent/superpotent steroid and/or TCI, or relapse/flare of symptoms within 1 week of discontinuation of topical therapy.

Lynde CW, et al. *J Cutan Med Surg* 2017.

Canadian Working Group: Selection criteria for systemic therapy

Patients with moderate-to-severe AD not adequately controlled with topical therapies* and:

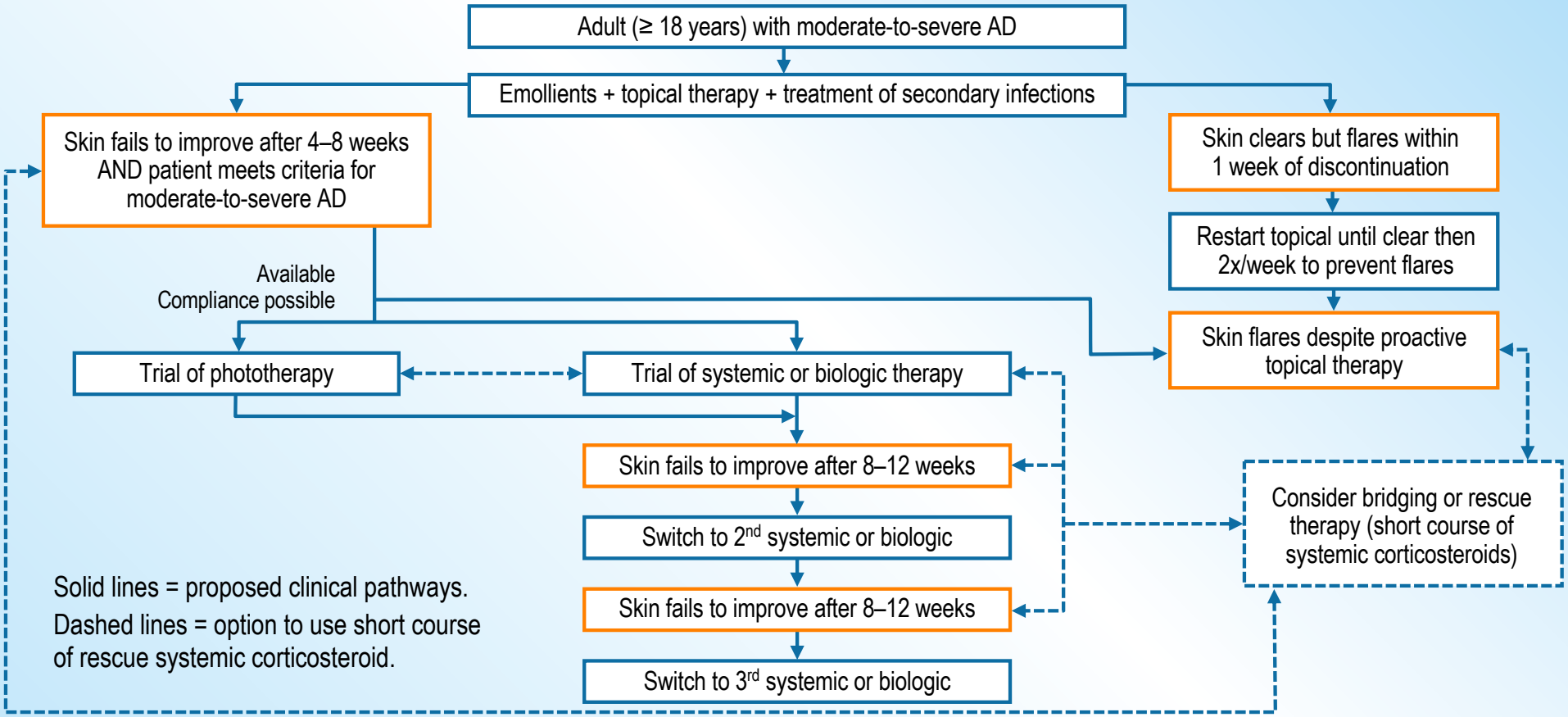
1. Pruritus NRS score ≥ 4
2. BSA ≥ 10%
3. PGA score ≥ 3
4. DLQI score ≥ 10

BSA: body surface area; DLQI: Dermatology Life Quality Index; NRS: numerical rating scale; PGA: Physician's Global Assessment

*Disease not adequately controlled by topical therapies or in whom topical treatments are not appropriate (e.g., contraindicated or not tolerated). Inadequate disease control defined as absence of meaningful improvement, judged by clinician and patient, within 4 to 8 weeks of initiating topical therapy with moderate- or potent/superpotent steroid and/or TCI, or relapse/flare of symptoms within 1 week of discontinuation of topical therapy.

Lynde CW, et al. *J Cutan Med Surg* 2017.

Canadian Working Group: Proposed algorithm for the treatment of moderate-to-severe AD in adults



Lynde CW, et al. *J Cutan Med Surg* 2017.

IEC Guidelines

Simpson EL, et al. *J Am Acad Dermatol* 2017;77:623–33.

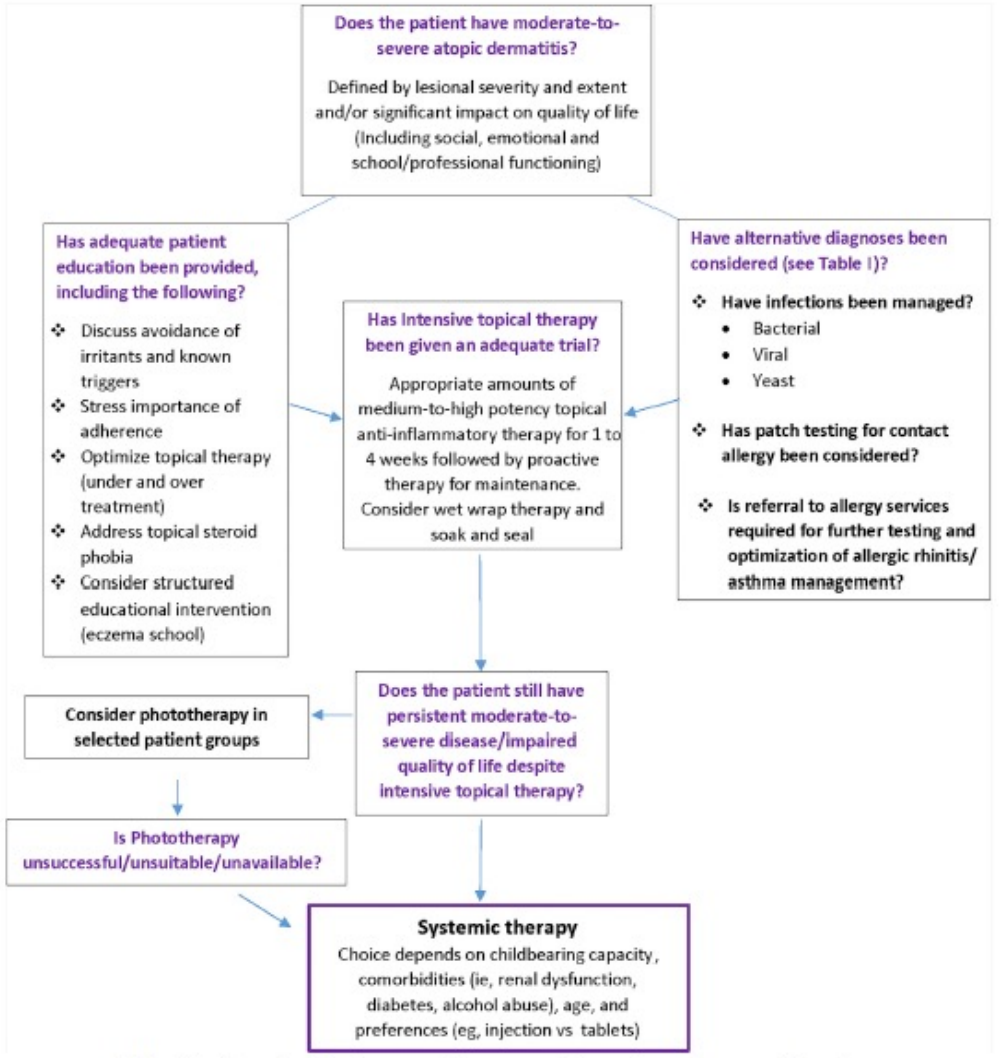


Fig 1. Algorithm to decide when systemic immunomodulatory therapy is warranted in patients with atopic dermatitis.

