STARTING DUPILUMAB AND TOUGH CASES

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LEARNING OBJECTIVES

- Understand the basic science of Atopic Dermatitis and how Dupilumab works
- Identify if Dupilumab is the right treatment choice for the patient, potential adverse events, and monitoring
- Review of tough cases

ATOPIC DERMATITIS

- Atopic dermatitis (AD) is the most common chronic inflammatory skin disease.
- Affects more than 9.6 million children and about 16.5 million adults in the United States.
- Typically begins in childhood, usually in the first six months of life
- Can exist with other allergic conditions: asthma and hay fever (allergic rhinitis).
- Itching is the hallmark of AD, with some data showing that more than 85% of people with the condition experience this distressing symptom every day.
- Characterized dry skin, weeping erythematous papules and plaques, and lichenification.

https://nationaleczema.org/eczema/types-of-eczema/atopic-dermatitis/

QUALITY OF LIFE

- The harmful effects of AD can include emotional and mental health, physical activity, social functioning, sleep disturbance, decreased work productivity, financial expenditure, leisure activities, and family relationships.
- Given that AD is a chronic disease that requires constant care, parents/guardians or the partner of the patient usually are affected as well.

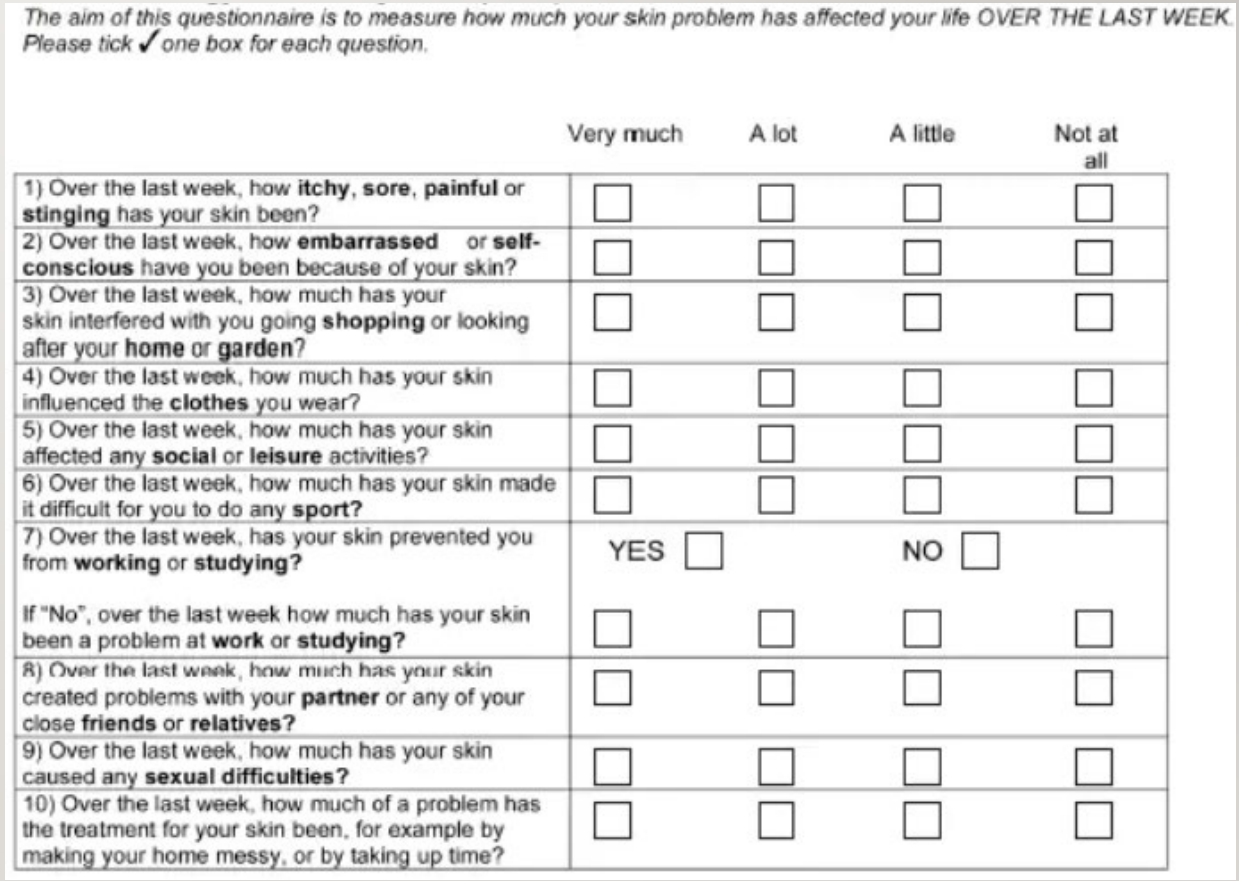
Frequently Used QOL Instruments for AD

Instrument	QOL Target	Specificity	Description[a]
Dermatitis Family Impact (DFI) questionnaire	Family QOL instrument	AD specific	10 items; score range, 0–30
Family Dermatology Life Quality Index (FDLQI)	Family QOL instrument	Dermatology specific	10 items; score range, 0–30
Infants' Dermatitis Quality of Life Index (IDQOL)	Children <4 y (proxy rating)	AD specific	10 items; score range, 0–30
Children's Dermatology Life Quality Index (CDLQI)	Children 4–16 y (self-completed)	Dermatology specific	10 items; score range, 0–30
Dermatology Life Quality Index (DLQI)	Adults	Dermatology specific	10 items; score range, 0–30
Quality of Life Index for Atopic Dermatitis (QoLIAD)	Adults	AD specific	25 items; score range, 0–25

Abbreviations: QOL, quality of life; AD, atopic dermatitis.
[a]The higher the score, the more QOL is impaired.

Quality of Life in Patients With Atopic Dermatitis *Cutis*. 2019 September;104(03):174-177

