Emerging Therapies in Atopic Dermatitis

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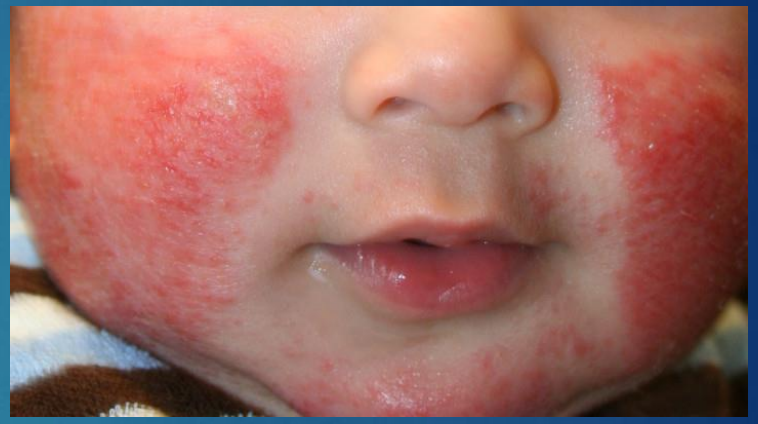
ATOPIC DERMATITIS

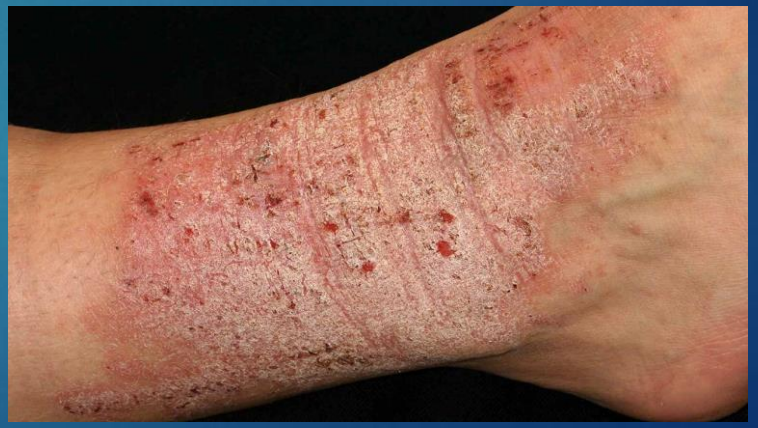
Common, yet complex inflammatory skin condition with many factors contributing to its pathogenesis

Clinical features include onset during infancy or early childhood, intense pruritus, and a chronically relapsing course

- acute inflammation and predilection for cheeks, scalp, and extensor sites (infants)
- chronic inflammation with lichenification and a predilection for flexural sites (children/adults)

Often associated with asthma, allergic rhinoconjunctivitis, and food allergies (Atopic March)



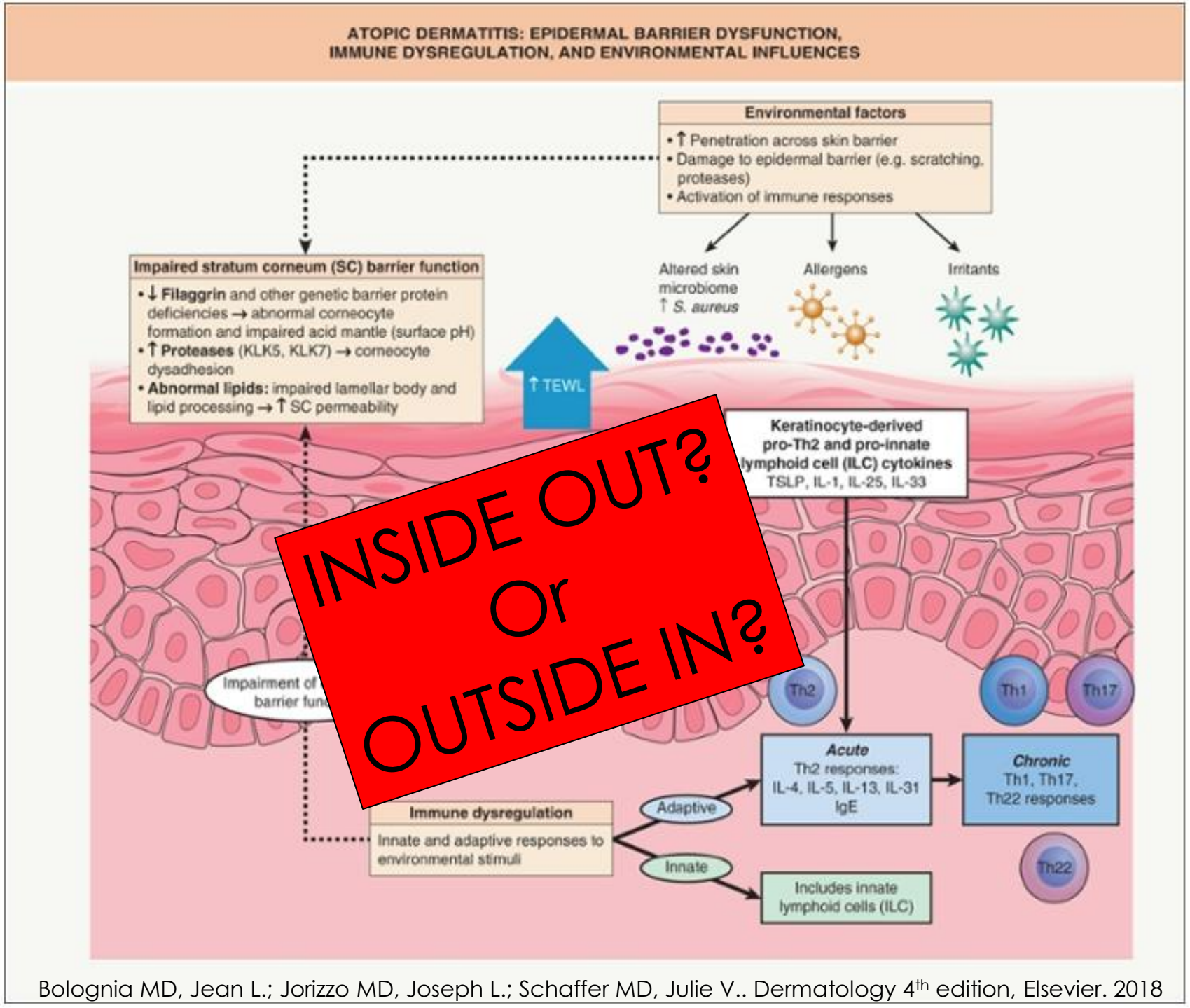


Pathogenesis

Divided into three major categories

- *epidermal barrier dysfunction*
- *immune dysregulation*
- alteration of the *microbiome*

