

Management of Atopic Dermatitis & Emerging Therapies

Mark Boguniewicz, MD
Professor, Division of Allergy-Immunology
Department of Pediatrics
National Jewish Health and University of
Colorado School of Medicine

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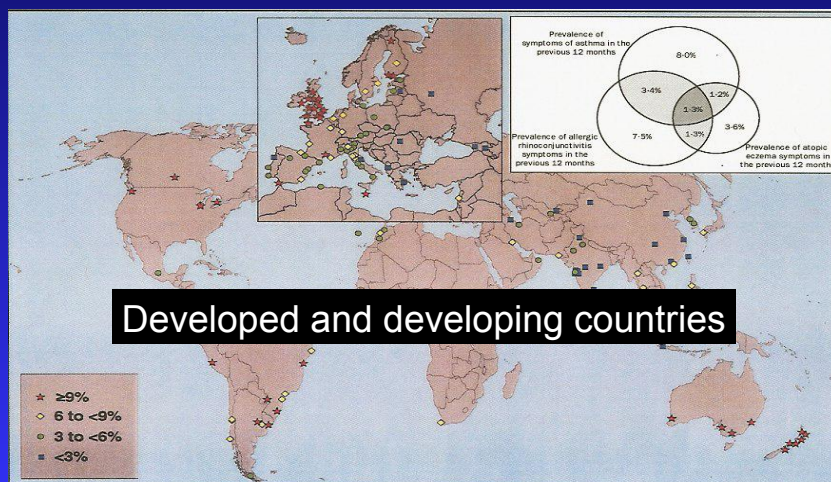
Atopic dermatitis: A practice parameter update 2012

Authors: Lynda Schneider, MD, Stephen Tilles, MD, Peter Lio, MD, Mark Boguniewicz, MD, Lisa Beck, MD, Jennifer LeBovidge, PhD, and Natalija Novak, MD

Joint Task Force Contributors: David Bernstein, MD, Joann Blessing-Moore, MD, David Khan, MD, David Lang, MD, Richard Nicklas, MD, John Oppenheimer, MD, Jay Portnoy, MD, Christopher Randolph, MD, Diane Schuller, MD, Sheldon Spector, MD, Stephen Tilles, MD, and Dana Wallace, MD

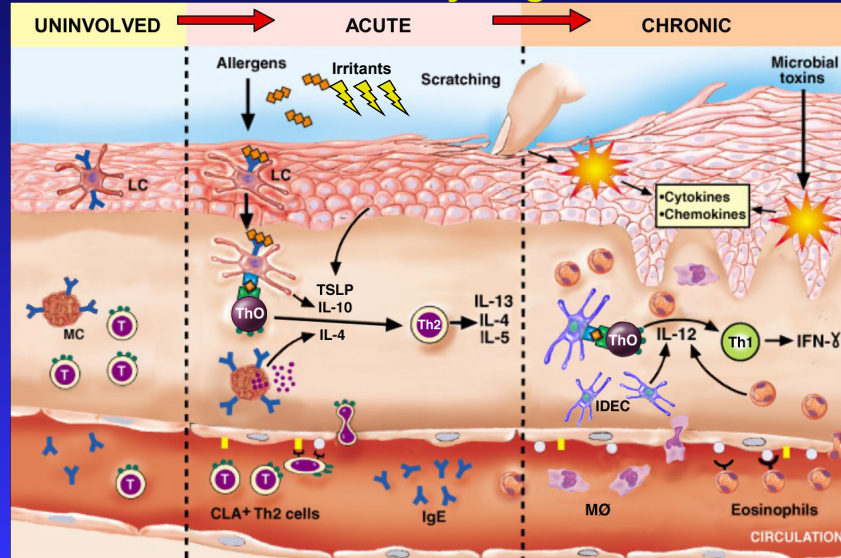
- **Category of evidence**
 - Ia - Evidence from meta-analysis of randomized controlled trials
 - Ib - Evidence from at least 1 randomized controlled trial
 - IIa - Evidence from at least 1 controlled study without randomization
 - IIb - Evidence from at least 1 other type of quasiexperimental study
 - III - Evidence from nonexperimental descriptive studies, such as comparative studies
 - IV - Evidence from expert committee reports, opinions or clinical experience of respected authorities or both
- **Strength of recommendation**
 - A - Directly based on category I evidence
 - B - Directly based on category II evidence or extrapolated recommendation from category I evidence
 - C - Directly based on category III evidence or extrapolated recommendation from category I or II evidence
 - D - Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
 - LB- Laboratory based
 - NR - Not rated