Systemic Treatment

	Evidence[1,2]	Dosage, considerations[3]
Cyclosporine	• Moderate- to high-quality large studies • Short-term use	• **Adults:** 150–300 mg/day • **Pediatric:** 2.5–5 mg/kg/day
Azathioprine	• Moderate-quality study • Large patient numbers • Short- and long-term (24 wk)	• **Adults:** 1–3 mg/kg/day • **Pediatric:** 1–4 mg/kg/day • Measure TPMT* before prescribing
Methotrexate	• Moderate-quality study • Large patient numbers • Short- and long-term (24 wk)	• **Adults:** 7.5–25 mg/wk • **Pediatric:** 0.2–0.7 mg/kg/wk

TPMT: thiopurine methyltransferase.
*Availability may be limited.
Not approved for AD by Health Canada.

1. Gooderham M, et al. *J Cutan Med Surg* 2017;21:31-39. 2. Roekevisch E, et al. *J Allergy Clin Immunol* 2014;133:429-438.
3. Sidbury R, et al. *J Am Acad Dermatol* 2014;71:327-349.

Systemic therapies for AD

Clinical evidence

	Cyclosporine	Azathioprine	Methotrexate
Decrease in clinical score (%)[1]	54–95	26–39	42–52
Treatment period in trials (wks)[1]	Max 52	Max 24	Max 24
Time to respond (wks)[1]	2	8–12	8–12
Time to relapse (wks)[1]	< 2	> 12	> 12
QOL[2]	Improved	Improved	Improved

Not approved for AD by Health Canada.
QOL: quality of life.

1. Wollenberg A, et al. *J Eur Acad Dermatol Venereol* 2016;30:729-747.
2. Gooderham M, et al. *J Cutan Med Surg* 2017;21:31-39.

Systemic treatment

Side effects

Cyclosporine	Azathioprine	Methotrexate
• Nausea • Headache • Paresthesia • Renal impairment • Hypertension • Sequelae of chronic immunosuppression	• Not well-tolerated – GI • Abnormalities in liver enzymes, blood counts (lymphocytopenia)	• Nausea • Elevated liver enzymes • More rarely pancytopenia, hepatic or pulmonary toxicity

Not approved for AD by Health Canada.
GI: gastrointestinal.

Gooderham M, et al. *J Cutan Med Surg* 2017;21:31-39.

Systemic treatment

Contraindications

Cyclosporine	Azathioprine	Methotrexate
• Renal impairment • Uncontrolled hypertension • Malignancies	• Unknown/low/absent TPMT activity • Malignancies • Concurrent allopurinol therapy • Pregnancy **Relative contraindications:** • Hepatic, renal impairment **Caution:** • Women of childbearing potential	**Relative contraindications:** • Liver disease • Renal impairment • Significant pulmonary disease • Blood dyscrasias • Active infection • Pregnancy • Excessive alcohol consumption **Caution:** • Women of childbearing potential*

Not approved for AD by Health Canada.

*Methotrexate must be stopped 3 months before conception.

TPMT: thiopurine methyltransferase.

Gooderham M, et al. *J Cutan Med Surg* 2017;21:31-39.

Other systemic treatments

	Oral/injectable corticosteroids	Mycophenolate mofetil
Use	• Short-term (acute flares) • Long-term use not recommended[1,2]	• Severe AD, if cyclosporine not effective or contraindicated[5]
Side effects	• Glucose intolerance, Cushing's syndrome, glaucoma, myopathy, hypertension, infections, cataracts, osteoporosis, avascular necrosis[3,4]	• Nausea, vomiting, abdominal cramping, headache, fatigue • Boxed warnings: embryo fetal toxicity, malignancies, serious infections[5,6]
Monitoring	If long-term use[5] • Blood pressure • Ophthalmologic • HPA axis suppression testing • Bone density	**Baseline only:** • Renal function, HIV* **Baseline and follow-up monitoring:** • TB, liver function, CBC, HCG*

*If indicated. Not approved for AD by Health Canada.
CBC: complete blood count; HPA: hypothalamic-pituitary-adrenal; HCG: human chorionic gonadotropin.

1. Saeki H, Nakahara T, Tanaka A et al. *J Dermatol* 2016;43:1117-1145. 2. Ring J, et al. *J Eur Acad Dermatol Venereol* 2012;26:1176-1193.
3. Akhavan A, Rudikoff D. *Semin Cutan Med Surg* 2008;27:151-155. 4. Walling HW, Swick BL. *Clin Cosmet Investig Dermatol* 2010;3:99-117.
5. Sidbury R, et al. *J Am Acad Dermatol* 2014;71:327-349. 6. Genentech. CellCept® (mycophenolate mofetil) product monograph. 2015.

Other treatments

Phototherapy

- **Use:** Unresponsive to topical treatments, maintenance therapy in chronic disease
- **Side effects:** Skin cancer, premature aging of skin
- **Considerations:** Avoid combination with cyclosporine, azathioprine; limited availability

1. Sidbury R, et al. *J Am Acad Dermatol* 2014;71:327-349.

Moderate-to-severe AD treatment: Phototherapy

Treatment
Phototherapy

European guidelines recommend:

- Medium-dose UVA1 and NB-UVB in adult patients
- Co-treatment with topical steroids and emollients at the beginning or to prevent a flare

Limitations

- Required 3–5 times per week for 6–12 weeks at site with available equipment
- Not effective on hair-covered areas
- Not suitable in patients whose AD worsens in response to sun exposure
- Long-term PUVA photochemotherapy carries risk of skin cancer

AD, atopic dermatitis; NB-UVB, narrowband ultraviolet B; PUVA, psoralen and ultraviolet A; UVA, ultraviolet A

Wollenberg A, et al. J Eur Acad Dermatol Venereol 2018;32:657–82
Image sourced from https://jddonline.com/phototherapy-for-psoriasis-a-safe-and-effective-treatment-modality

AD Treatment – Canadian Consensus Guidelines

Approach to the Assessment and Management of Adult Patients With Atopic Dermatitis: A Consensus Document

Journal of Cutaneous Medicine and Surgery
2018, Vol. 22(1S) 3S–5S

DOI: 10.1177/1203475418803627
journals.sagepub.com/home/jcms

Canadian Dermatology Association

Association canadienne de dermatologie

Melinda J. Gooderham[1,2*], Chih-ho Hong[2,3*], Lorne Albrecht[2,4], Robert Bissonnette[5], Gurbir Dhadwal[2,6], Robert Gniadecki[7], Parbeer Grewal[2,7,8], Mark G. Kirchhof[9], Ian Landells[10], Perla Lansang[11,12], Chuck W. Lynde[2,13], Kim A. Papp[2,14], Yves Poulin[15], Gordon Sussman[16], Irina Turchin[17], Marni Wiseman[18], and Jensen Yeung[2,11,12,19]

Approach to the Assessment and Management of Adult Patients With Atopic Dermatitis: A Consensus Document.

Section V: Consensus Statements on the Assessment and Management of Adult Patients With Moderate-to-Severe Atopic Dermatitis