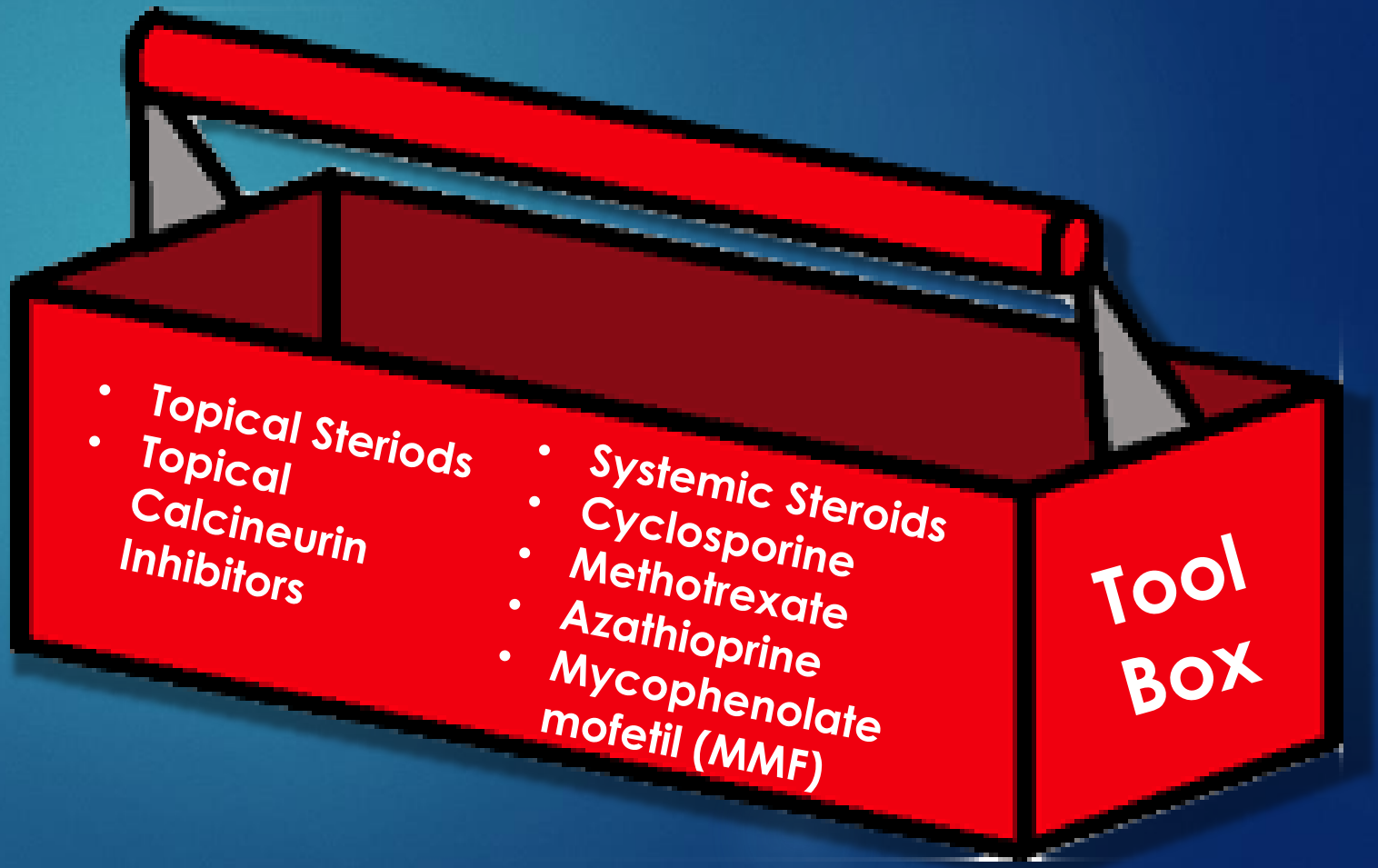
Each of these can be modulated by genetic and environmental factors



Bolognia MD, Jean L.; Jorizzo MD, Joseph L.; Schaffer MD, Julie V.. Dermatology 4th edition, Elsevier. 2018

Treatment: General Approach

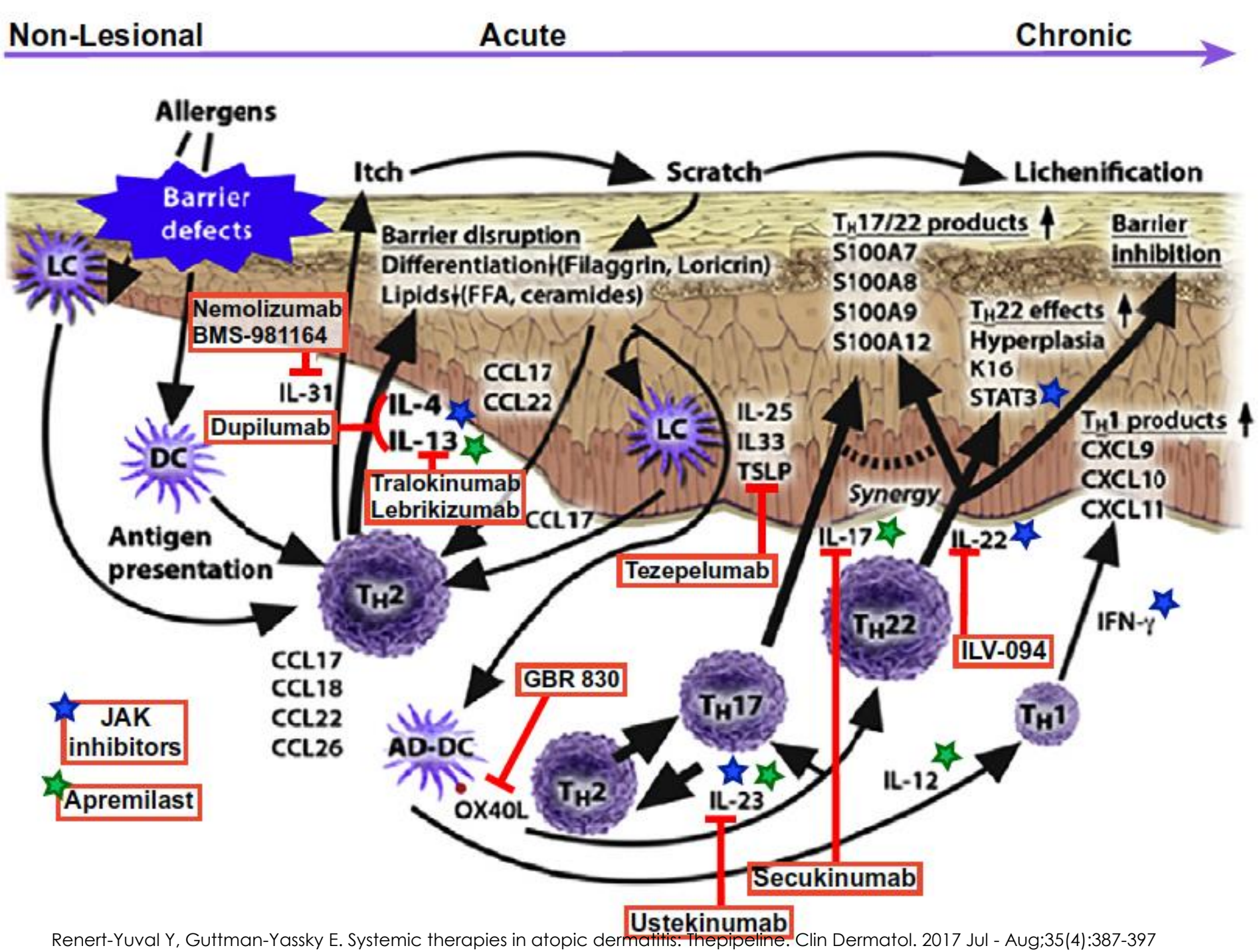
- A "proactive approach" may modify the overall disease course and prevent atopic comorbidities
- Management includes
  - education
  - gentle skin care
  - moisturizer use
  - topical agents
- Severe Disease
  - phototherapy
  - systemic medications



IS ATOPIC DERMATITIS THE NEW PSORIASIS?