Global variations in prevalence of eczema symptoms in children from ISAAC Phase 3



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

Atopic dermatitis: a disease of altered skin barrier and immune dysregulation



Boguniewicz M, et al. Immunol Rev 2011;242:233

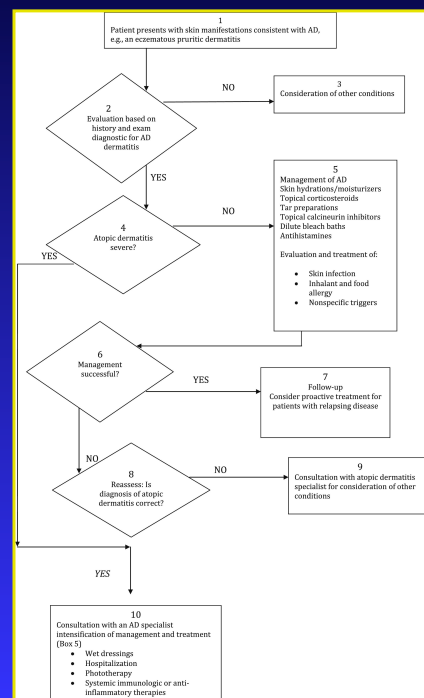
Recent insights into atopic dermatitis and implications for management of infectious complications

Increased susceptibility to infections or colonization with microbial organisms: *Staphylococcus aureus*, Herpes simplex



Boguniewicz M, et al. J Allergy Clin Immunol 2010;125:4

Fig 1. Flow chart of the diagnosis and management of AD



J Allergy Clin Immunol 2013;131:295

Differential diagnosis of AD

Congenital disorders

- Netherton's syndrome

Chronic dermatoses

- Seborrheic dermatitis
- Contact dermatitis (allergic or irritant)
- Nummular eczema
- Lichen simplex chronicus

Infections and infestations

- Scabies
- HIV-associated dermatitis

Malignancy

- Cutaneous T cell lymphoma (mycosis fungoides/Sézary syndrome)

Immunodeficiencies

- Wiskott-Aldrich syndrome
- SCID
- Hyper-IgE syndrome
- *DOCK8* mutations
- IPEX

Metabolic disorders

- Zinc deficiency
- Pyridoxine (vitamin B₆) and niacin deficiency
- Multiple carboxylase deficiency
- Phenylketonuria

Proliferative disorder

- Letterer-Siwe disease

Dedicator of cytokinesis 8

- *DOCK8* encodes a protein implicated in the regulation of the actin cytoskeleton
- Susceptibility to viral infections, defective CD4+ and CD8+ T-cell activation and TH17 cell differentiation, impaired eosinophil homeostasis and dysregulation of IgE, eczema
- Mutations in *DOCK8* are responsible for many cases of AR HIE syndrome

Engelhardt KR, et al. J Allergy Clin Immunol 2009;124:1289

DOCK8 mutations

Herpes simplex virus,
Human papilloma virus,
Molluscum contagiosum



Figure 1. Characteristic Dermatologic Findings.
Among the characteristic dermatologic findings in the patients in the study were atopic dermatitis with scattered superimposed molluscum contagiosum lesions on the inside of the arm (Panel A), chronic ulcerative anogenital herpes simplex virus infection (Panel B), perioral and acral warts (Panel C), and molluscum contagiosum on the back (Panel D).