Journal of Cutaneous Medicine and Surgery
2018, Vol. 22(1S) 30S–35S

DOI: 10.1177/1203475418803625
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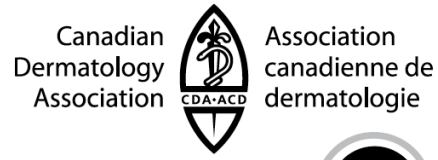
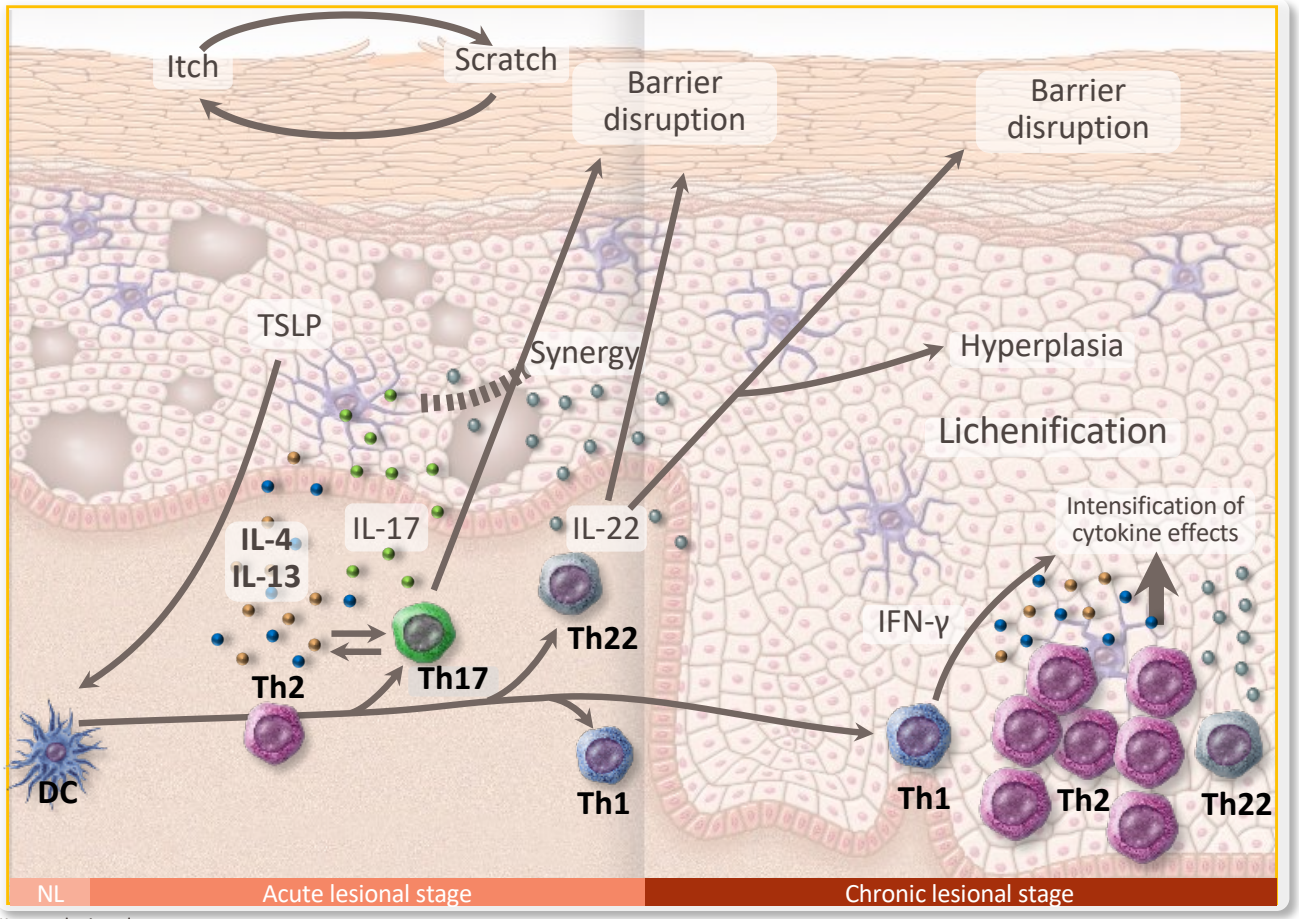


Chih-ho Hong[1,2*], Melinda J. Gooderham[2,3*], Lorne Albrecht[2,4], Robert Bissonnette[5], Gurbir Dhadwal[2,6], Robert Gniadecki[7], Parbeer Grewal[2,7,8], Mark G. Kirchhof[9], Ian Landells[10], Perla Lansang[11,12], Chuck W. Lynde[2,13], Kim A. Papp[2,14], Yves Poulin[15], Gordon Sussman[16], Irina Turchin[17], Marni Wiseman[18], and Jensen Yeung[2,11,12,19]

6. The objectives of therapy are to reduce skin inflammation and pruritus, restore skin barrier function, and improve quality of life.
   Voting Result: 8, 6, 2, 1, 0
7. Moisturizers, topical corticosteroids, and topical calcineurin inhibitors have been shown to significantly reduce signs and symptoms of AD and are first-line therapy.
   Voting Result: 11, 6, 0, 0, 0
8. UVB phototherapy may be beneficial for patients with moderate-to-severe AD, where accessible.
   Voting Result: 6, 8, 1, 1, 1
9. Systemic therapies that are indicated for the treatment of moderate-to-severe AD should be used for patients who fail first-line therapy. Currently, in many countries, dupilumab is the only systemic therapy indicated for the long-term treatment of moderate-to-severe AD.
   Voting Result: 8, 7, 2, 0, 0
10. When medications indicated for the treatment of AD are not available, conventional systemic therapies may be used off-label. MTX may be considered for stable moderate-to-severe disease. Short-term CsA may be considered for rapid control in patients who experience acute flares or have unstable disease.
    Voting Result: 7, 9, 0, 1, 0
11. Consider systemic corticosteroids only in short courses as rescue therapy.
    Voting Result: 4, 13, 0, 0, 0

Dupilumab

The Type 2 Inflammatory Pathway is Predominant in AD

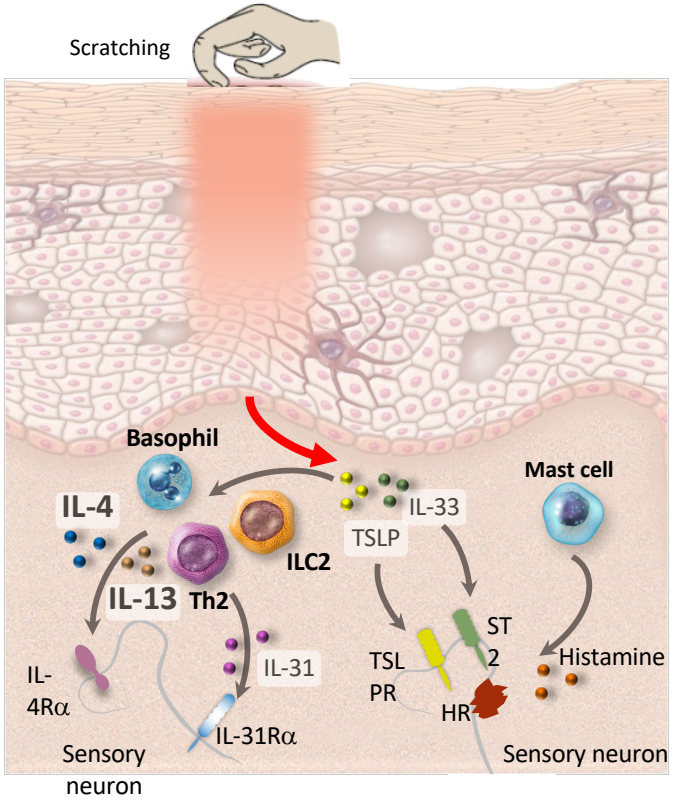


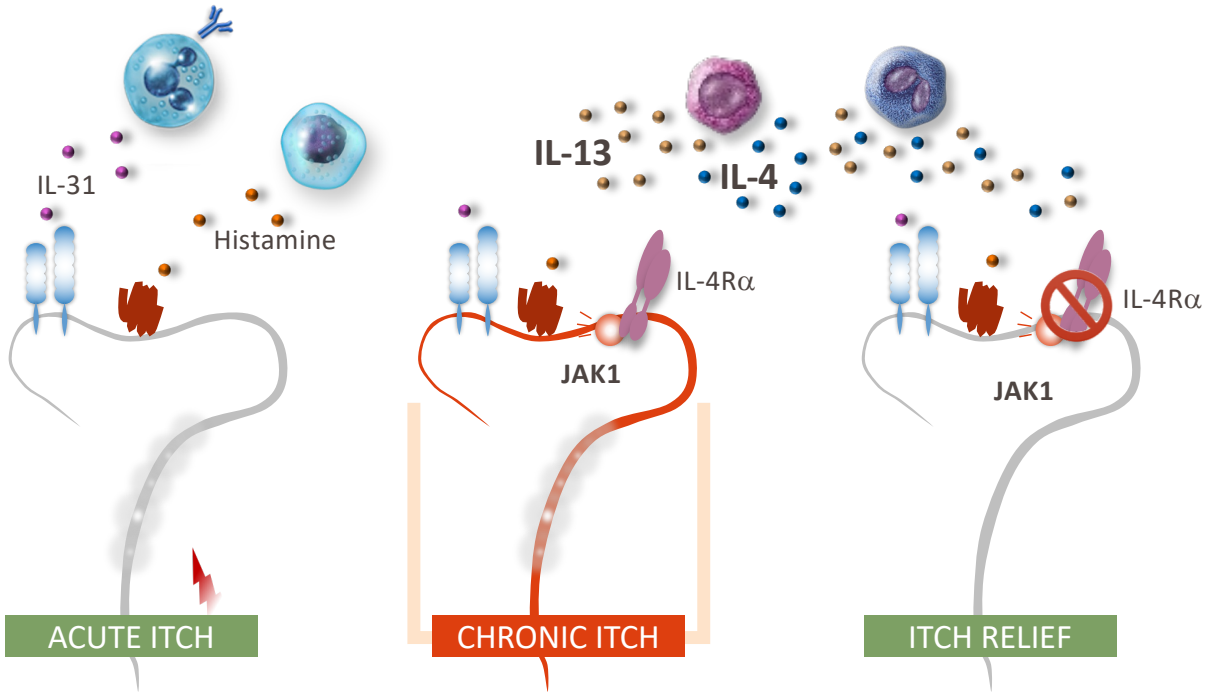
- In acute lesions there is continued activation of type 2 inflammatory pathways with intensification in chronic stages of disease, leading to further barrier defects[1,2]
- There is also some activation of Th22, Th17 and Th1 cells[1,2]

NL, non-lesional.