NEW TARGETS

- PDE4 inhibition
- IL-4 antagonism
- IL-13 antagonism
- IL-31 antagonism
- IL-22 antagonism
- Janus Kinase inhibition
- Neurokinin-1 Receptor inhibition
- IL-12/23 antagonism
- IL-17 antagonism
- TSLP inhibition



Renert-Yuval Y, Guttman-Yassky E. Systemic therapies in atopic dermatitis: Thepipeline. Clin Dermatol. 2017 Jul - Aug;35(4):387-397

TABLE I. New or in the pipeline: Topicals

Target	Compound	Indication	Phase
AhR	Tapinarof/benvitimod	Moderate-severe	2a →
PDE4	Crisaborole (Eucrisa)	Mild-moderate	3 in EU (FDA 2016)
PDE4	Roflumilast	Moderate	2a →?
PDE4	RVT-501	Mild-moderate	2a →
JAK1, JAK3	Tofacitinib	Moderate-severe	2a → STOP
JAK1, JAK2	INCB18424	Mild-moderate	2a →
JAK1, JAK3	LEO 124249/JTE-052	Mild-moderate	2a
S aureus	R mucosa bacteria	Antecubital AD	1/2
S aureus	Coagulase-negative *Staphylococcus*	Moderate-severe on ventral arms	1/2

→, Drug development program is ongoing, phase 3 is planned but not yet running; →?, unknown future of drug development program; → *STOP*, drug development program has been stopped; *EU*, European Union; *FDA*, US Food and Drug Administration.

TABLE II. New or in the pipeline: Biologics

Target	Compound	Indication	Phase
TSLP	Tezepelumab	Moderate-severe	2a →
Oral	Anti-Oral	Moderate-severe	2a →
IL-4/IL-13R	Dupilumab (Dupixent)	Moderate-severe	Approved by FDA, 2017; approval pending in EU
IL-4	Pitrakinra	Moderate-severe	2a →?
IL-13	Tralokinumab	Moderate-severe	3
IL-13	Lebrikizumab	Moderate-severe	3
IL-5	Mepolizumab	Moderate-severe	2a
IgE	QGE031/ligelizumab	Moderate-severe	2a →?
IL-12/IL-23	Ustekinumab (Stelara)	Moderate-severe	2a →
IL-22	Fezakinumab (intravenous)	Moderate-severe	2a →
IL-17A	Secukinumab (Cosentyx)	Moderate-severe	2a →
IL-31 receptor A	CIM331/nemolizumab	Moderate-severe	2b →
IL-31	BMS-981164	Moderate-severe	1b →?

→, Drug development program is ongoing, phase 3 is planned but not yet running; →?, unknown future of drug development program; *EU*, European Union; *FDA*, US Food and Drug Administration.

ELSEVIER

Journal of Allergy and Clinical Immunology

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Reviews and feature article

Therapeutic pipeline for atopic dermatitis: End of the drought?

Amy S. Paller MS, MD [a] ✉, Kenji Kabashima MD, PhD [b], Thomas Bieber MD, PhD, MDRA [c]

TABLE III. New or in the pipeline: Small molecules

Target	Compound	Indication	Phase
CRTH2	OC000459	Moderate-severe	2a → STOP
CRTH2	QAW 039	Moderate-severe	2b → STOP
PDE4	Apremilast (Otezla)	Moderate-severe	2a → STOP
H4R	ZPL389	Moderate-severe	2a →
JAK 1/2	Baricitinib	Moderate-severe	2b →
JAK 1	Pf-04965842	Moderate-severe	2a →
JAK 1	Upadacitinib (ABT 494)	Moderate-severe	2a →
NK1R	VLY-686/tradipitant	Moderate-severe	2a →
NK1R	Serlopitant	Moderate-severe	2a →

→, Drug development program is ongoing, phase 3 is planned but not yet running; → *STOP*, drug development program has been stopped.

THE NEW KIDS ON THE BLOCK?