Zhang Q, et al. N Engl J Med 2009;361

First line management and treatment

- Summary statement 12. Skin hydration... the clinician should recommend hydration with warm soaking baths for at least 10 minutes followed by the application of a moisturizer. (D)
- Summary statement 14. Topical corticosteroids. If atopic dermatitis is not controlled by moisturizers alone, then the clinician should recommend a topical corticosteroid.(A)
- Summary statement 19. Topical calcineurin inhibitors. Clinicians may consider the use of tacrolimus ointment which has been shown to be effective and safe in both adults and children over 2 years... (A)

J Allergy Clin Immunol 2013;131:295

Topical calcineurin inhibitors

- Topical preparations approved for use in AD down to 2 yrs age
 - Tacrolimus (Protopic) ointment 0.03 (ages 2-15 yrs) & 0.1% (>15 yrs) for moderate-severe AD
 - Pimecrolimus (Elidel) cream 1% for mild-moderate AD
 - Boxed warning in 2006 but no change in label

Boguniewicz M, et al. J Allergy Clin Immunol 1998;102:637

Eichenfield LF, Lucky AW, Boguniewicz M, et al. J Am Acad Dermatol 2002;46:495

Report of the Topical Calcineurin Inhibitor Task Force of the ACAAI and AAAAI

- In children < 2 years of age with poorly controlled persistent AD who require more than hydration and use of emollients to keep their skin disease under control, use of off label therapy may be necessary as most topical steroids or other immunomodulators have not been studied or approved in this age group.

Fonacier L, et al. J Allergy Clin Immunol 2005;115:1249-53

Tacrolimus studies

- Efficacy and safety of tacrolimus ointment treatment for up to 4 years in patients with atopic dermatitis

Hanifin JM, et al. J Am Acad Dermatol 2005;53:S186

- Tacrolimus ointment is safe and effective in the treatment of atopic dermatitis: Results in 8000 patients

Koo JYM, et al. J Am Acad Dermatol 2005;53:S195

- Pneumococcal seroconversion after vaccination for children with atopic dermatitis treated with tacrolimus ointment

Stiehm ER, et al. J Am Acad Dermatol 2005;53:S206

Safety and tolerability of 1% pimecrolimus cream among infants: Experience with 1133 patients treated for up to 2 years

- Infants treated intermittently with 1% pimecrolimus cream for up to 2 years demonstrated normal immune responses to vaccinations and did not show increases in the incidence of systemic or skin infections over time
- The ID rate of HSV infections was 0.8 cases/1000 pt-mo of follow-up monitoring among patients treated with 1% pimecrolimus cream in the blinded studies and 1.3 cases/1000 pt-mo of follow-up monitoring in blinded & open studies vs 1.7 cases/1000 pt-mo of follow-up monitoring among patients who received the vehicle

Paul C, et al. Pediatrics 2006;117:118

Risk of lymphoma

- Nested case-control study evaluating association between topical immunomodulators and lymphoma in a cohort of 293,253 AD patients
- Topical steroid, pimecrolimus and tacrolimus use not associated with increased risk of lymphoma
- Severity of AD main factor associated with increased risk of lymphoma

Arrelano F, et al. J Invest Dermatol 2006;126:1682

Safety and Efficacy of Pimecrolimus in AD: A 5-Year Randomized Trial (Petite)

- 2418 infants enrolled in 5-year open-label study randomized to PIM (n = 1205; with short-term TCSs for disease flares) or TCSs (n = 1213)
- Primary objective to compare safety; secondary objective to document PIM's long-term efficacy
- Treatment success defined as IGA score of 0 (clear) or 1 (almost clear)

Sigurgeirsson B, et al. Pediatrics 2015;135 (April):597-606

- Both PIM and TCSs had rapid onset of action with >50% of patients achieving treatment success by week 3
- After 5 years, >85% and 95% of patients in each group achieved overall and facial treatment success, respectively
- PIM group required substantially fewer steroid days than the TCS group (7 vs 178)
- Profile and frequency of adverse events similar in 2 groups; in both groups, no evidence for impairment of humoral or cellular immunity
- Data support the use of PIM as a first-line treatment of mild-to- moderate AD in infants and children