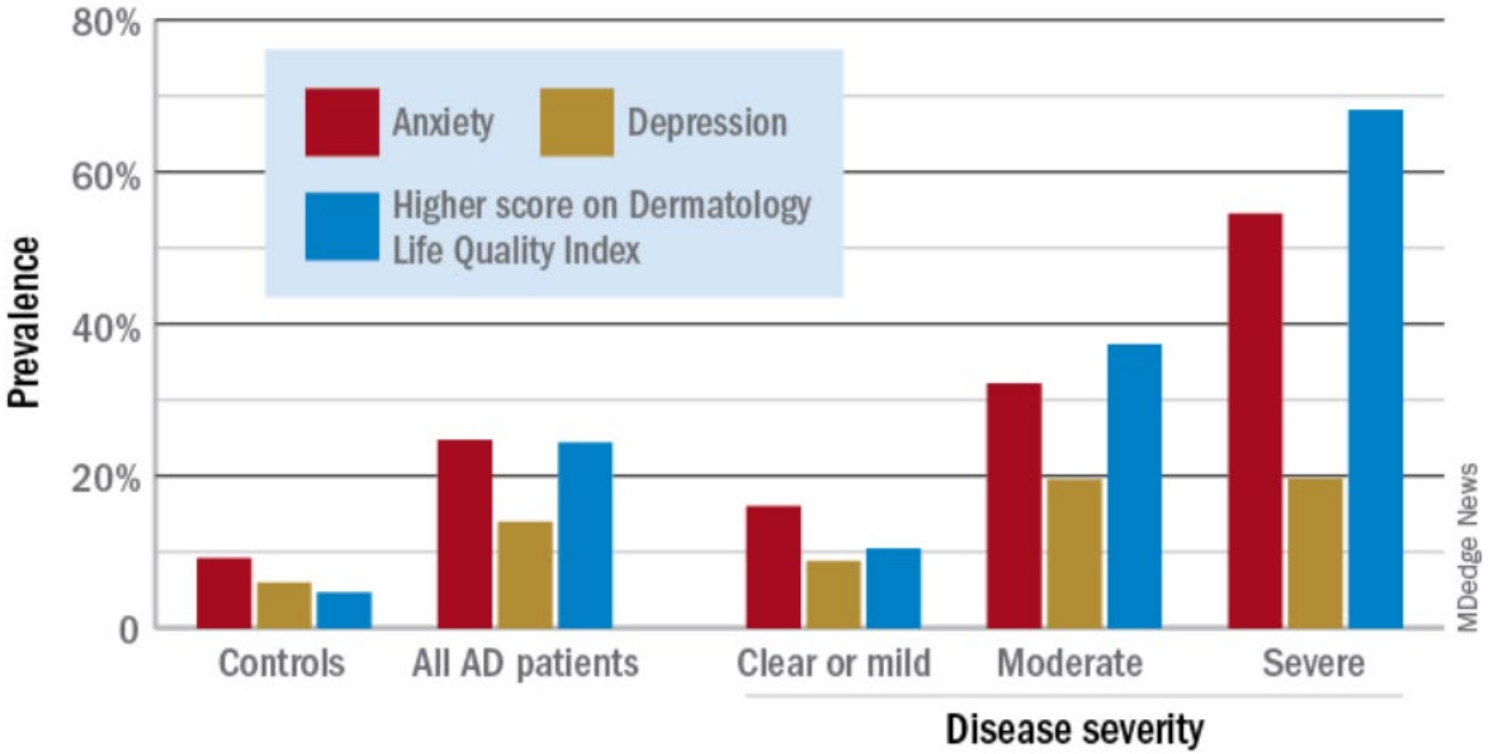
DERMATOLOGY LIFE QUALITY INDEX (DLQI)



The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK.
Please tick ✓ one box for each question.

	Very much	A lot	A little	Not at all
1) Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	☐	☐	☐	☐
2) Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	☐	☐	☐	☐
3) Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	☐	☐	☐	☐
4) Over the last week, how much has your skin influenced the **clothes** you wear?	☐	☐	☐	☐
5) Over the last week, how much has your skin affected any **social** or **leisure** activities?	☐	☐	☐	☐
6) Over the last week, how much has your skin made it difficult for you to do any **sport?**	☐	☐	☐	☐
7) Over the last week, has your skin prevented you from **working** or **studying?**	YES ☐		NO ☐	
If "No", over the last week how much has your skin been a problem at **work** or **studying?**	☐	☐	☐	☐
8) Over the last week, how much has your skin created problems with your **partner** or any of your close **friends** or **relatives?**	☐	☐	☐	☐
9) Over the last week, how much has your skin caused any **sexual difficulties?**	☐	☐	☐	☐
10) Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	☐	☐	☐	☐

Disease burden in patients with atopic dermatitis



Note: Two-stage sampling process of survey data involved a group of 1,278 adults to determine prevalence and an oversample of 602 AD patients to assess severity differences.

Source: J Invest Dermatol. 2018. doi: 10.1016/j.jid.2018.08.028

PATHOPHYSIOLOGY

- Although the pathophysiology of AD is not completely understood, numerous studies demonstrate that skin barrier dysfunction and immune dysregulation play an important role.
- The epidermis plays a crucial role as a physical and functional barrier, and skin barrier defects are the most significant pathologic findings in AD skin.
- Filaggrin (FLG) and other key proteins are responsible for epidermal function. Defects in these proteins facilitate allergen and microbial penetration into the skin.