Phosphodiesterase 4 inhibitors

Rema Zebda, DO, and Amy S. Paller, MD
Chicago, Illinois

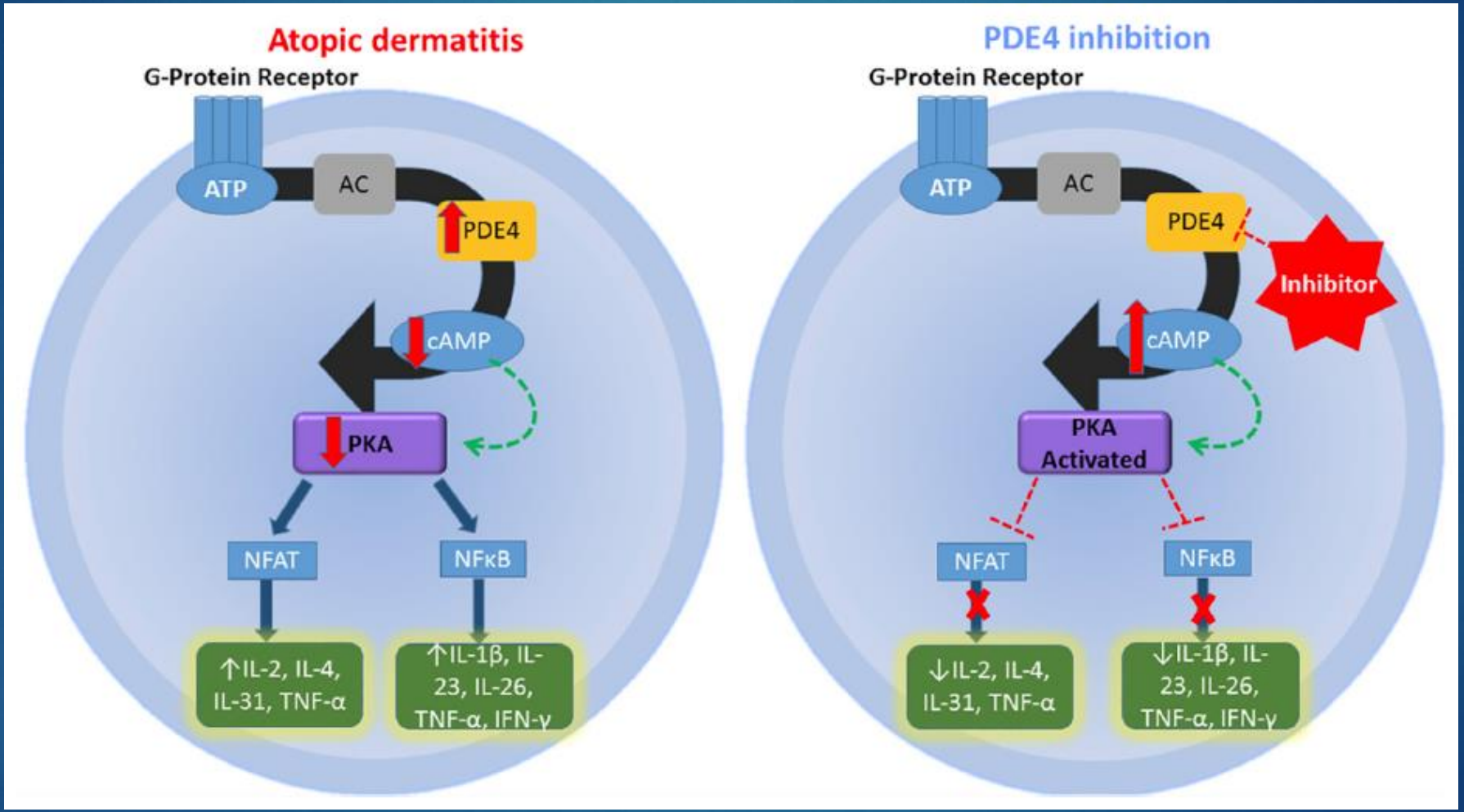


Table I. Studies performed or in progress with a PDE4 inhibitor for AD

Study no.	Study type	Location	Indication	Age	Study size	Duration	Primary end points	Results posted	References
AN2728 (crisaborole)									
NCT01652885	Phase I/II: 2 open-label, single-group studies[48]	United States	AD	12-17 y	23	28 d	Treatment-related AEs/SAEs, pharmacokinetics	No SAEs, 10 of 23 subjects with treatment related AE; limited systemic exposure	https://clinicaltrials.gov/ct2/show/NCT01652885
NCT01602341	Phase II: multicenter, randomized, double-blind, parallel-group study	United States	AD	12-17 y	86	29 d	ADSI score	Greatest improvement at d 8 and d 29 with 1% concentration	https://clinicaltrials.gov/ct2/show/NCT01602341
NCT02118792	Phase III: multicenter, randomized, double-blind, vehicle-controlled study	United States	Mild/Mod AD	≥2 y	764	28 d	% with ISGA score clear or almost clear at d 29; time to ISGA treatment success; change from baseline in AD signs at d 29	Primary end point and reduced pruritus achieved with crisaborole more than vehicle; local application site pain reported by 4.4% of active vs 1.2% placebo; no SAEs reported	https://clinicaltrials.gov/ct2/show/NCT02118792
NCT02118766	Phase III: multicenter, randomized, double-blind, vehicle-controlled study (parallel to NCT0211-8792)[49]	United States	Mild/Mod AD	≥2 y	763	28 d	% with ISGA score clear or almost clear at d 29; time to ISGA treatment success; change from baseline in AD signs at d 29		
NCT01301508	Phase III: multicenter, randomized, double-blind, vehicle-controlled, parallel-group study[50]	Australia	Mild/Mod AD	18-75 y	46	6 wk	Improvement in ADSI score	At d 28, greater decrease in ADSI score in active-treated (68%) vs vehicle-treated (20%) lesion; local application site reactions in 12% of subjects; no SAEs	https://clinicaltrials.gov/ct2/show/NCT01301508
NCT03260595	Phase I: single-center, randomized, vehicle-controlled, parallel-group study	Japan	Healthy Men	20-55 y	32	4 d	Skin irritation index	Open for enrollment	https://clinicaltrials.gov/ct2/show/NCT03260595
NCT03233529	Phase II: randomized, double-blind, vehicle-controlled (biomarker) study	Canada	Mild/Mod AD	≥18 y	40	4 wk	TSS and biomarkers	Open for enrollment	https://clinicaltrials.gov/ct2/show/NCT03233529
NCT03250663	Phase IV: randomized, double-blind, parallel-group (adherence) study	United States	Mild/Mod AD	2-64 y	40	12 mo	Impact of Internet-reporting intervention on adherence	Open for enrollment	https://clinicaltrials.gov/ct2/show/NCT03250663
OPA-15406									
NCT01702181	Phase I: multicenter, randomized, blinded, vehicle-and-active comparator-controlled, sequential dose cohort study	United States	AD	18-65 y	92	4 wk	AEs/SAEs, drug levels	None	https://clinicaltrials.gov/ct2/show/NCT01702181
NCT02334787	Phase I: single-center, randomized, double-blind, parallel-group, placebo-controlled	Japan	Healthy Men	20-40 y	32	2 wk	Pharmacokinetic parameters	Highest AUC12 h with OPA-15406 3%; no reported AEs or SAEs	https://clinicaltrials.gov/ct2/show/NCT02334787
NCT02914548	Phase II: multicenter, randomized, double-blind, parallel-group, vehicle-controlled, comparison study	Japan	AD	15-70 y	200	Not listed	IGA response rate	None	https://clinicaltrials.gov/ct2/show/NCT02914548
NCT03018691	Phase II: multicenter, randomized, double-blind, parallel- group, vehicle-controlled study	Japan	AD	2-14 y	73	4 wk	No. and % of subjects with AEs	None	https://clinicaltrials.gov/ct2/show/NCT03018691
NCT02068352	Phase II: multicenter, randomized, double-blind, vehicle-controlled, three-arm, parallel-group study	United States	Mild/Mod AD	10-70 y	94	8 wk	Incidence and severity of AEs and incidence of success in IGA score	Improvement in IGA, EASI, pruritus with OPA-15406 1%; negligible blood levels; most common treatment-related AEs: worsening AD/pruritus, headache, nasopharyngitis	https://clinicaltrials.gov/ct2/show/NCT02068352
NCT02945657	Phase II: multicenter, open-label study	United States	AD	2-18 y	32	28 d	Plasma concentrations drug and metabolite	None	https://clinicaltrials.gov/ct2/show/NCT02945657

Table I. Cont'd

Study no.	Study type	Location	Indication	Age	Study size	Duration	Primary end points	Results posted	References
E6005/RVT-501									
NCT01179880	Phase I/II: 2 randomized, investigator-blind, parallel-group, vehicle-controlled studies[51]	Japan	Males with AD or Healthy Men	20-65 y	76	Not listed	Pharmacokinetic parameters	No skin irritation or photosensitzation; plasma concentrations below the limit of quantification	https://clinicaltrials.gov/ct2/show/NCT01179880
NCT02094235	Phase I/II: 2 randomized, double-blind, parallel-group, vehicle-controlled studies	Japan	Mild/Mod AD	2-15 y	62	Not listed	Pharmacokinetic parameters and AEs	None	https://clinicaltrials.gov/ct2/show/study/NCT02094235
NCT01461941	Phase II: randomized, single-blinded, parallel-group, vehicle-controlled study	Japan	AD	20-64 y	78	4 wk, 8-wk extension	Changes in pruritus and EASI score	None	https://clinicaltrials.gov/ct2/show/NCT01461941
NCT02950922	Phase II: randomized, double-blinded, parallel-group, vehicle-controlled study	United States, Canada	AD (≤25% mild)	12-70 y	157	28 d	Pharmacokinetics and safety parameters	None	https://clinicaltrials.gov/ct2/show/NCT02950922
DRM02									
NCT01993420	Phase II: randomized, double-blind, vehicle controlled study	Canada	AD	18-70 y	21	6 wk	Change in PLA	None	https://clinicaltrials.gov/ct2/show/NCT01993420
GW842470X									
NCT00356642	Phase I: randomized, single-blind, dose-rising study	Europe	AD	18-67 y	45	Single + repeat 10-d exposure	Safety and pharmacokinetics	None	https://clinicaltrials.gov/ct2/show/NCT00356642
NCT00354510	Phase II: randomized, double-blind, placebo-controlled study	Europe	Mod AD	18-65 y	190	21 d	Clinical efficacy (EASI score)	None	https://clinicaltrials.gov/ct2/show/NCT00354510
Leo-29102									
NCT01447758	Phase I: multicenter, randomized, double-blind, parallel-group, prospective study	Germany	AD	18-65 y	58	7 d or 6 wk (2 sets)	Pharmacokinetics and safety parameters	None	https://clinicaltrials.gov/ct2/show/NCT01447758
NCT01005823	Phase I: randomized, double-blind, parallel-group	Europe	AD	18-55 y	36	7 d	AEs	None	https://clinicaltrials.gov/ct2/show/NCT01005823
NCT00958516	Phase I: double-blind, single-group, vehicle-controlled study	Europe	Male adults with skin irritation on examination	18-65 y	32	5 d	Phototoxic reaction	None	https://clinicaltrials.gov/ct2/show/NCT00958516
NCT00891709	Phase I: randomized, double-blind, vehicle-controlled, parallel-group study	Europe	Healthy Men	18-55 y	64	Not listed	Safety and tolerability	None	https://clinicaltrials.gov/ct2/show/NCT00891709
NCT01423656	Phase I: randomized, single-blinded, parallel-group study	Europe	Healthy	18-55 y	102	Not listed	AEs	None	https://clinicaltrials.gov/ct2/show/NCT01423656
NCT01037881	Phase II: randomized, double-blinded, parallel-group study of treatment efficacy of Leo-29102 vs vehicle vs Elidel cream	Canada, Europe	Mild/Mod AD	18-65 y	183	4 wk	Change in EASI score	None	https://clinicaltrials.gov/ct2/show/NCT01037881
Roflumilast									
NCT01856764	Phase II: multicenter, randomized, double-blind, parallel-group, vehicle-controlled study	Europe	Mod AD	18-65 y	40	15 d	Change in Modified Local SCORAD	No significant change (d 15) in SCORAD, TEWL, pruritus; 5 reported AEs: application site pain, elevated LFT results, and nasopharyngitis	https://clinicaltrials.gov/ct2/show/NCT01856764