1. Noda S, et al. J Allergy Clin Immunol. 2015;135:324-336. 2. Weidinger S, et al. Nat Rev Dis Primers. 2018;4(1):1.

Type 2 Cytokines Mediate Chronic Itch in AD[1]





Adapted from Oetjen 2017.[1]

- Type 2 cytokines directly activate both mouse and human sensory neurons[1]
- Sensory neuron-specific deletion of IL-4Rα or JAK1 reduces chronic itch[1]

HR, histamine receptor; JAK, Janus kinase; ST2, suppressor of tumorigenicity.

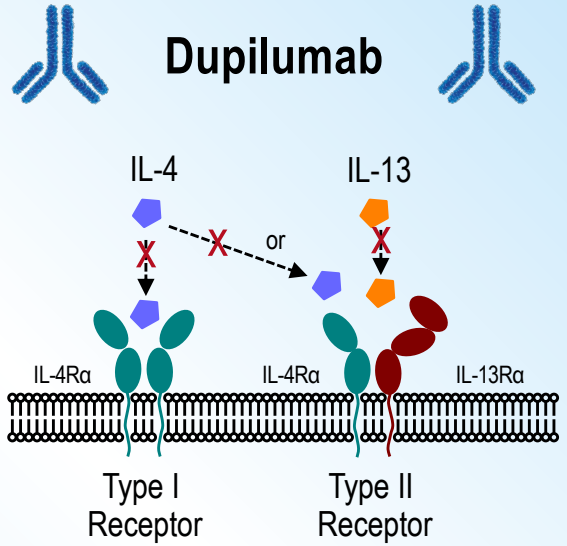
1. Oetjen KL, et al. *Cell*. 2017;171(1):217-228.e13.

Adapted from Trier AM, et al. Curr Opin Immunol. 2018;54:7-12.

Immunopathology of AD and role of dupilumab

Role of dupilumab

- Human monoclonal IgG4 antibody
- Targets IL-4Rα subunit of IL-4 and IL-13 receptors
- Blocks both IL-4 and IL-13 dependent signalling pathways

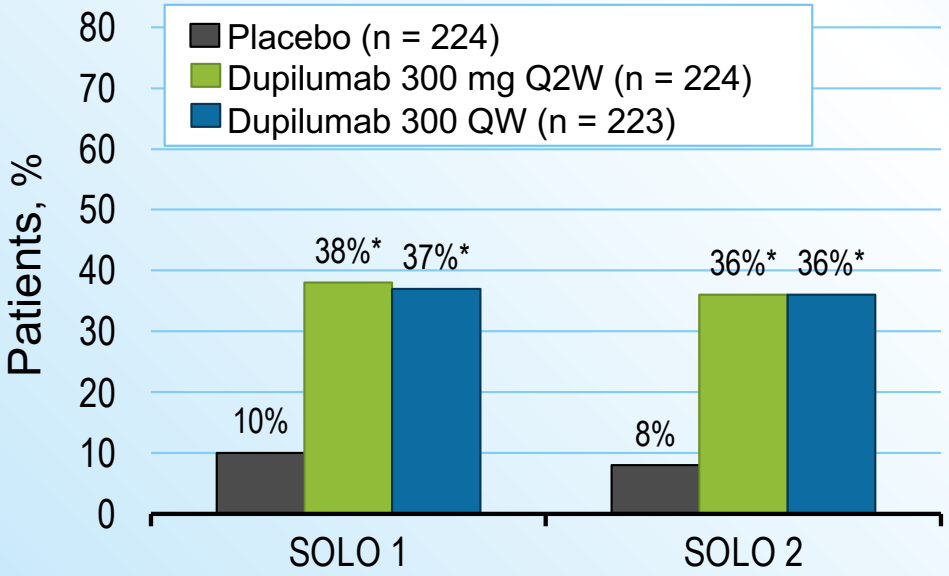


Dupilumab inhibits IL-4 signalling via the Type I receptor and both IL-4 and IL-13 signalling via the Type II receptor