Sigurgeirsson B, et al. Pediatrics 2015;135 (April):597-606

Dilute bleach baths

- Summary Statement 30: Clinicians should consider the addition of dilute bleach baths twice weekly to reduce the severity of AD, especially in patients with recurrent skin infections. (A)*

*Single study of a small cohort, only 9/15 pts in active treatment evaluated at 3 mo; EASI score (primary outcome) significantly different at baseline for 2 groups (IGA not signif different); at 3 mo, no change in proportion of *S. aureus*-positive pts (despite oral ABX at start & nasal mupirocin 5d/mo)

- Huang JT, et al. Pediatrics 2009;123:e808

Identification and elimination of triggering factors

- Summary Statement 34: The clinician might consider food allergens as triggers of AD more commonly in young infants and children. (D) The clinician should be aware that for children less than 5 years of age with moderate-to-severe AD, the Food Allergy Expert Panel suggested consideration of limited food allergy testing if the child has persistent AD in spite of optimized management and topical therapy, the child has a reliable history of an immediate allergic reaction after ingestion of the food, or both.
- Summary Statement 35: The clinician should not recommend extensive elimination diets based only on positive skin or specific IgE test results because potential nutritional deficiency can occur, and even with multiple positive skin test results, most patients will react to few foods on oral challenge. (B)

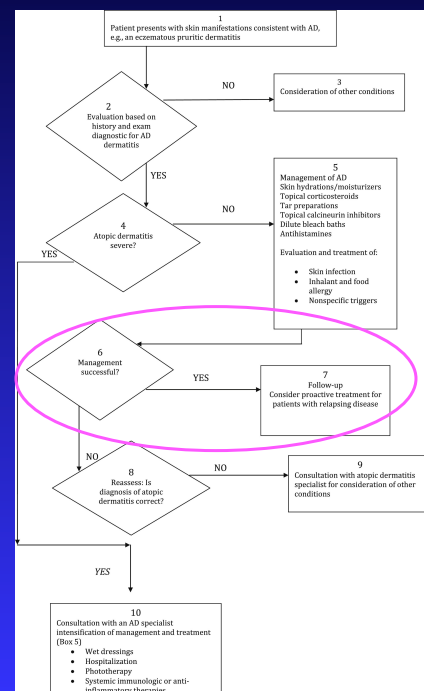
NJH Food Challenge Unit

- First controlled OFCs done at NJH in the 1970's
- Depending on reason for avoidance, ~85 % of foods being avoided can be returned to diet after OFC, indicating that vast majority of restricted foods could be tolerated
- Reliance on allergy tests to determine need for food elimination diet is not sufficient, especially in children with AD

J Pediatr 2011;158:578

Moving from reactive to proactive therapy

Fig 1. Flow chart of the diagnosis and management of AD



J Allergy Clin Immunol 2013;131:295

Intermittent topical fluticasone propionate

- After stabilization of AD with daily therapy, FP applied to areas of previous involvement that appeared visually normal as maintenance therapy 2x/week in adult and pediatric patients, suggesting better disease control with less need for topical steroids vs reactive therapy for flares
 - Van Der Meer, et al. Br J Dermatol 1999;140:1114
 - Hanifin JM, et al. Br J Dermatol 2002;147:528
 - Berth-Jones J, et al. BMJ 2003;326:1367

Topical calcineurin inhibitors

- Summary Statement 22: Once a flare is controlled, the clinician might consider prescribing tacrolimus ointment twice daily, twice weekly to eczema-prone areas to prevent future flares. (A)

If the patient still has severe, recalcitrant atopic dermatitis...