AD, Atopic dermatitis; *ADSI*, Atopic Dermatitis Severity Index; *AE*, adverse event; *AUC*, area under the curve; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *ISGA*, Investigator's Static Global Assessment; *LFT*, liver function test; *Mild/Mod*, mild-to-moderate; *PDE4*, phosphodiesterase; *PLA*, Physician Lesion Assessment; *SAE*, serious adverse event; *SCORAD*, SCORing Atopic Dermatitis; *TEWL*, transepidermal water loss; *TSS*, Total Sign Score.

PDE-4 Pipeline

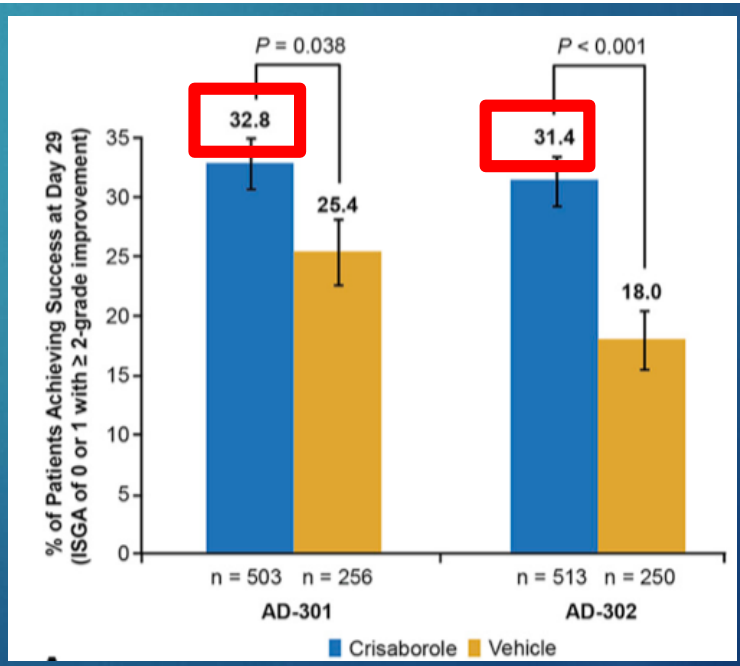
Topical Anti-Inflammatory Therapy: Crisaborole 2%

- Crisaborole 2% ointment is a phosphodiesterase-4 (PDE-4) inhibitor FDA-approved for the treatment of mild-moderate AD in patients ≥ 2yrs
- PDE-4 inhibitor ↑ intercellular cAMP→ ↓ production of proinflammatory cytokines
- Common side effect
  - stinging or burning (4.4%)

Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults

Amy S. Paller, MS, MD,[a] Wynnis L. Tom, MD,[b,c] Mark G. Lebwohl, MD,[d] Robin L. Blumenthal, PhD,[e] Mark Boguniewicz, MD,[f,g] Robert S. Call, MD,[h] Lawrence F. Eichenfield, MD,[b,c] Douglass W. Forsha, MD,[i] William C. Rees, MD,[j] Eric L. Simpson, MD,[k] Mary C. Spellman, MD,[e] Linda F. Stein Gold, MD,[l] Andrea L. Zaenglein, MD,[m] Matilda H. Hughes, CCRA,[e] Lee T. Zane, MD,[e] and Adelaide A. Hebert, MD[n]

Chicago, Illinois; San Diego, La Jolla, and Palo Alto, California; New York, New York; Denver, Colorado; Richmond and Burke, Virginia; West Jordan, Utah; Portland, Oregon; Detroit, Michigan; Hershey, Pennsylvania; and Houston, Texas



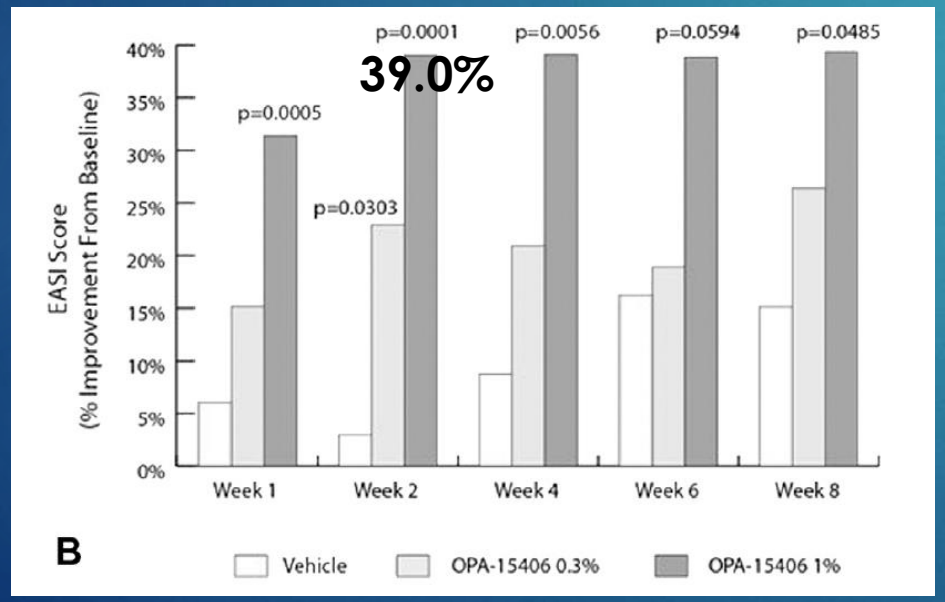
Investigator's Global Assessment (IGA)		
SCORE	**CATEGORY**	**DEFINITION**
0	Clear	No signs of inflammatory AD
1	Almost Clear	Faint, barely detectable erythema and/or trace residual elevation in limited areas; neither excoriation nor oozing/crusting are present
2	Mild	Light pink erythema and slightly perceptible elevation; excoriation, if present, is mild
3	Moderate	Dull red, clearly distinguishable erythema and clearly perceptible elevation but not extensive; excoriation or oozing/crusting, if present, are mild to moderate.
4	Severe	Deep/dark red erythema, and marked and extensive elevation; excoriation and oozing/crusting are present.