SOLO 1 & 2: Primary and key secondary endpoint met

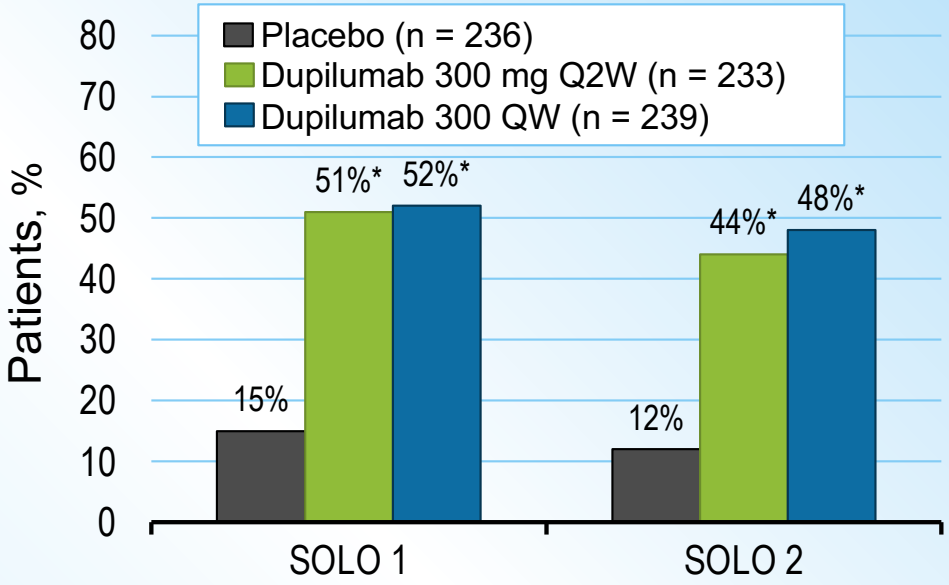
Primary Endpoint

IGA 0,1 (clear/almost clear) and ≥2-point improvement from baseline at Week 16



Key Secondary Endpoint

EASI-75 at Week 16

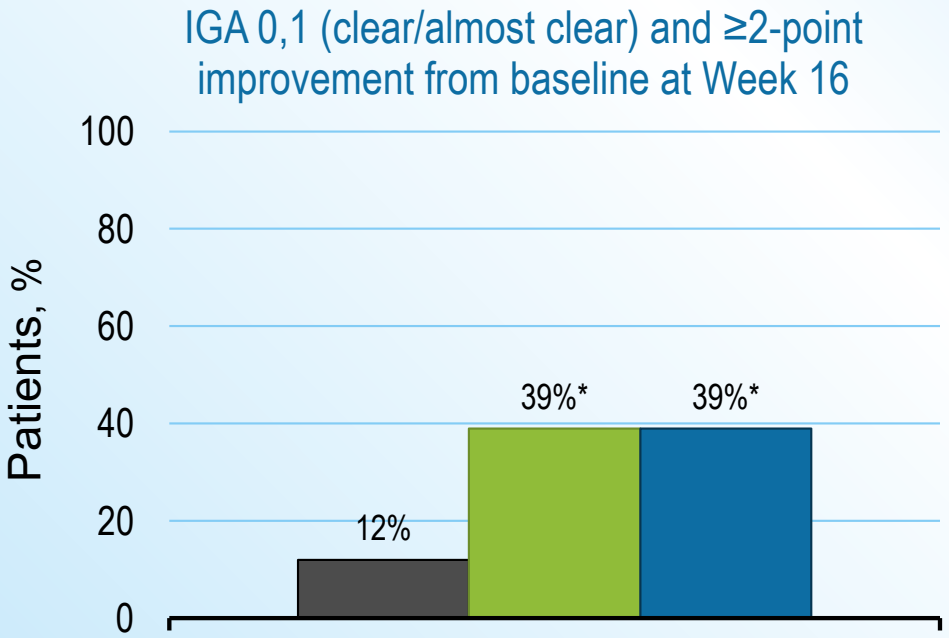


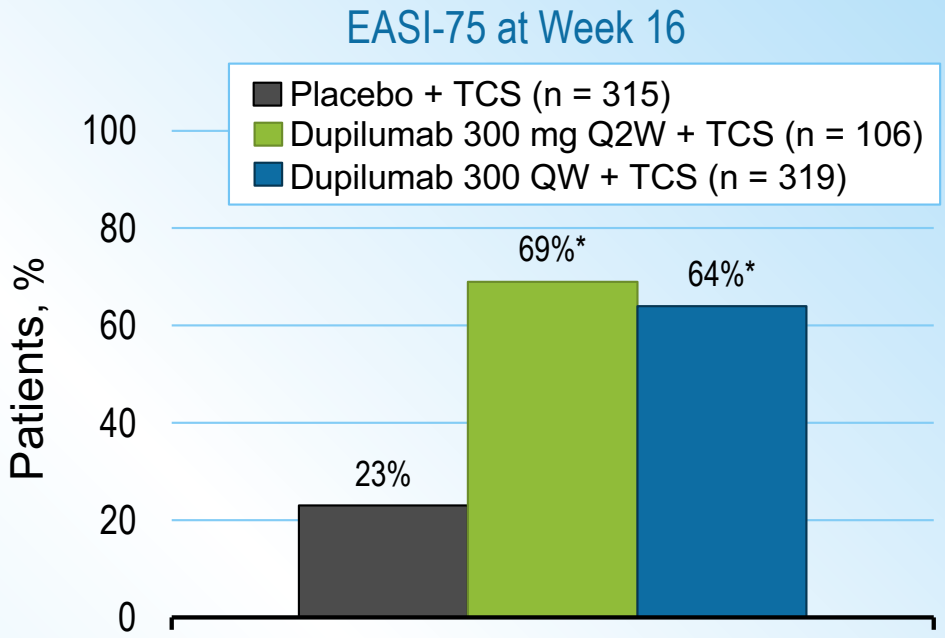
*P < 0.001 vs placebo.

EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment; QW: weekly; Q2W: every 2 weeks.

Simpson EL, et al. *N Engl J Med* 2016;375:2335–2348.

CHRONOS: Co-primary endpoint met at 16 weeks

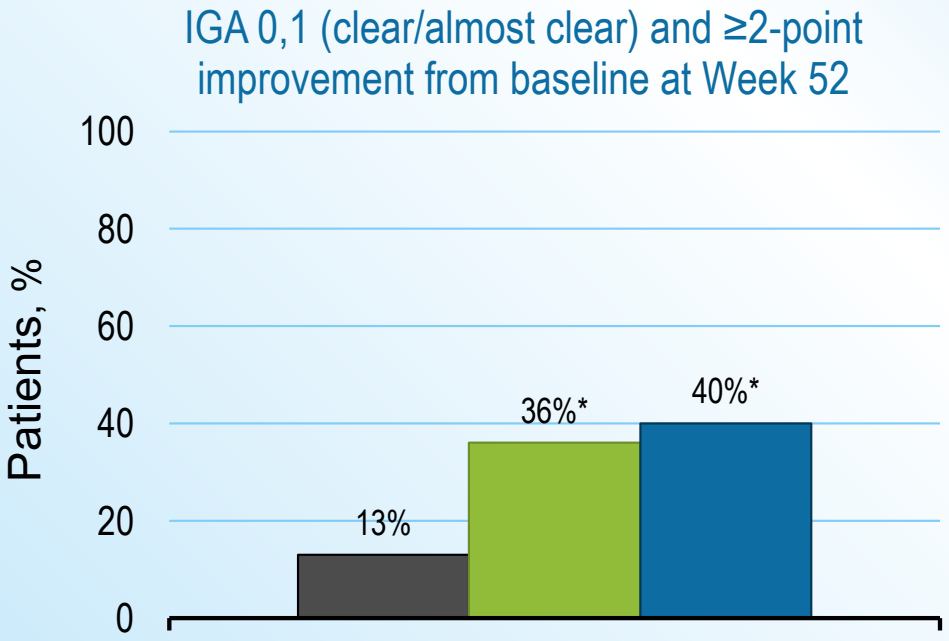


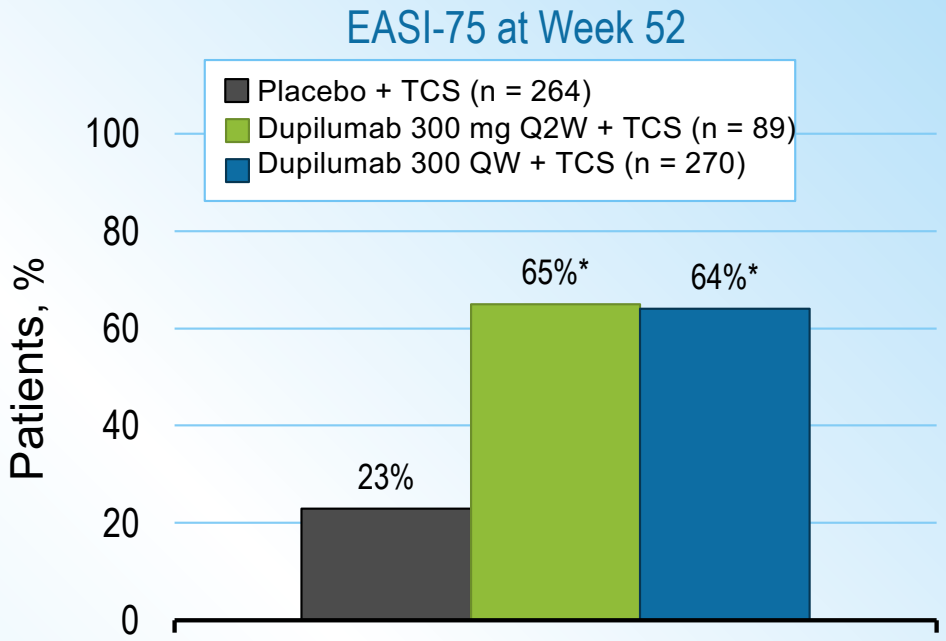


*P < 0.0001 vs placebo.
EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment; QW: weekly; Q2W: every 2 weeks; TCS: topical corticosteroid.

Blauvelt A, et al. *Lancet* 2017;389:2287-2303.