Fitzpatrick's Dermatology in Gen Med 2012; 170

Consultation with an AD specialist

- Summary Statement 45: The clinician should refer patients refractory to first-line therapy to an AD specialist. (D)

Hospitalization

- Summary Statement 49: The clinician might consider hospitalization, which can result in an improvement in AD by removing the patient from environmental allergens, irritants and stressors and by providing patient/caregiver education, addressing sleep disturbance and psychosocial issues, intensifying treatment, and improving adherence with the treatment regimen. (D)

Wet dressings

- Summary Statement 46: The clinician should recommend application of wet-wrap dressings in combination with topical corticosteroids for treatment of refractory AD. (A) Wet dressings help with skin barrier recovery, increase the efficacy of topical steroids when used concomitantly, and protect the skin from persistent scratching, allowing more rapid healing of excoriated lesions. (B)

Day Hospital Program/Wet wrap therapy



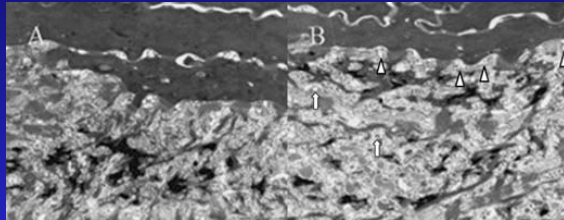
Boguniewicz M, et al. Semin Cutan Med Surg 2008;27:115

The effect of wet-wrap dressing on epidermal barrier in patients with atopic dermatitis

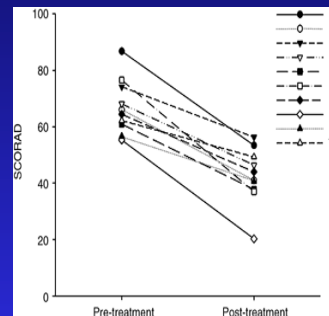
- To examine the difference of non-lesional and lesional atopic skin and evaluate change between epidermal barrier function before & after treatment, SCORAD, epidermal water content, TEWL, skin surface lipids, immunohistochemical staining of filaggrin and loricrin, transmission electron microscopic examination, and calcium ion capture cytochemistry in 10 severe AD pts

Lee JH, et al. J Eur Acad Dermatol Venereol 2007;21:1360

The effect of wet-wrap dressing on epidermal barrier in patients with atopic dermatitis



Transmission electron microscopic examination showing lamellar body before (a) and after (b) the treatment. The number (arrow) and secretion (arrowhead) of lamellar body were both increased after the treatment ($\times 20\,000$)

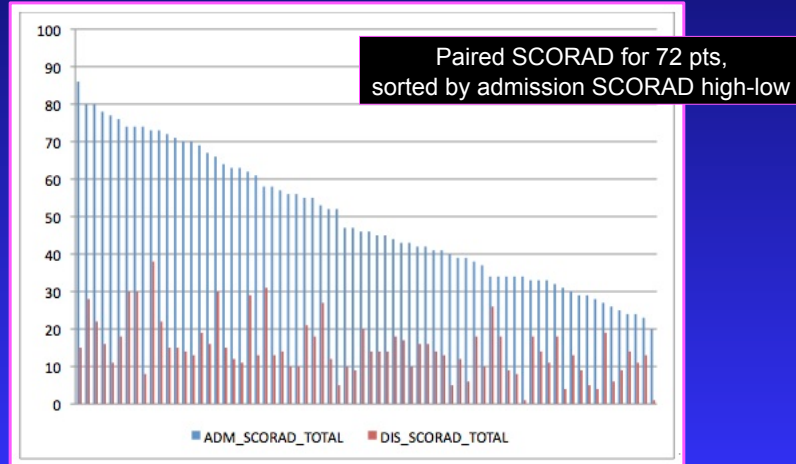


Lee JH, et al. J Eur Acad Dermatol Venereol 2007;21:1360

- Epidermal barrier abnormality in AD confirmed
- Use of wet-wrap dressing resulted in recovery of epidermal barrier with clinical improvement associated with release of lamellar body and restoration of intercellular lipid lamellar structure
- One week after D/C of wet-wrap dressings, increased water content and decreased transepidermal water loss still maintained