Allergy Asthma Proc. 2019 Mar; 40(2): 84–92

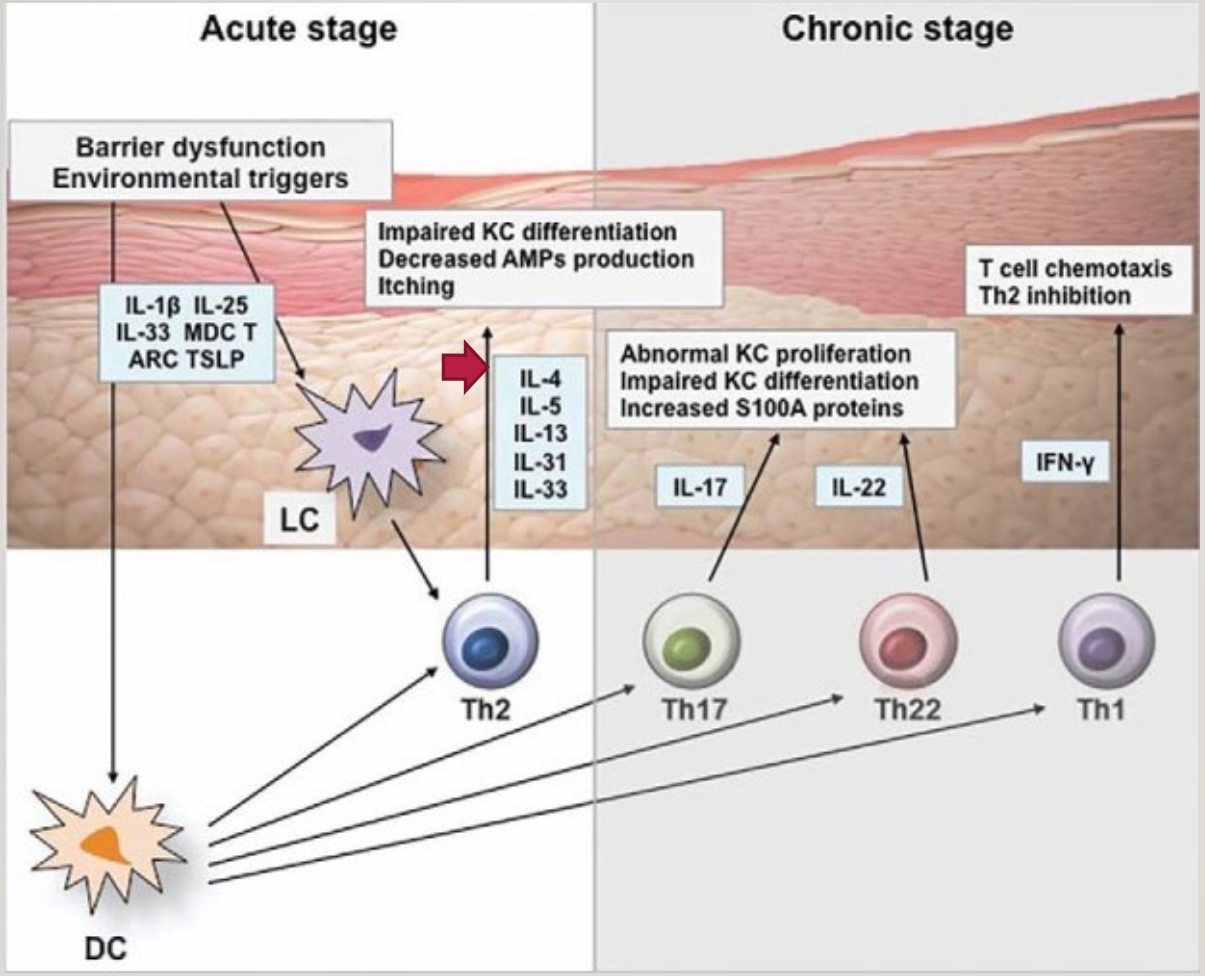
PATHOPHYSIOLOGY

- Disrupted epidermal barrier and environmental triggers stimulate keratinocytes to release certain inflammatory cytokines, which activate dendritic cells and Langerhans cells.
- Activated dendritic cells stimulate Th2 cells to produce IL-4, IL-5, IL-13, IL-31, and IL-33, which leads to barrier dysfunction, decreased AMP production, impaired keratinocyte differentiation, and itch symptoms.
- The IL-4, IL-13 and IL-31 inflammatory pathways have been identified as hallmark features in the pathogenesis of this disease.
- Chronic AD is characterized by recruitment of Th1, Th22, and Th17 subsets, which results in epidermal thickening and abnormal keratinocyte proliferation.

AMP = antimicrobial peptide; IL = interleukin; Th = T-helper type

Allergy Asthma Proc. 2019 Mar; 40(2): 84–92

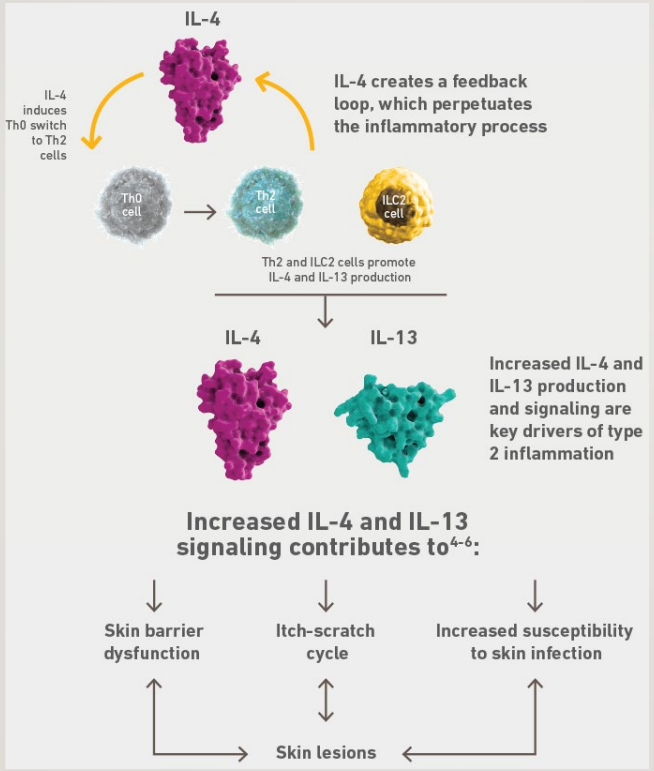
PATHOPHYSIOLOGY



depicts where IL-4 and IL-13 are located in the inflammatory cascade

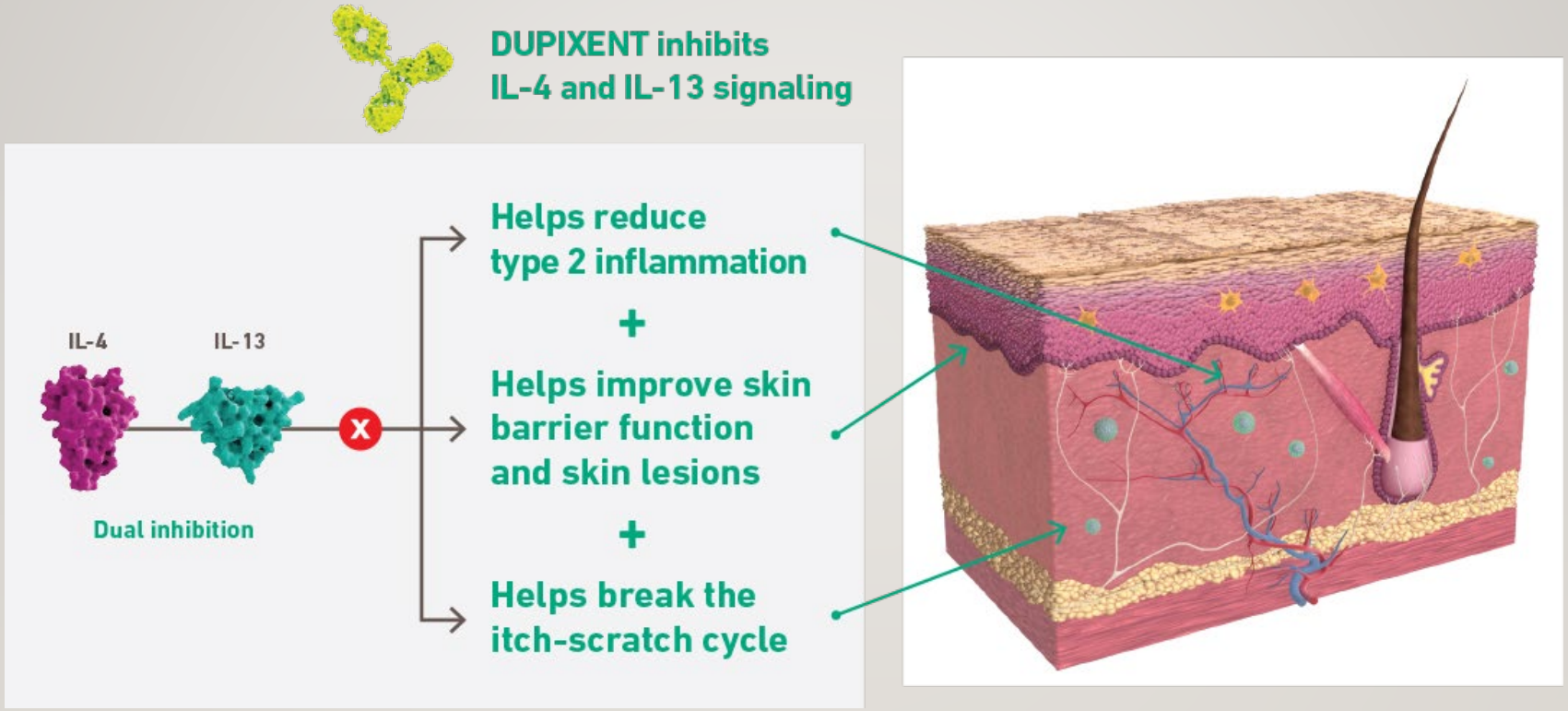
Allergy Asthma Proc. 2019 Mar; 40(2): 84–92

PATHOPHYSIOLOGY



https://www.dupixenthcp.com/atopicdermatitis/about/mechanism-of-action

PATHOPHYSIOLOGY



https://www.dupixenthcp.com/atopicdermatitis/about/mechanism-of-action

DIPILUMAB

- Fully human monoclonal antibody that inhibits signaling of interleukin (IL)-4 and IL-13.
- FDA approved as a treatment for moderate-to-severe atopic dermatitis in adults in March 2017, in patients aged 12–17 in March 2019, and in children ages 6–11 in May 2020.
  - Approval was based on efficacy and safety results from three phase 3 studies (SOLO 1 & 2 and CHRONOS) that included more than 2,500 patients.
  - Patients presented with moderate-to-severe disease, with a median 50% Body Surface Area (BSA) affected by atopic dermatitis and median disease duration of 25 years.
  - Dupilumab improved the signs and symptoms of atopic dermatitis, including pruritus, symptoms of anxiety and depression, and quality of life, as compared with placebo.
  - Injection-site reactions and conjunctivitis were most common reported adverse events.