CHRONOS: Significant, sustained improvements in IGA and EASI-75 at Week 52

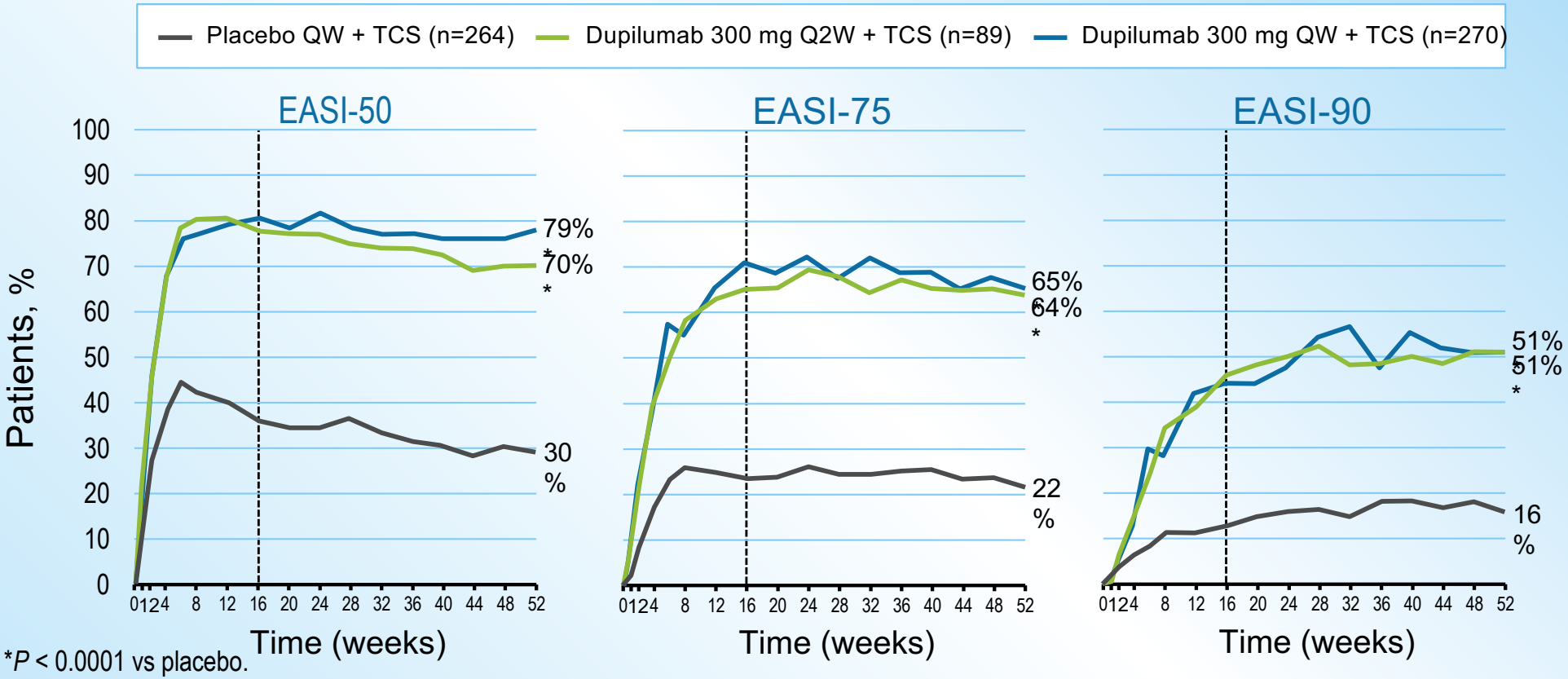




*P < 0.0001 vs placebo.
EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment; QW: weekly; Q2W: every 2 weeks; TCS: topical corticosteroid.

Blauvelt A, et al. *Lancet* 2017;389:2287-2303.

CHRONOS: Sustained improvements in EASI-50/75/90 responses at Week 52

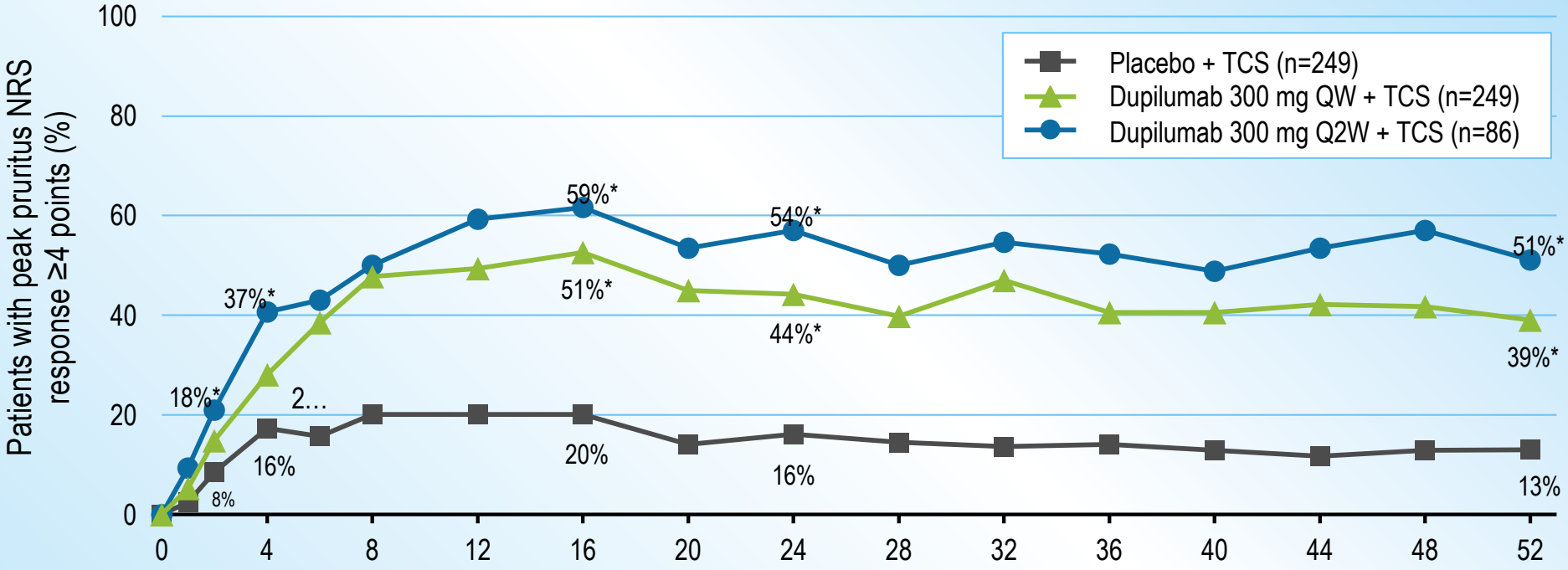


*P < 0.0001 vs placebo.

EASI: Eczema Area and Severity Index; QW: weekly; Q2W: every 2 weeks; TCS: topical corticosteroid.

Blauvelt A, et al. *Lancet* 2017;389:2287-2303.

CHRONOS: Rapid, sustained improvements in pruritus



*$P < 0.0001$ vs placebo.
NRS: numeric rating scale; QW: weekly; Q2W: every 2 weeks; TCS: topical corticosteroid.

Blauvelt A, et al. *Lancet* 2017;389:2287-2303.

CHRONOS: Adverse events

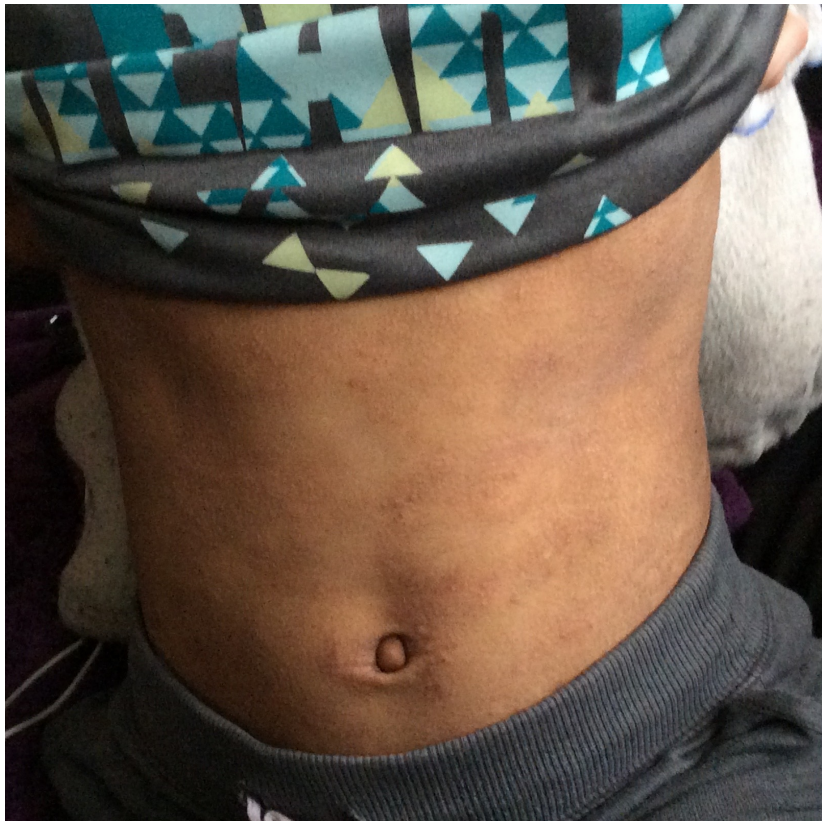
% (n)	Placebo + TCS (n = 315)	Dupilumab 300 mg Q2W + TCS (n = 110)	Dupilumab 300 mg QW + TCS (n = 315)
Total AEs	1493	478	1482
Total SAEs	22	5	10
≥1 AE	83 (266)	88 (97)	83 (261)
Death*	0	0	<1 (1)
≥1 SAE	5 (16)	4 (4)	3 (9)
AE leading to treatment discontinuation	8 (24)	2 (2)	3 (9)
Infections and infestations Nasopharyngitis Upper respiratory tracts infection Sinusitis Influenza	58 (182) 19 (61) 10 (32) 3 (9) 5 (17)	57 (63) 23 (25) 10 (11) 2 (2) 4 (4)	53 (166) 19 (60) 14 (43) 6 (18) 3 (9)
Eye disorders Conjunctivitis	15 (46) 8 (25)	31 (34) 14 (15)	32 (102) 19 (61)