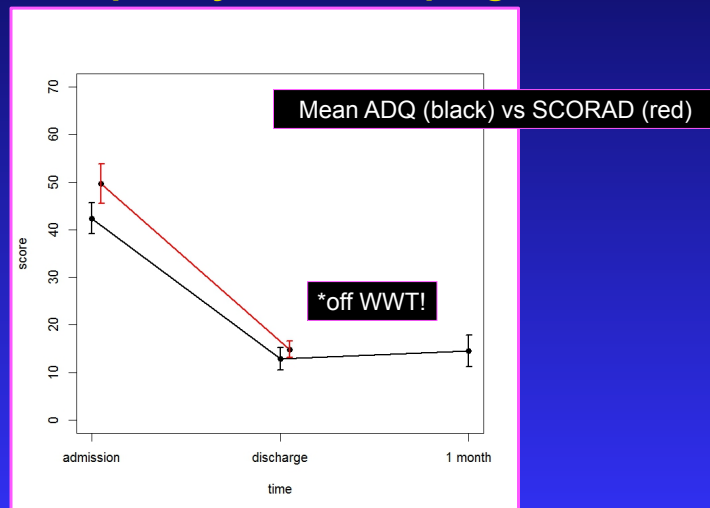
Lee JH, et al. J Eur Acad Dermatol Venereol 2007;21:1360

Wet wrap therapy in children with moderate to severe atopic dermatitis in a multidisciplinary treatment program



Nicol NH, et al. J Allergy Clin Immunol: In Prac 2014;2:400

Wet wrap therapy in children with moderate to severe atopic dermatitis in a multidisciplinary treatment program



Nicol NH, et al. J Allergy Clin Immunol: In Prac 2014;2:400

Systemic immunomodulating agents

- Summary Statement 47: Immunomodulating agents, such as cyclosporine, mycophenolate mofetil, azathioprine, IFN- γ , and corticosteroids, have been shown to provide benefit for patients with severe refractory AD, although the clinician should consider their potential serious adverse effects. (A)*

*Systemic treatments NOT all equal!

J Allergy Clin Immunol 2013;131:295

Joint Task Force Practice Parameter: AD & immunotherapy

- Summary Statement 50: On the basis of several studies of dust mite immunotherapy, the clinician might consider allergen immunotherapy in selected patients with AD with aeroallergen sensitivity. (B)

B - Directly based on category II evidence or extrapolated recommendation from category I evidence

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International consensus on allergy immunotherapy

- Controversy about potential role of AIT as a therapeutic intervention for patients with AD and aeroallergen sensitivity
- Large dose-finding phase II study in HDM- sensitized patients with AD showed significant SCORAD decrease after 8 weeks with effect maintained over 1 year, including lower steroid use
- Recent meta-analysis proved moderate-level evidence of efficacy. However, largest prospective placebo-controlled study included in this meta-analysis showed efficacy only in severely affected patients (SCORAD score >50)
- Recent systematic review with Grading of Recommendations Assessment, Development and Evaluation system reported improvement in clinical symptoms with serious methodological shortcomings noted
- Only SLIT study performed with HDM allergens in children with AD described a positive outcome only in those with mild-to-moderate AD

Jutel M, et al. J Allergy Clin Immunol 2015;136:556

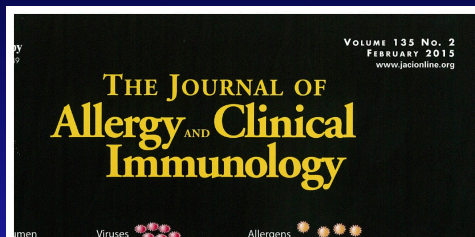
AD: Emerging Therapies

- Novel therapies directed at
 - Skin barrier abnormalities
 - Immune dysregulation
 - Microbial aspects
 - Pruritus