Key clinical-trial evidence about dupilumab
Author: Anoma Ranaweera B.V.Sc; PhD (Clinical Biochemistry, University of Liverpool, UK). Chief Editor: Dr Amanda Oakley, Dermatologist, Hamilton, New Zealand, January 2017.

DIPILUMAB

- Dosage
  - Adult (18+ yrs): Loading dose 600mg, Maintenance dose 300mg q o week.
  - Pediatric (6-17 yrs): Weight based
    - 60kg or more: Loading dose 600mg, Maintenance dose 300mg q o week.
    - 30kg to 60kg: Loading dose 400mg, Maintenance dose 200mg q o week.
    - 15kg to 30kg: Loading dose 600mg, Maintenance dose 300mg q 4 weeks.

    - Supplied in 200mg and 300mg prefilled syringe or prefilled pen
- Lab Monitoring: None per package insert (CBC, CMP in our clinic initially and once a year)
- No black box warnings
- The long-term safety profile observed in OLE trials (~3 years) was generally consistent with the safety profile observed in controlled studies.

DIPILUMAB

- A Literature Review of Real-World Effectiveness and Safety of Dupilumab for Atopic Dermatitis.
  - Dupilumab demonstrated high efficacy, high effectiveness, favorable safety, and improvement in comorbidities caused by AD.
  - Analyses of clinical trial data revealed that dupilumab brought improvement in pruritus, pain/discomfort, anxiety/depression, QOL, and usual activities of patients with AD as in the real-world evidence.
  - Conjunctivitis
    - Results of clinical trials as well as real world data, revealed that dupilumab is associated with increased incidence of conjunctivitis in patients with AD.
    - In most patients, the severity is mild to moderate with onset 2 weeks to 4 months after initiation.
    - The most common ocular symptoms were irritation (97%), redness (83%), pruritus (62%), discharge (62%).
    - Dose adjustment or discontinuation is needed in certain cases.
    - Real-world data suggests that dupilumab-associated conjunctivitis was associated with higher baseline serum levels of IgE.

A Literature Review of Real-World Effectiveness and Safety of Dupilumab for Atopic Dermatitis.
Masahiro Kamata. Yayoi Tada. Published July 29, 2021. https://www.sciencedirect.com/science/article/pii/S2667026721000436

DIPILUMAB

- A Literature Review of Real-World Effectiveness and Safety of Dupilumab for Atopic Dermatitis.
  - Positioning (with new Jak options)
    - Dupilumab demonstrated higher efficacy with a favorable safety profile for refractory patients with moderate-to-severe AD than conventional therapy.
    - Jak inhibitors inhibit the pathway of AD pathogenesis more specifically than conventional drugs, which enables higher efficacy in eruption and pruritus with tolerable safety
    - Dupilumab is more suitable for patients who have suffered from cutaneous infection, including eczema herpeticum; those suffering from depression and/or anxiety; and those with asthma than Jak inhibitors.
      - Dupilumab has evidence of reducing the risks of cutaneous infection

A Literature Review of Real-World Effectiveness and Safety of Dupilumab for Atopic Dermatitis.
Masahiro Kamata. Yayoi Tada. Published July 29, 2021. https://www.sciencedirect.com/science/article/pii/S2667026721000436

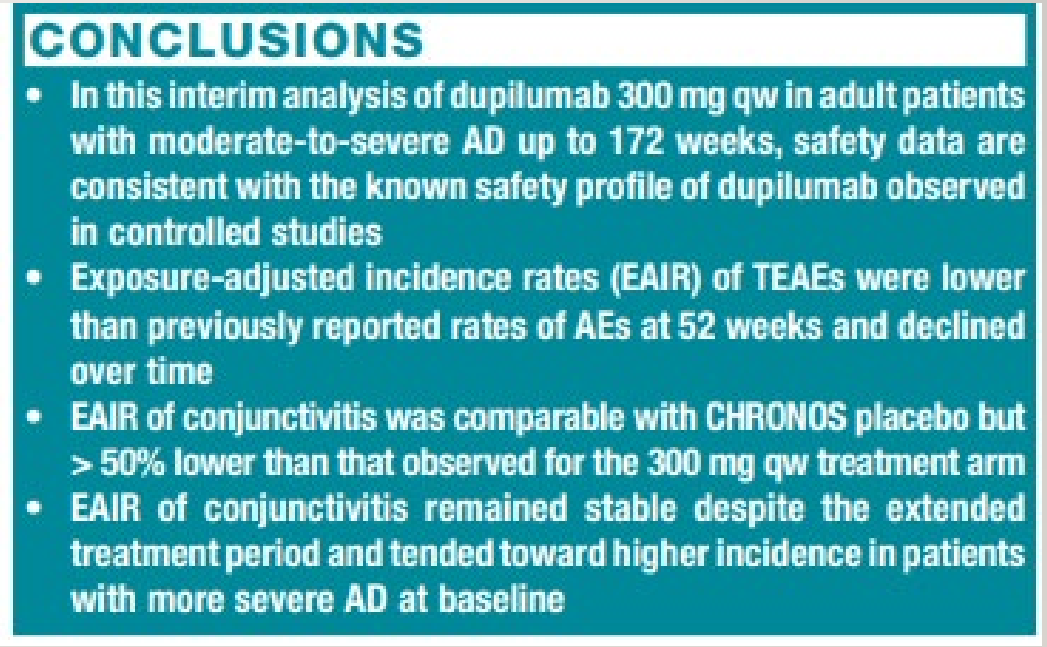
DIPILUMAB

- Safety of Long-Term Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis up to 172 Weeks: Results from an Open-Label Extension (OLE) Trial
  - Adult patients ≥ 18 years of age with moderate-to-severe AD who had previously participated in any dupilumab parent study (phase 1–3) were enrolled in this long-term, multicenter, OLE study with an initial duration of 3 years
  - This analysis examined the overall population of patients treated with 300 mg dupilumab weekly (dose not approved by FDA)
  - Concomitant treatments for AD, including topical corticosteroids (TCS) and topical calcineurin inhibitors, were permitted
  - RESULTS: Dupilumab is generally well tolerated, and Safety findings were consistent with the known dupilumab safety profile

American Academy of Allergy, Asthma and Immunology Annual Meeting. Phoenix AZ. Feb 25-28, 2022. Poster Presentation.

DIPILUMAB

- Safety of Long-Term Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis up to 172 Weeks: Results from an Open-Label Extension (OLE) Trial



American Academy of Allergy, Asthma and Immunology Annual Meeting. Phoenix AZ. Feb 25-28, 2022. Poster Presentation.