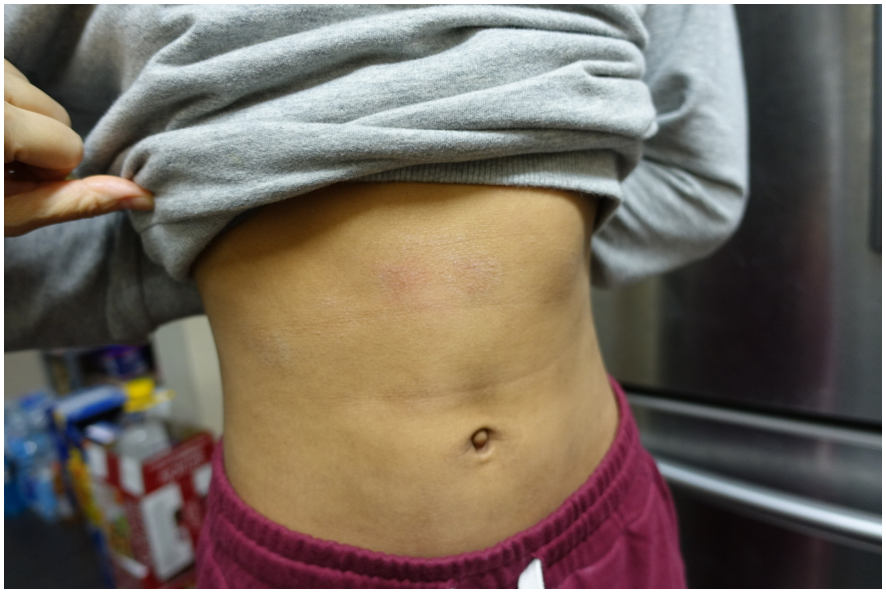
*Motor vehicle accident.

AE: adverse event; QW: weekly; Q2W: every 2 weeks; SAE: severe adverse event; TCS: topical corticosteroids.

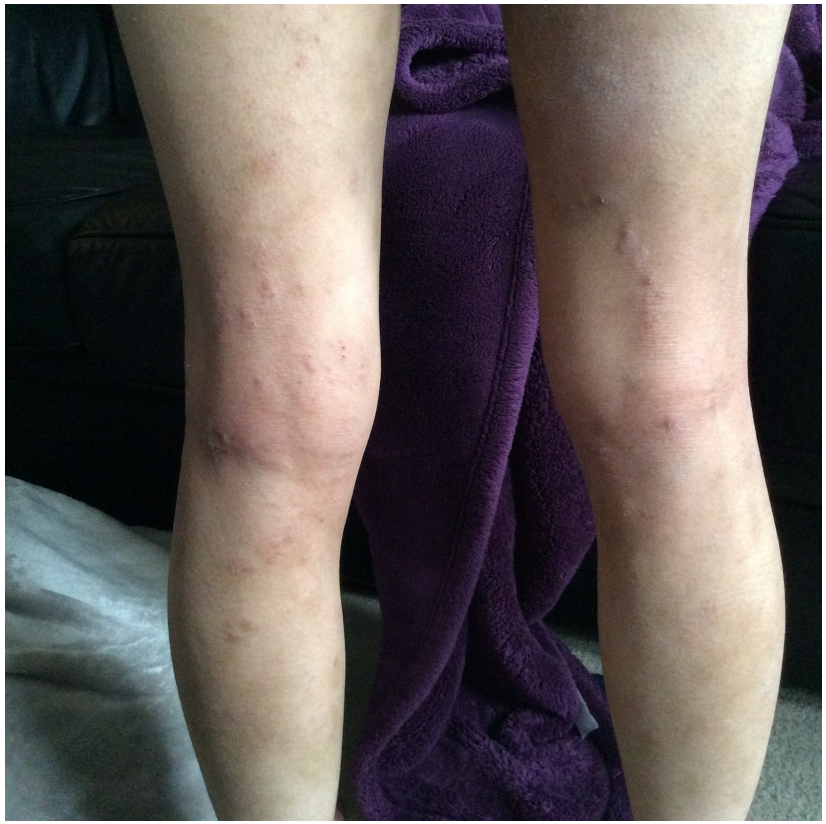
Blauvelt A, et al. *Lancet* 2017;389:2287-2303.