Interventional studies in AD using biologics

Immunologic target	Agent	Manufacturer	Registered Clinical Trials	References
IgE	QGE-031	Novartis	NCT01552629	(82)
IL-4 receptor alpha	REGN668/SAR231893/Dupilumab	Regeneron/Sanofi	NCT01259323	
			NCT01385657	
			NCT01548404	
			NCT01639040	
			NCT01859988	
			NCT01949311	
			NCT01979016	
			NCT02210780	
			NCT02260986	
			NCT02277743	
			NCT02277769	
			NCT02395133	
IL-5	Mepolizumab	GlaxoSmithKline	NCT02347176	(87, 88)
IL-13	Tralokinumab	AstraZeneca/MedImmune	NCT02340234	
	Lebrikizumab	Hoffman-La Roche/Genentech	NCT01941537	
IL-22	ILV-094	Pfizer	NCT01614756	
IL-31	BMS-981164	BMS/Zymogenetics	NCT01986933	
IL-31 receptor	CIM 331	Roche/Chugai	NCT01732510	
TSLP	MK-8226	Merck	NCT00757042	
	AMG 157*	Amgen		

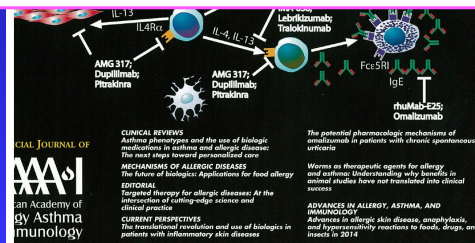
Howell MD, et al. Allergy 2015;70:887



Editorial

Targeted therapy for allergic diseases: At the intersection of cutting-edge science and clinical practice

Mark Boguniewicz, MD, and Donald Y. M. Leung, MD, PhD Denver, Colo



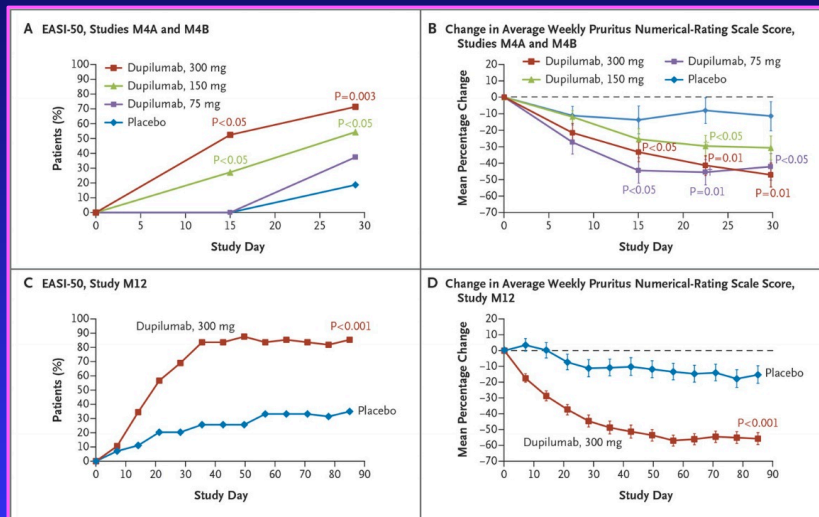
ORIGINAL ARTICLE

Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis

Lisa A. Beck, M.D., Diamant Thaçi, M.D., Jennifer D. Hamilton, Ph.D., Neil M. Graham, M.D., Thomas Bieber, M.D., Ph.D., M.D.R.A., Ross Rocklin, M.D., Jeffrey E. Ming, M.D., Ph.D., Haobo Ren, Ph.D., Richard Kao, Dr.P.H., Eric Simpson, M.D., Marius Ardeleanu, M.D., Steven P. Weinstein, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Emma Guttman-Yassky, M.D., Ph.D., Mayte Suárez-Fariñas, Ph.D., Melissa D. Hager, M.A., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Allen R. Radin, M.D.

Beck LA, et al. N Engl J Med 2014;371:130-9

Key efficacy end points



Beck LA, et al. N Engl J Med 2014;371:130

The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization

- Asian patients show a more psoriasiform phenotype with more prominent epidermal hyperplasia and elongated rete ridges, parakeratosis, and hypogranulosis, typical features in patients with psoriasis
- More significant increases in CD11c⁺ myeloid DC and FcεRI⁺ DC counts seen in Asian patients with AD vs in EA patients with AD
- Asian AD shows significantly higher induction of T_H17- and T_H22-related cytokines (*IL17A*, *IL19*, and *IL22*) and IL-17/IL-22–induced keratinocyte markers (*S100A12*) in lesional and/or nonlesional skin c/w EA patients with AD

Noda S, et al. J Allergy Clin Immunol 2015; Sept 28 [epub ahead of print]

Implications for specific therapy?