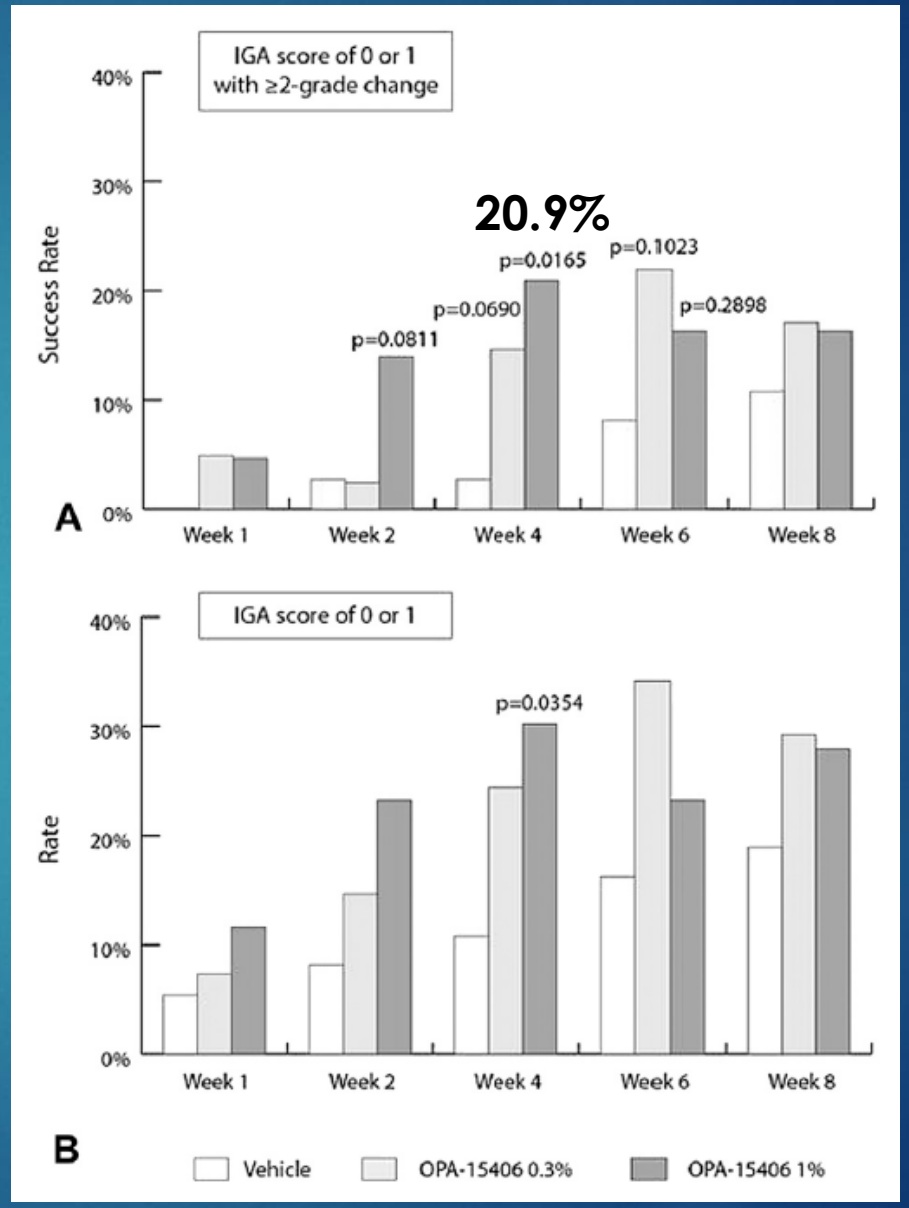
ORIGINAL ARTICLES

OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): A phase-II randomized, double-blind, placebo-controlled study

Jon M. Hanifin, MD,[a] Charles N. Ellis, MD,[b] Ilona J. Frieden, MD,[c] Regina Fölster-Holst, MD,[d] Linda F. Stein Gold, MD,[e] Angelo Secci, MD,[f] Angela J. Smith, PA,[f] Cathy Zhao, PhD,[f] Elena Kornyeyeva, MD, PhD,[f] and Lawrence F. Eichenfield, MD[g]

Portland, Oregon; Ann Arbor and Detroit, Michigan; San Francisco and San Diego, California; Kiel, Germany; and Princeton, New Jersey





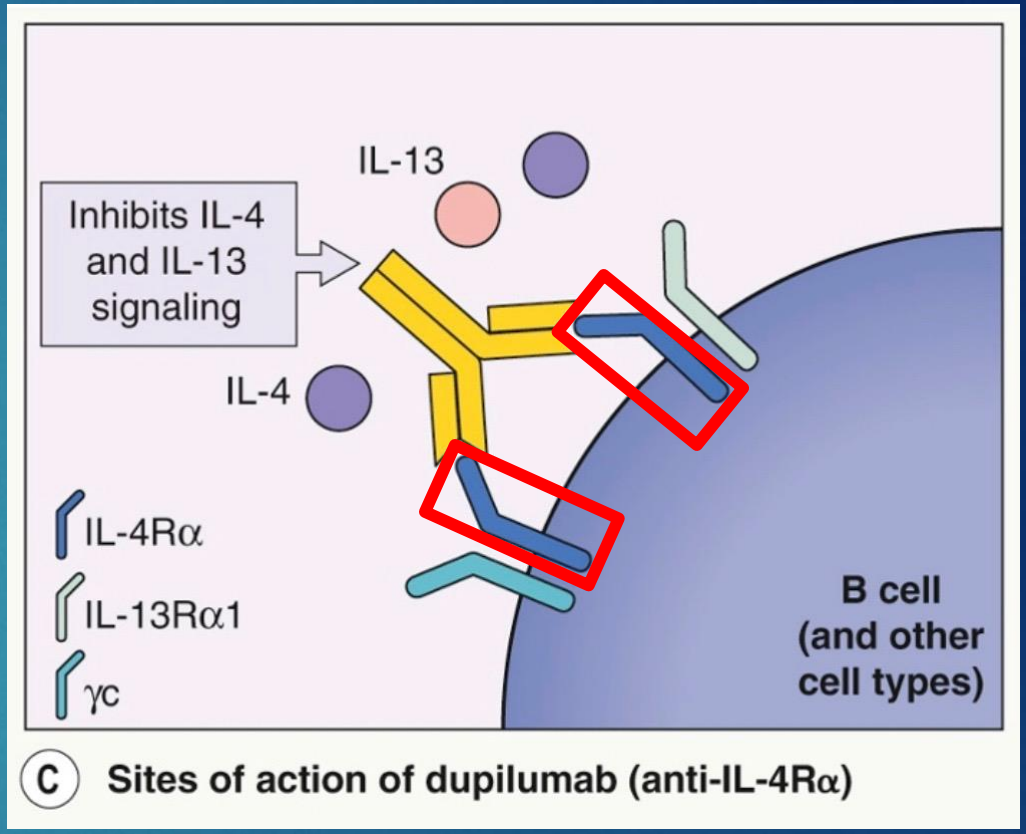
IL-4 and IL-13

Transgenetic mice with↑IL-4 in epidermis have[1]

- Atopic dermatitis-like lesions
- Pruritus
- Altered microbiome
- ↑ IgE levels

Key roles[2,3]

- IgE production
- Eosinophil recruitment
- **Th2 differentiation (activation of IL-4Ra → STAT6)**[4]
  - Dupilumab (a monoclonal antibody that targets the IL-4Ra, is FDA-approved in adults for the treatment of AD)[5]