DIPILUMAB

- Dupilumab Treatment Significantly Improves Skin Barrier Structure and Function in Adult and Adolescent Patients With Moderate-to-Severe Atopic Dermatitis
  - The dupilumab skin BArrier function and LIpidomics STudy in Atopic Dermatitis (BALISTAD) study was an open-label, exploratory study on skin barrier function
  - Trans-epidermal Water Loss (TEWL) was repeatedly assessed in conjunction with skin tape stripping (STS) from lesional and non-lesional skin of 26 AD patients treated with dupilumab and from normal skin of 26 healthy volunteers over 16 weeks

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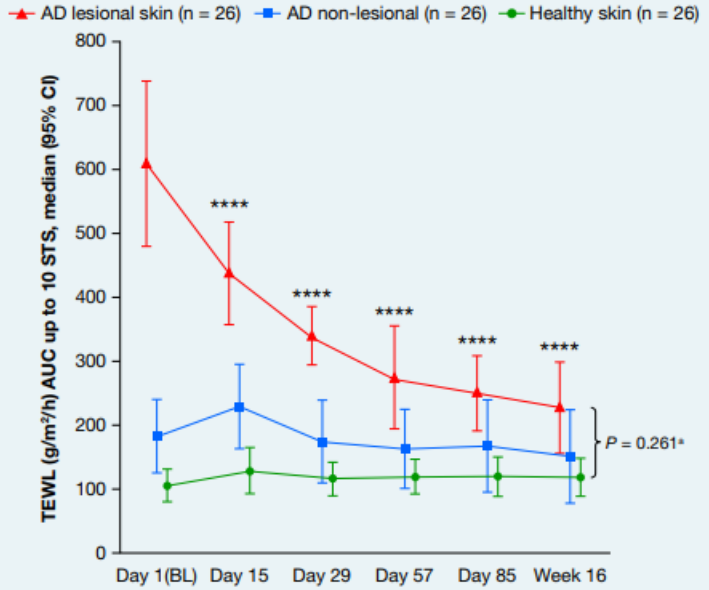
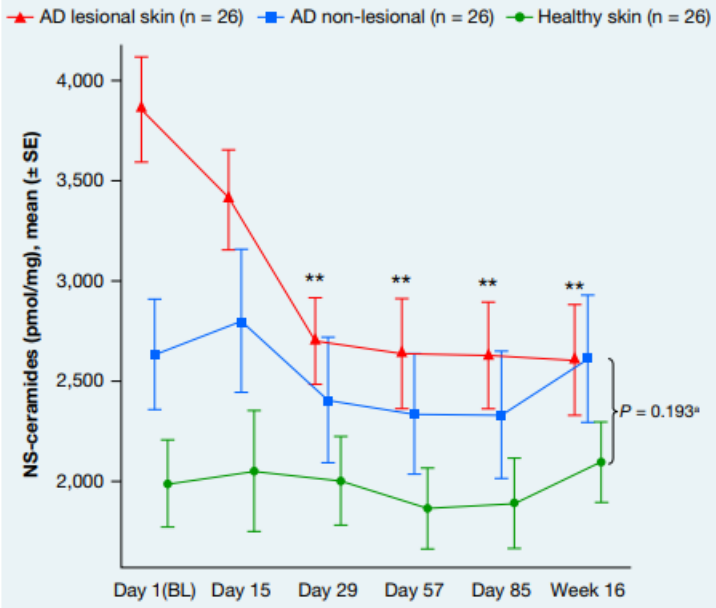
RESULTS

Figure 1. Improvement in median (95% CI) TEWL AUC after 10 STS over time.



[a]At Week 16, the adjusted mean (95% CI) TEWL AUC in AD lesional skin was not significantly different from that of healthy volunteers (ANCOVA; $P = 0.261$). ****$P < 0.0001$ vs baseline. At baseline, the median TEWL AUC in AD lesional skin was significantly different from that of healthy volunteers ($P < 0.0001$). BL, baseline; CI, confidence interval.

Figure 2. Total NS-ceramides over time.



[a]At Week 16, the mean NS-ceramides levels in AD lesional skin were not significantly different from that of healthy volunteers ($P = 0.193$). **$P < 0.01$ vs baseline. At baseline, there was a significant difference in NS-ceramides between lesional and healthy skin ($P < 0.0001$). NS, non-hydroxy fatty acid sphingosine.

CONCLUSION

- **Dupilumab treatment significantly improved the epidermal barrier and normalized skin barrier function in patients with moderate-to-severe AD as assessed by TEWL, lipid composition, and FLG breakdown products**

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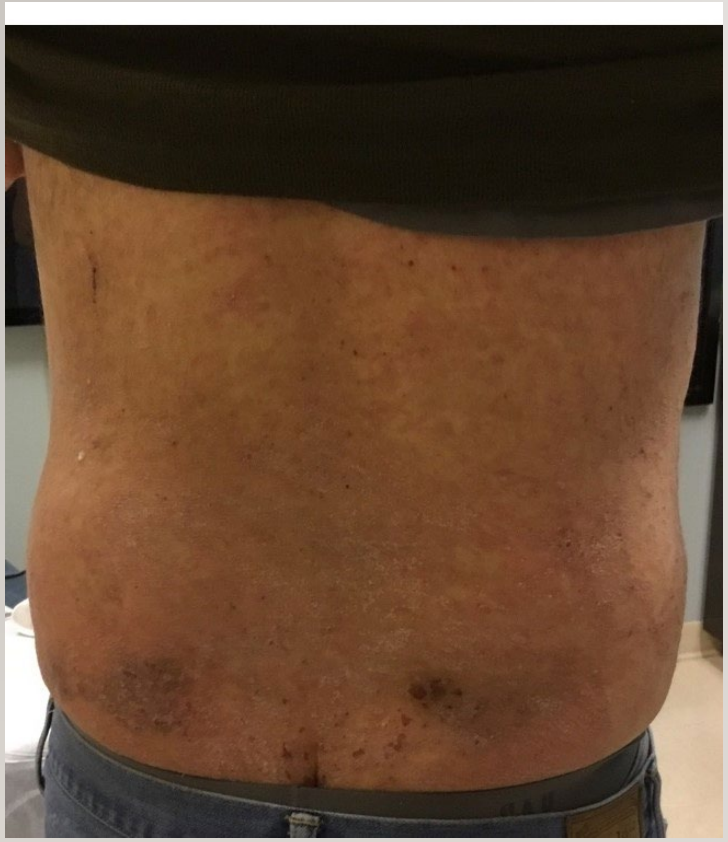
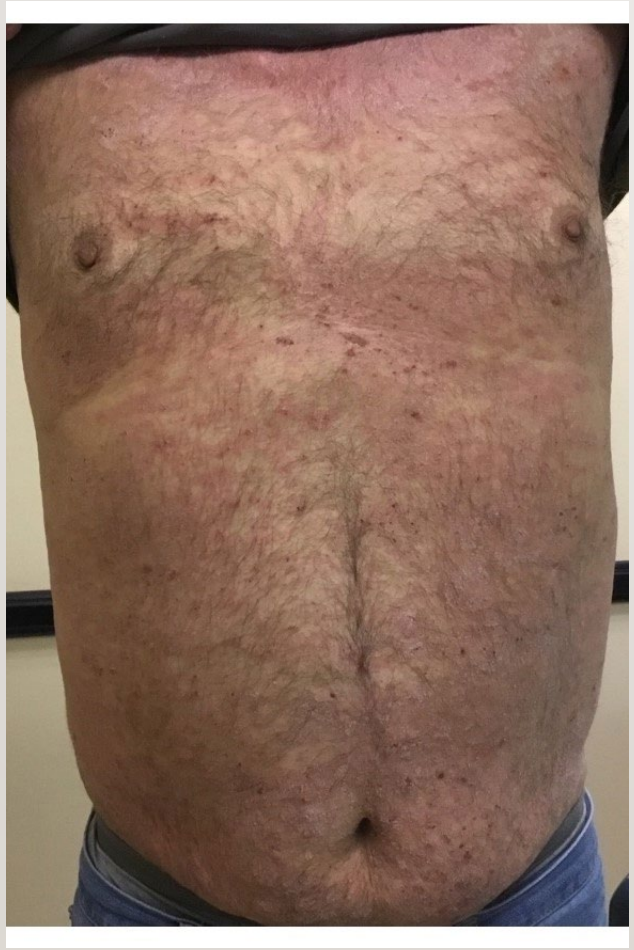
CASE STUDY #1