- The more “psoriasis-like” phenotype of Asian AD provides a rationale for testing of IL-17/IL-23–targeted strategies that are successfully tested in patients with psoriasis in addition to TH2-specific therapeutics

Noda S, et al. J Allergy Clin Immunol 2015;Sept 28 [epub ahead of print]

Studies in AD using biologic therapies approved for other diseases

Immunologic target	Agent	Manufacturer	Approved for	References
CD2/LFA-3	Alefacept (Amevive [®])	Astellas	Psoriasis	(64, 65)
CD11a/LFA-1	Efalizumab (Raptiva [®])	Genentech/MerckSerono	Psoriasis*	(66, 118, 119)
CD20	Rituximab (Rituxan [®])	Genentech/Biogen Idec	Chronic Lymphocytic Leukemia Non-Hodgkin's Lymphoma Rheumatoid Arthritis	(57, 58)
IgE	Omalizumab (Xolair [®])	Genentech/Novartis	Asthma Chronic Idiopathic Urticaria	(52-55, 120, 121)
IL-6R	Tocilizumab (Actemra [®])	Hoffman-La Roche/Genentech	Juvenile Idiopathic Arthritis Rheumatoid Arthritis	(107)
IL-12/23p40	Ustekinumab (Stelara [®])	Janssen	Psoriasis Psoriatic Arthritis	(114, 115, 122)
TNF-alpha	Etanercept (Enbrel [®])	Amgen	Ankylosing Spondylitis Psoriasis Psoriatic Arthritis Rheumatoid Arthritis	(104, 123)
	Infliximab (Remicade [®])	Janssen	Ankylosing Spondylitis Crohn's Disease Psoriasis Psoriatic Arthritis Rheumatoid Arthritis	(103)

*Removed from the market due to risk of developing progressive multifocal leukoencephalopathy (PML).

Howell MD, et al. Allergy 2015;70:887

Emollient enhancement of skin barrier from birth offers effective atopic dermatitis prevention

- Randomized controlled trial in US & UK of 124 neonates at high risk for AD
- Parents in intervention arm instructed to apply full-body emollient at least once/day starting within 3 weeks of birth; parents in the control arm asked to use no emollients
- Primary feasibility outcome was percentage of families willing to be randomized. Primary clinical outcome was cumulative incidence of AD at 6 mo, as assessed by a trained investigator

Simpson EL, et al. J Allergy Clin Immunol 2014;134:818-23

- 42% of eligible families agreed to be randomized into the trial. All participating families in the intervention arm found the intervention acceptable.
- A statistically significant protective effect was found with use of daily emollient on cumulative incidence of AD with a relative risk reduction of 50% (relative risk, 0.50; 95% CI, 0.28-0.9; P = .017)
- No emollient-related adverse events and no differences in adverse events between groups
- Emollient therapy from birth represents a feasible, safe, and effective approach for AD prevention

Simpson EL, et al. J Allergy Clin Immunol 2014;134:818-23

Application of moisturizer to neonates prevents development of atopic dermatitis

- Prospective, randomized controlled trial to investigate whether protecting skin barrier with daily moisturizer for first 32 wks of life to 59/118 high risk neonates (based on having a parent or sibling with AD) prevents development of AD and allergic sensitization
- 32% fewer neonates in moisturizer group had AD/eczema by week 32 than controls (P = .012)
 - No significant effect of moisturizer on allergic sensitization (based on sIgE egg white) although sensitization rate significantly higher in infants who had AD/eczema (OR, 2.86; 95% CI, 1.22-6.73)
- Daily moisturizer during the first 32 wks of life reduces risk of AD/eczema in infants

Horimukai K, et al. J Allergy Clin Immunol 2014;134:824-30