Bolognia MD, Jean L.; Jorizzo MD, Joseph L.; Schaffer MD, Julie V.. Dermatology 4th edition, Elsevier. 2018

1. **LS Chan, N Robinson, Xu L**: Expression of interleukin-4 in the epidermis of transgenic mice results in a pruritic inflammatory skin disease: an experimental animal model to study atopic dermatitis.*J Invest Dermatol.* 117:977-983 2001 11676841
2. **Chen L, Lin SX, L Overbergh, et al.**: The disease progression in the keratin 14 IL-4-transgenic mouse model of atopic dermatitis parallels the up-regulation of B cell activation molecules, proliferation and surface and serum IgE. *Clin Exp Immunol.*142:21-30 2005 16178852
3. **GR Lee, RA Flavell**: Transgenic mice which overproduce Th2 cytokines develop spontaneous atopic dermatitis and asthma. *Int Immunol.* 16:1155-1160 2004 15226271
4. **K Shimoda, J van Deursen, MY Sangster, et al.**: Lack of IL-4-induced Th2 response and IgE class switching in mice with disrupted Stat6 gene. *Nature.* 380:630-633 1996 8602264
5. **LA Beck, D Thaçi, JD Hamilton, et al.**: Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med.*371:130-139 2014 25006719

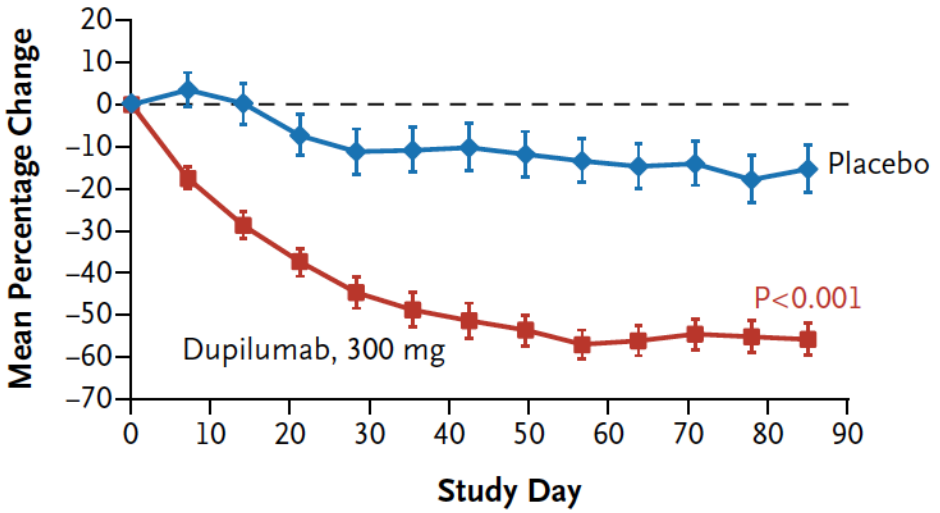
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

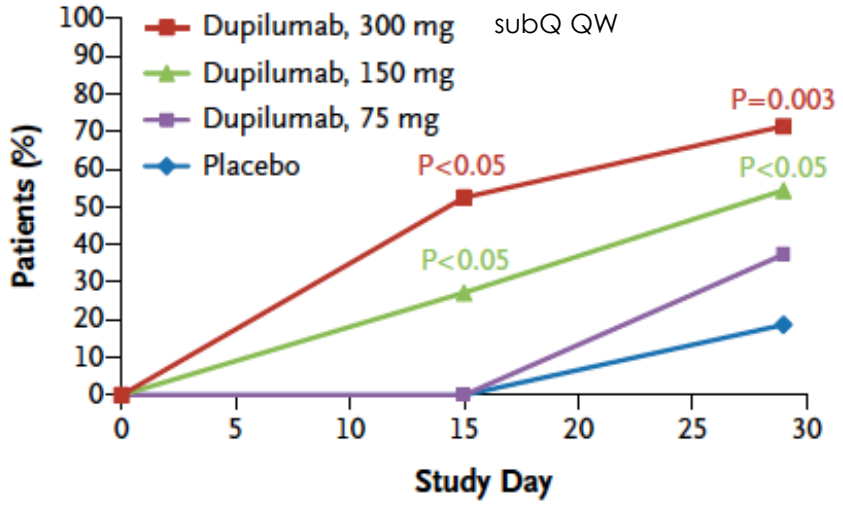
Lisa A. Beck, M.D., Diamant Thaçi, M.D., Jennifer D. Hamilton, Ph.D., Neil M. Graham, M.D., Thomas Bieber, M.D., Ph.D., M.D.R.A., Ross Rocklin, M.D., Jeffrey E. Ming, M.D., Ph.D., Haobo Ren, Ph.D., Richard Kao, Dr.P.H., Eric Simpson, M.D., Marius Ardeleanu, M.D., Steven P. Weinstein, M.D., Ph.D., Gianluca 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.

D Change in Average Weekly Pruritus Numerical-Rating Scale Score, Study M12

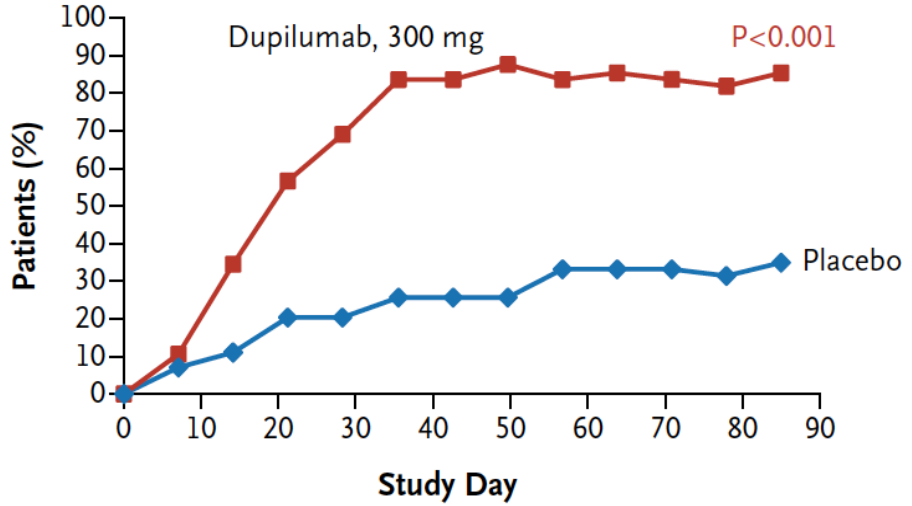


> 50%↓

A EASI-50, Studies M4A and M4B



C EASI-50, Study M12



≅ 80%

WHAT IS THE EASI?