- 51 yo male presents with "rash" x 1 year.
  - Only treatment – clobetasol on and off x 3 months. OTC moisturizers
  - No previous history of skin rashes as an adult or child
  - Patient has history of Asthma x 3 years – Advair Inhaler
  - Nonsmoker, no ETOH
  - Meds –Simvastatin for high lipids, Zolpidem for anxiety
  - Otherwise healthy. Last physical 6 months ago – labs WNL
  - Main concerns rash worsening and "constant itching and scratching"





- Exam – Erythematous, scaling excoriated patches of trunk and limbs. BSA-80
- Few patches with honey colored crusting

- DX: Atopic Dermatitis with secondary Impetigo

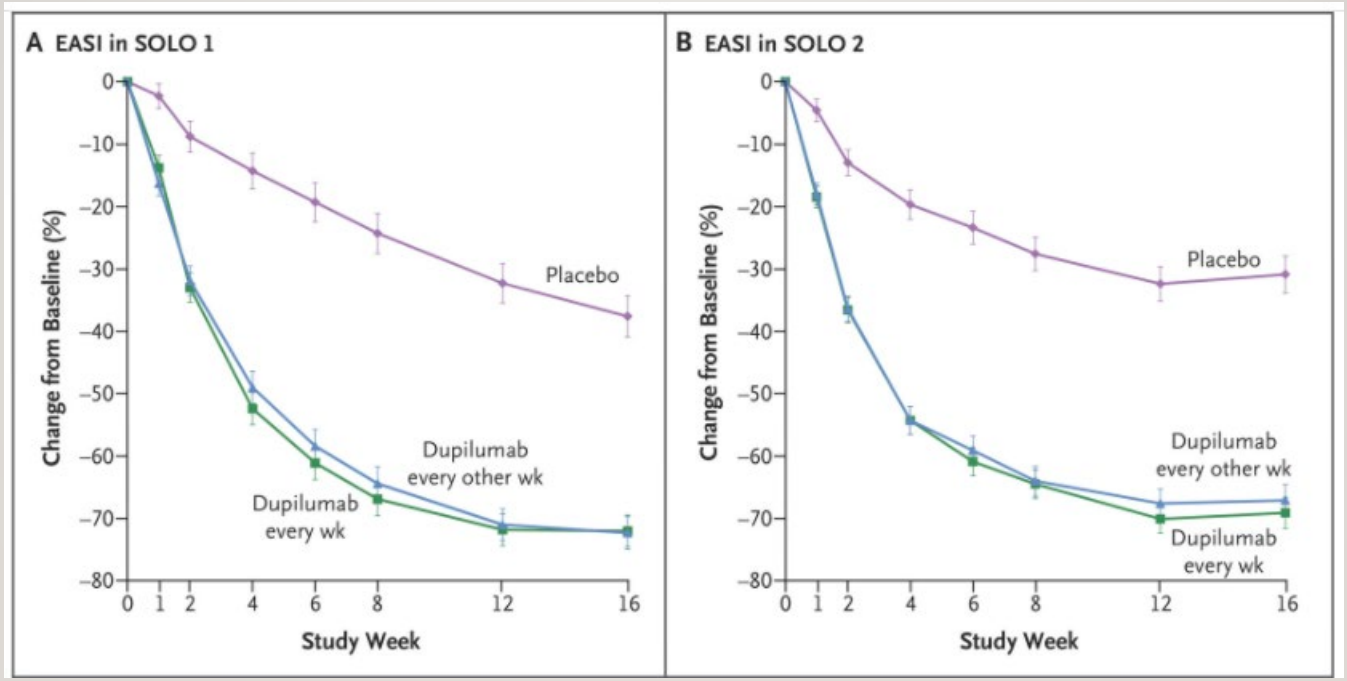
Photos from K. Kucera PAC
With permission from patient.

CASE STUDY #1

- Decision Points
  - QOL severely affected – need rapid onset of action and obtain clear or almost clear skin
  - Skin infection – antibiotic
  - Large body surface area and chronic disease – Systemic therapy – avoid flares
  - Severe itching/scratching – break cycle
- Treatment Plan
  - Augmentin 875mg BID x 14 days
  - Prednisone taper for quick relief – 60mg x 3 days, 40mg x 3 days, 20mg x 3 days
  - Allegra 180mg qam, Hydroxyzine 25mg 1-2 qhs
  - Begin Dupilumab, Obtain copy of labs from PCP
  - Discontinue Clobetasol, Start Triamcinolone cream very sparingly only prn, Moisturizer
  - Patient Education !!

In the SOLO 1 and SOLO 2 trials, an improvement of at least 75% on the EASI (EASI-75) at week 16 was reported in significantly more patients receiving each regimen of dupilumab than among those receiving placebo