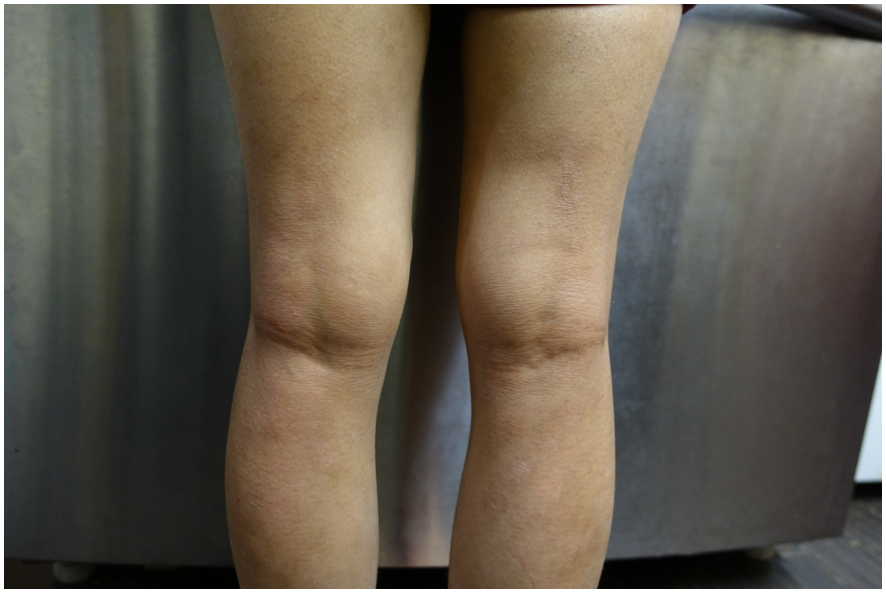
12 yr old treated with Dupilumab 2020



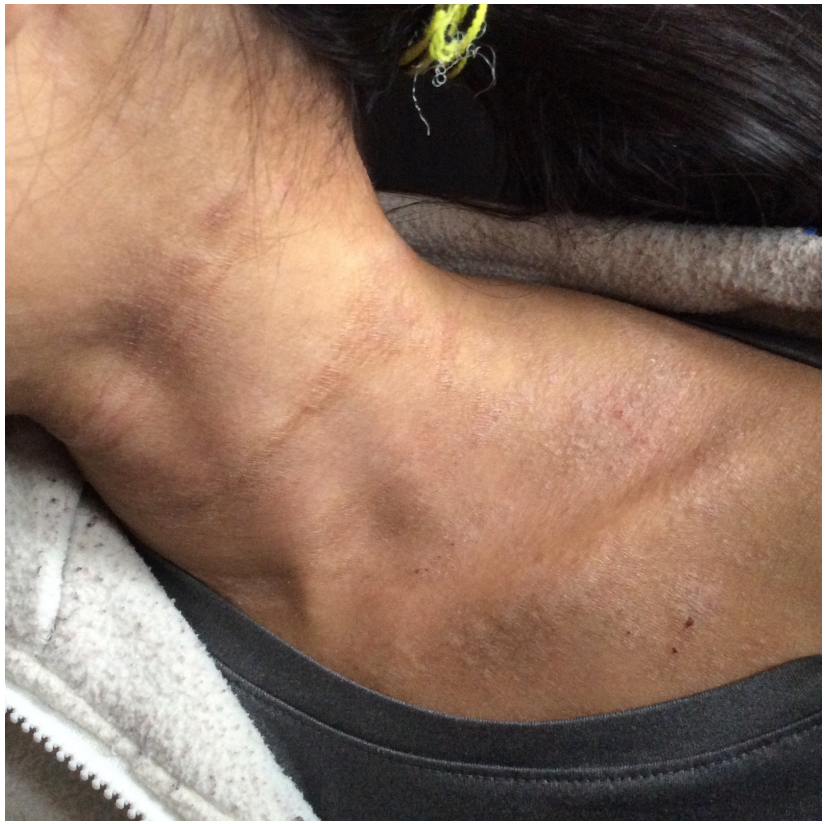


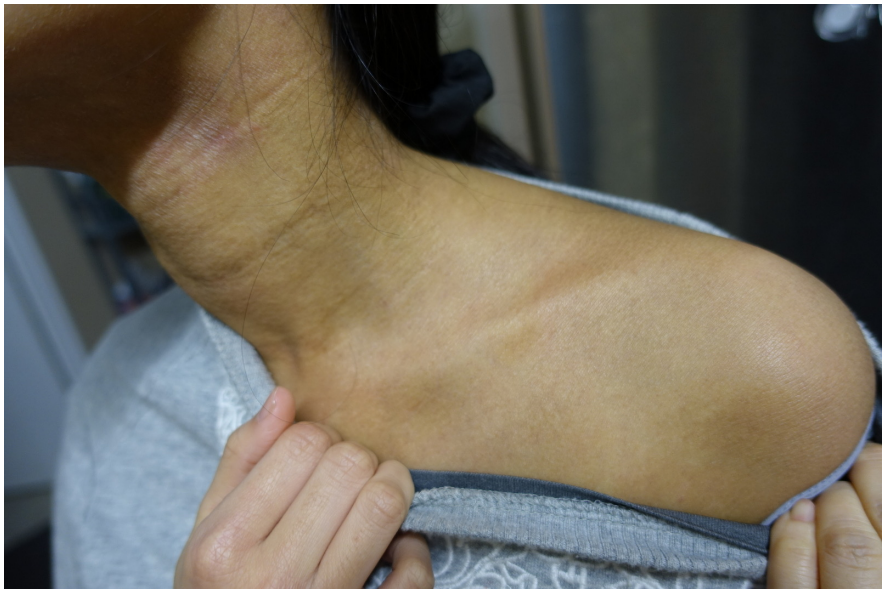
12 yr old treated with Dupilumab 2020



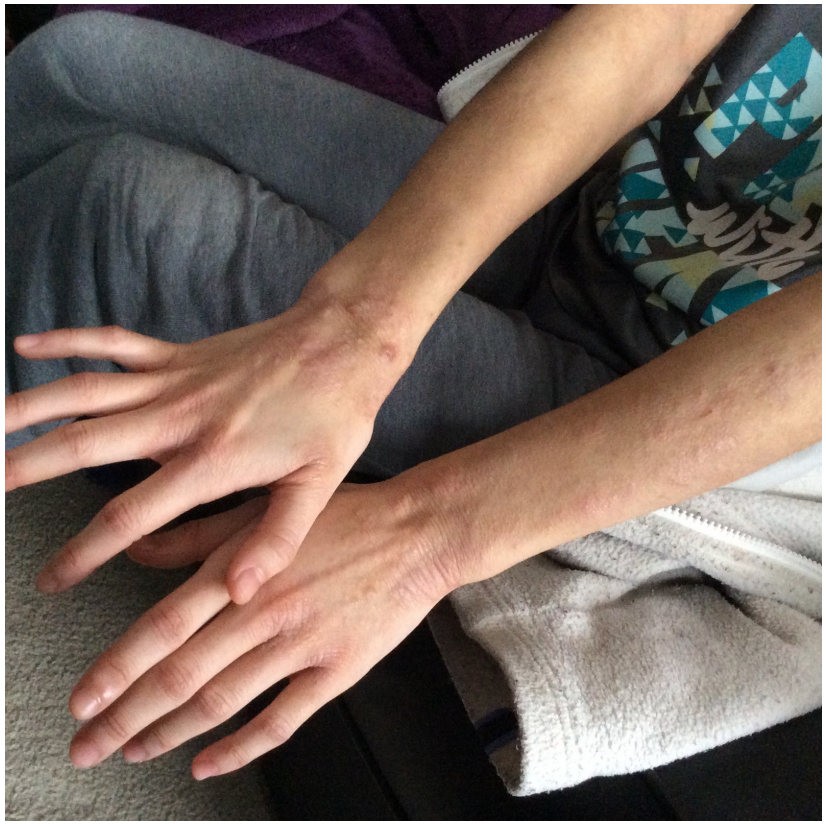


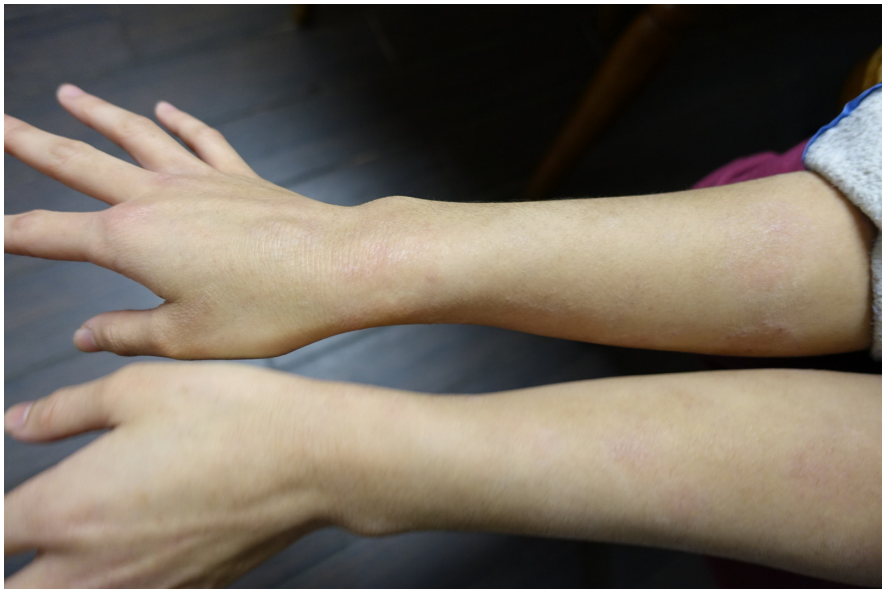
12 yr old treated with Dupilumab 2020





12 yr old treated with Dupilumab 2020





Tralokinumab

Tralokinumab inhibits IL-13 from binding to the type II receptor

- The IL-13Rα1 subunit binds to IL-13 with moderate affinity
- Tralokinumab binds to IL-13 with 1000-fold greater affinity than IL-13Rα1 binds to IL-13
- Thus, it is likely that tralokinumab prevents IL-13 from interacting with the IL-13Rα1 subunit thus inhibiting subsequent downstream signalling

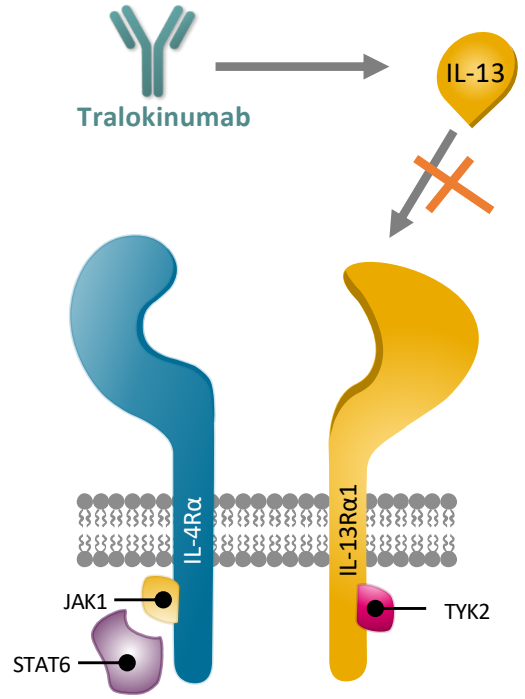


Figure adapted from Bieber T. *Allergy.* 2020;75:54–62

Thanks!

Any questions?

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