Monotherapy



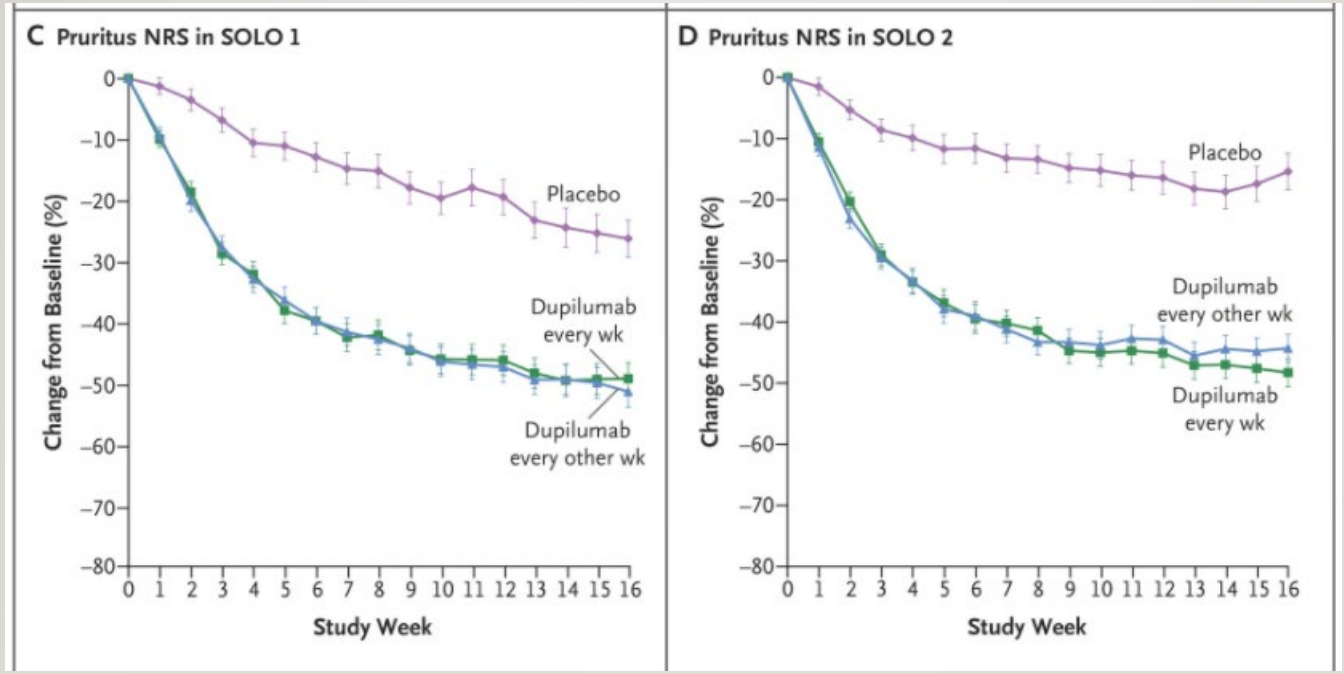
Mean percent change in the EASI score from baseline to week 16

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. Eric L. Simpson, Thomas Bieber, Emma Guttman-Yassky, et al. The New England Journal of Medicine. Dec 15, 2016

In SOLO 1 and SOLO 2 trials, an improvement of at least 3 points or 4 points in the peak score on the pruritus numerical rating scale occurred at week 16 in significantly more patients receiving dupilumab than in those receiving placebo

By week 2, patient-reported scores with respect to itching were significantly better among patients receiving dupilumab than among those receiving placebo

Monotherapy

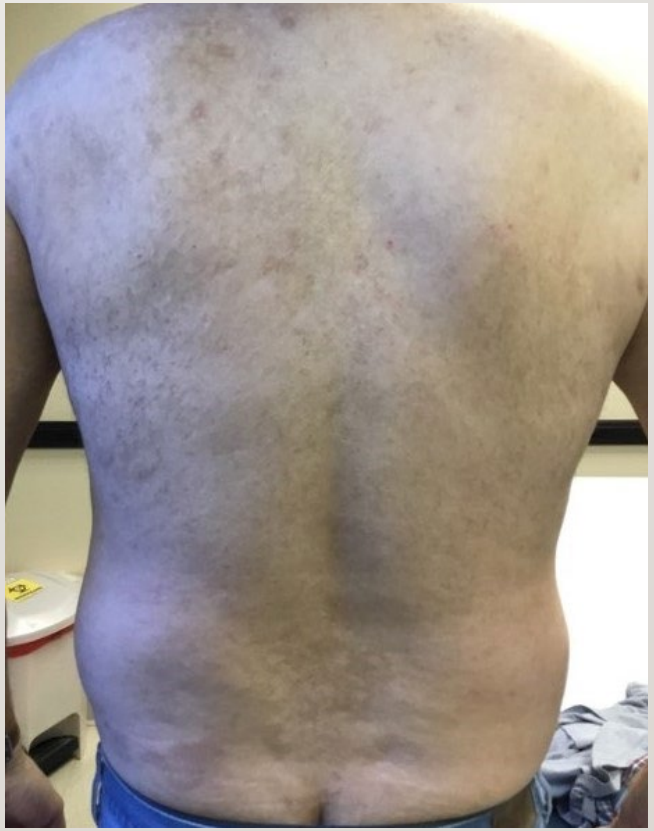


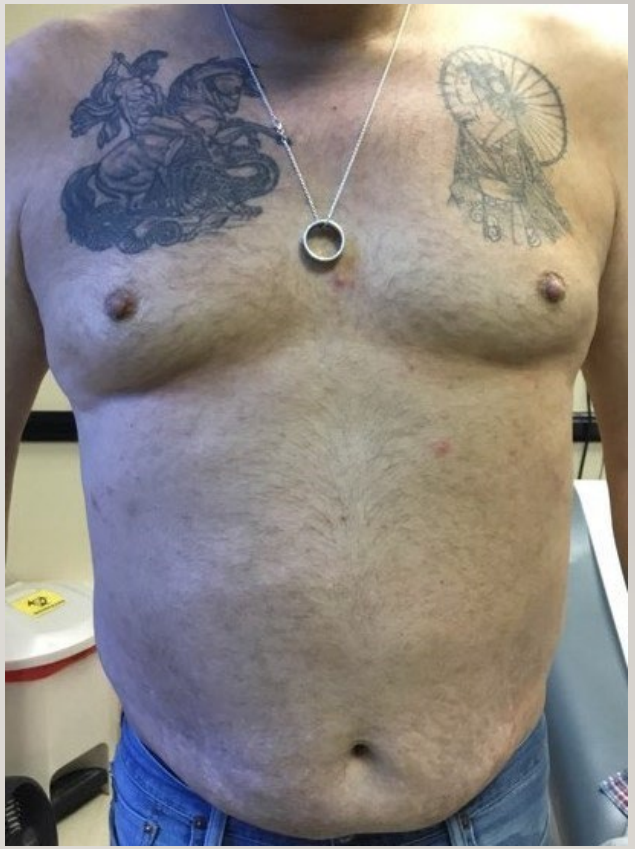
Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. Eric L. Simpson, Thomas Bieber, Emma Guttman-Yassky, et al. The New England Journal of Medicine. Dec 15, 2016

- Exam – Mild scaling with few areas of post inflammatory changes
- BSA-3%

- DX: Atopic Dermatitis – Well controlled – no flares since initiation of Dupilumab

- Patient continues Antihistamines and Moisturizer Daily





12 months since initiation of Dupilumab

Photos from K. Kucera PAC
With permission from patient.

CASE STUDY #2

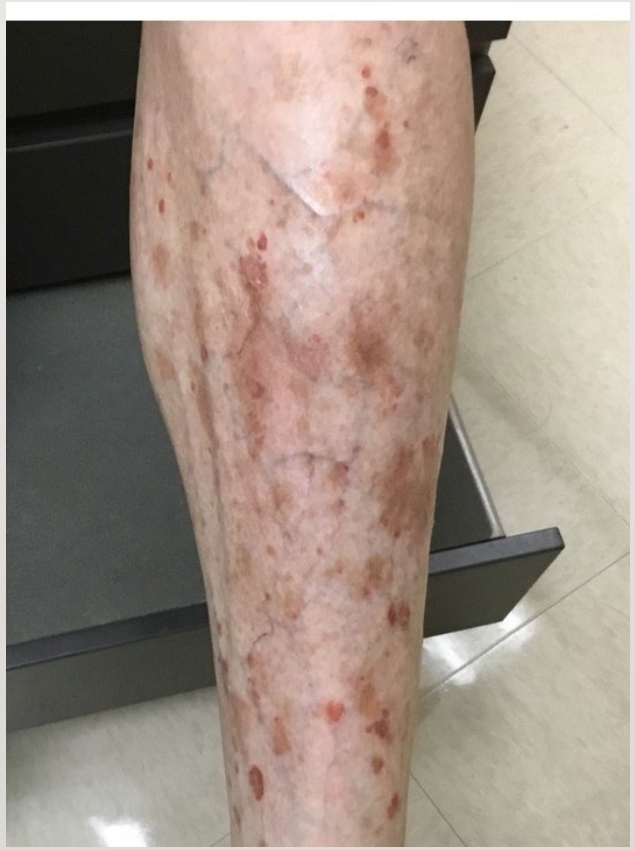
- 61 yo male with "rash" x 4 years
  - Itching, bleeding and "cannot wear shorts when I go to Vegas"
    - "I'm tired of it and it looks horrible"
  - Patient reports he has seen 3 dermatology providers
    - Capillaritis – Triamcinolone BID
    - Dermatitis Unspecified – Ultravate BID
      - Bx – Pigmnented Purpuric Dematosis
    - Psoriasis – Risankizumab
  - Current treatment – Using Ultravate every day
    - Has been on Skyrizi for 6 months but continuing topical steroids everyday or flare

CASE STUDY #2

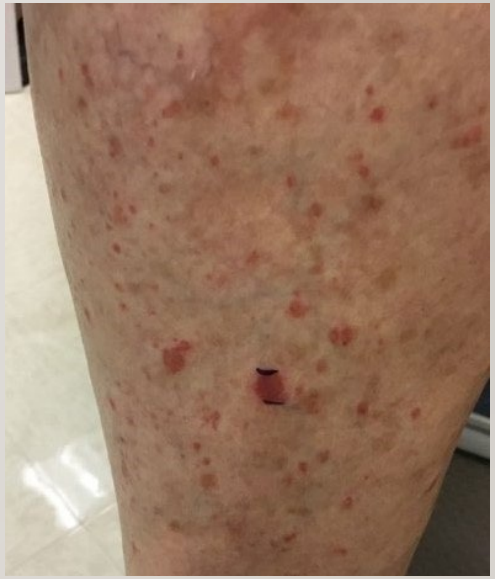
- No previous history of skin rashes as adult or child
- Nonsmoker, + ETOH 2-3 per day
  - (how many days have you had an alcoholic beverage in the past year? 365)
- Medication
  - Diabetes- metformin, sitagliptin, canagliflozin
  - Hypertension – losartan
  - High lipids – atorvastatin
  - Anxiety – buspirone
- Recent labs
  - CBC – WNL
  - CMP – Glucose 122, AST 42, otherwise WNL

- Exam – Few erythematous scaling patches of lower legs. Post inflammatory changes. Moderate degree of atrophy/thinning noted of skin.

- DX: Dermatitis with Steroid Atrophy



Right lower leg 6/2021
Initial visit



Left shin 4/2019
At time of biopsy

Photos from K. Kucera PAC
With permission from patient.

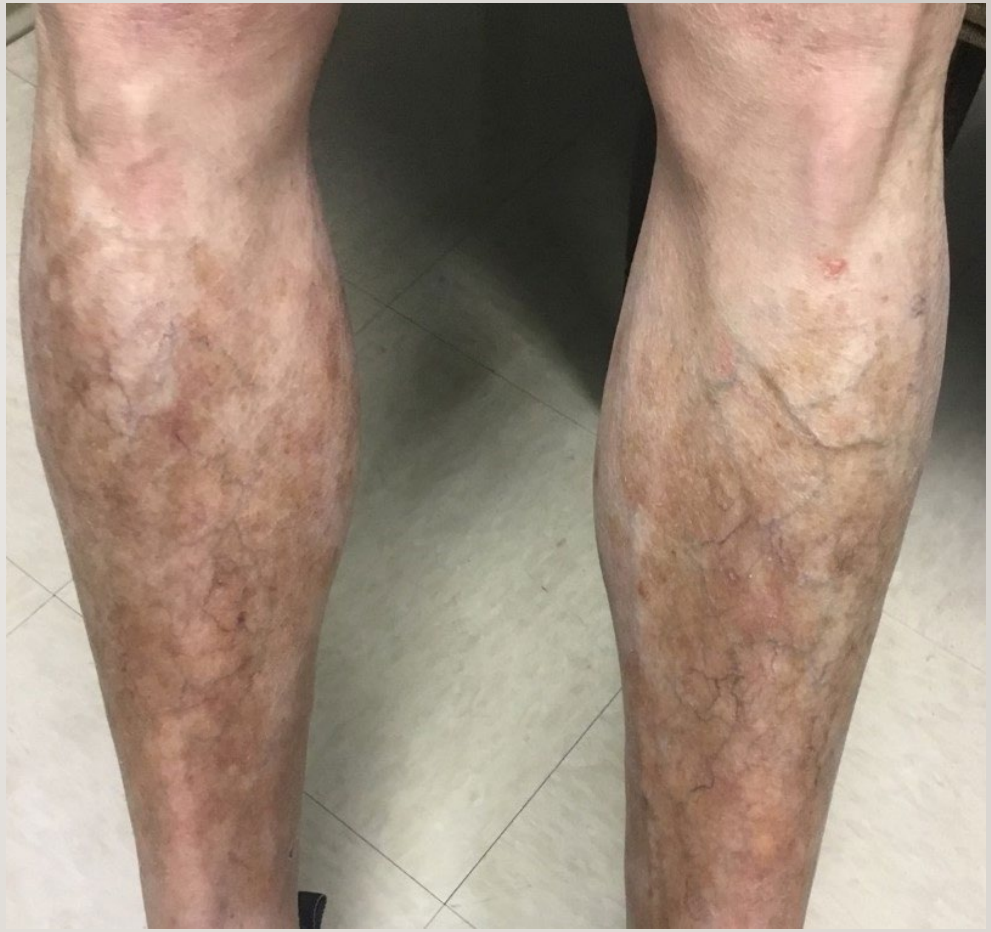
CASE STUDY #2

- Decision Points
  - QOL severely affected – need to obtain clear or almost clear skin
  - Chronic disease – Systemic therapy – avoid flares
  - Severe itching/scratching – break cycle
  - Severe steroid atrophy- skin repair
  - Psoriasiform Dermatitis – Overlying disease states- Dermatitis/Psoriasis with AD being the driving factor
- Treatment Plan
  - Discontinue Risankizumab
  - Allegra 180mg qam, Hydroxyzine 25mg 1-2 qhs
  - Begin Dupilumab
  - Wean off topical steroids. Topical TCIs and JAK and Moisturizers
  - Patient Education and Importance of Compliance

- Exam – Macular post inflammatory changes only. Some atrophy persists.

- DX: Dermatitis – Controlled
- DX: Steroid Atrophy – Improved

- Stable on dupilumab, no reported flares, not using topical steroids but continuing moisturizers



Lower legs 1/2022
6 months on dupilumab

Photos from K. Kucera PAC
With permission from patient.