Recording the EASI score								
Body region	Redness	Thickness	Scratching	Lichenification	Severity score	Area score	Multiplier	Region score
Head/neck	_____	+_____	+_____	+_____	=_____	X_____	X 0.1 (If ≤7 yrs, X 0.2)	=_____
Trunk	_____	+_____	+_____	+_____	=_____	X_____	X 0.3	=_____
Upper limbs	_____	+_____	+_____	+_____	=_____	X_____	X 0.2	=_____
Lower limbs	_____	+_____	+_____	+_____	=_____	X_____	X 0.4 (If ≤7 yrs, X 0.3)	=_____
The final EASI score: add up the 4 region scores								=_____ (0-72)

https://www.dermnetnz.org/topics/easi-score/

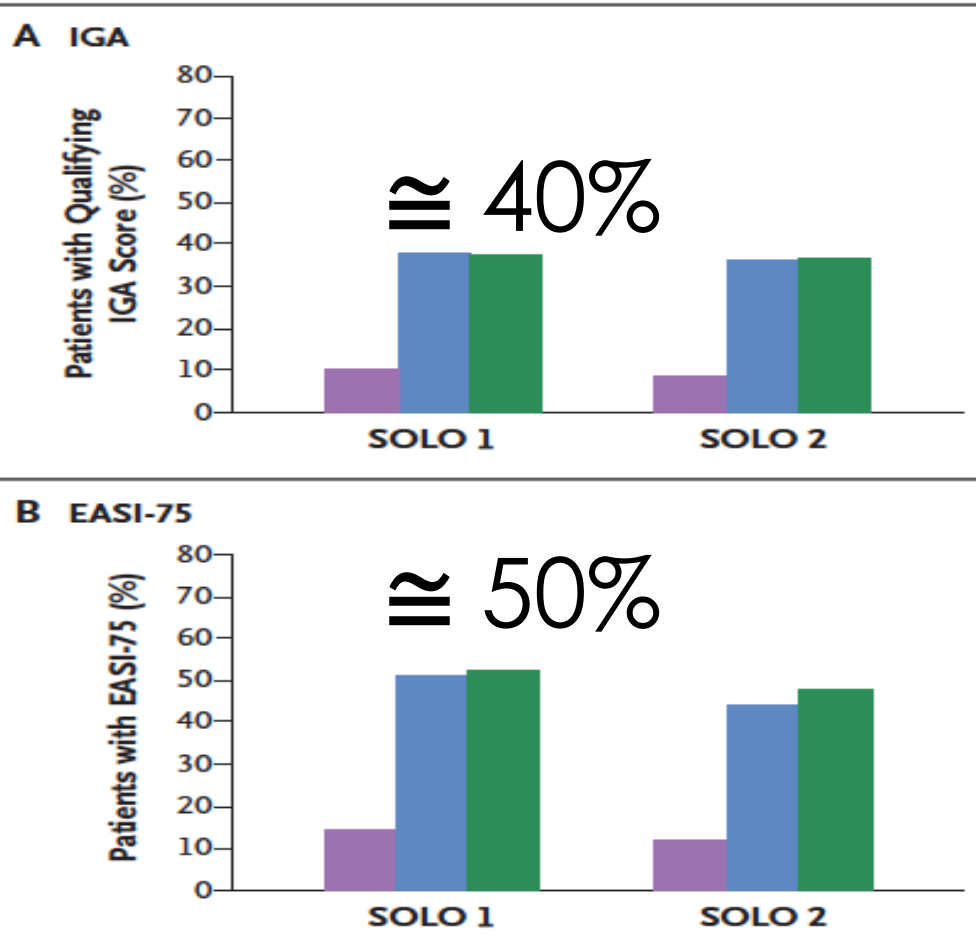
The NEW ENGLAND JOURNAL of MEDICINE

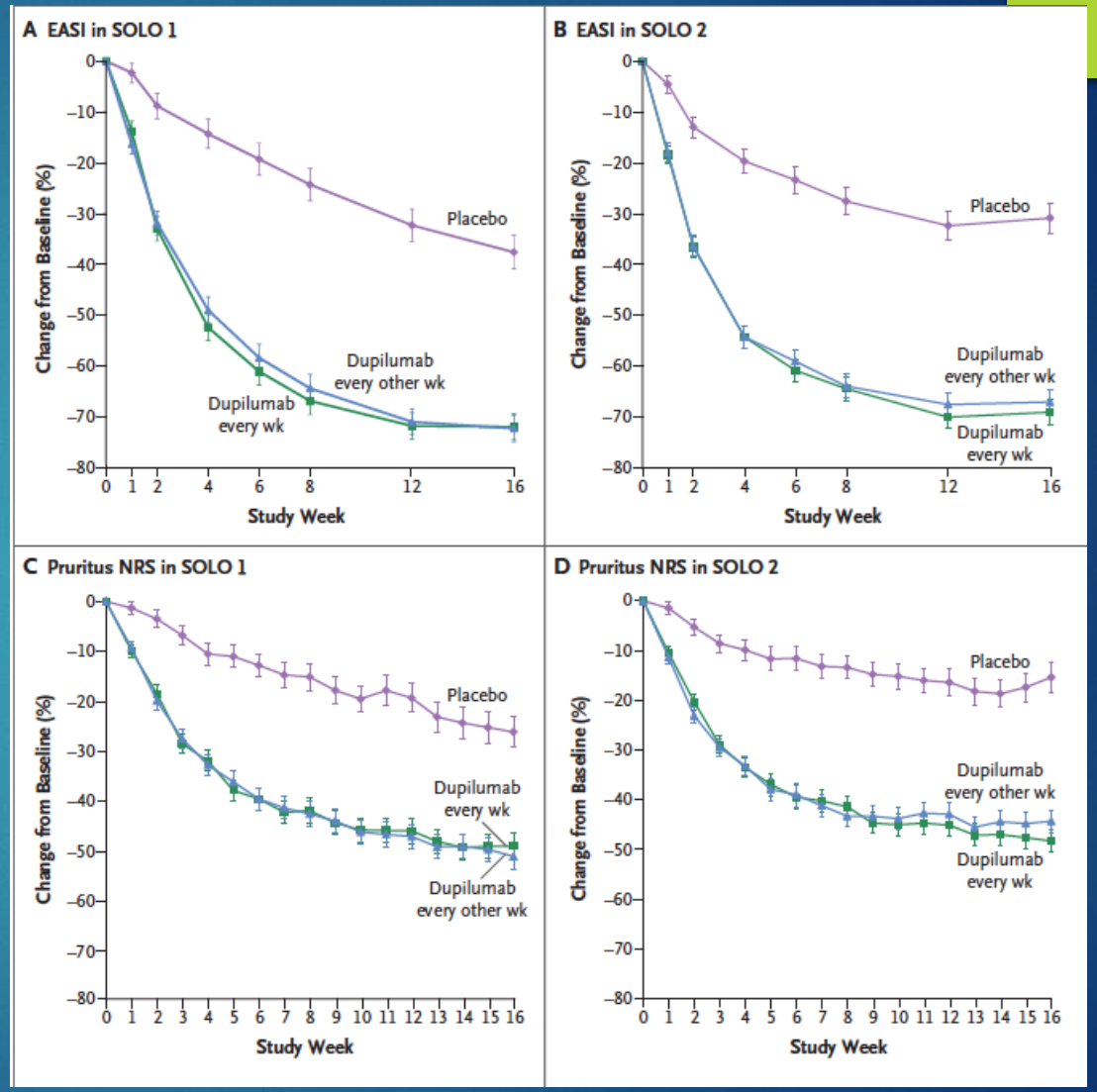
ORIGINAL ARTICLE

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis

E.L. Simpson, T. Bieber, E. Guttman-Yassky, L.A. Beck, A. Blauvelt, M.J. Cork, J.I. Silverberg, M. Deleuran, Y. Kataoka, J.-P. Lacour, K. Kingo, M. Worm, Y. Poulin, A. Wollenberg, Y. Soo, N.M.H. Graham, G. Pirozzi, B. Akinlade, H. Staudinger, V. Mastey, L. Eckert, A. Gadkari, N. Stahl, G.D. Yancopoulos, and M. Ardeleanu, for the SOLO 1 and SOLO 2 Investigators*

Placebo | Dupilumab every other wk | Dupilumab every wk

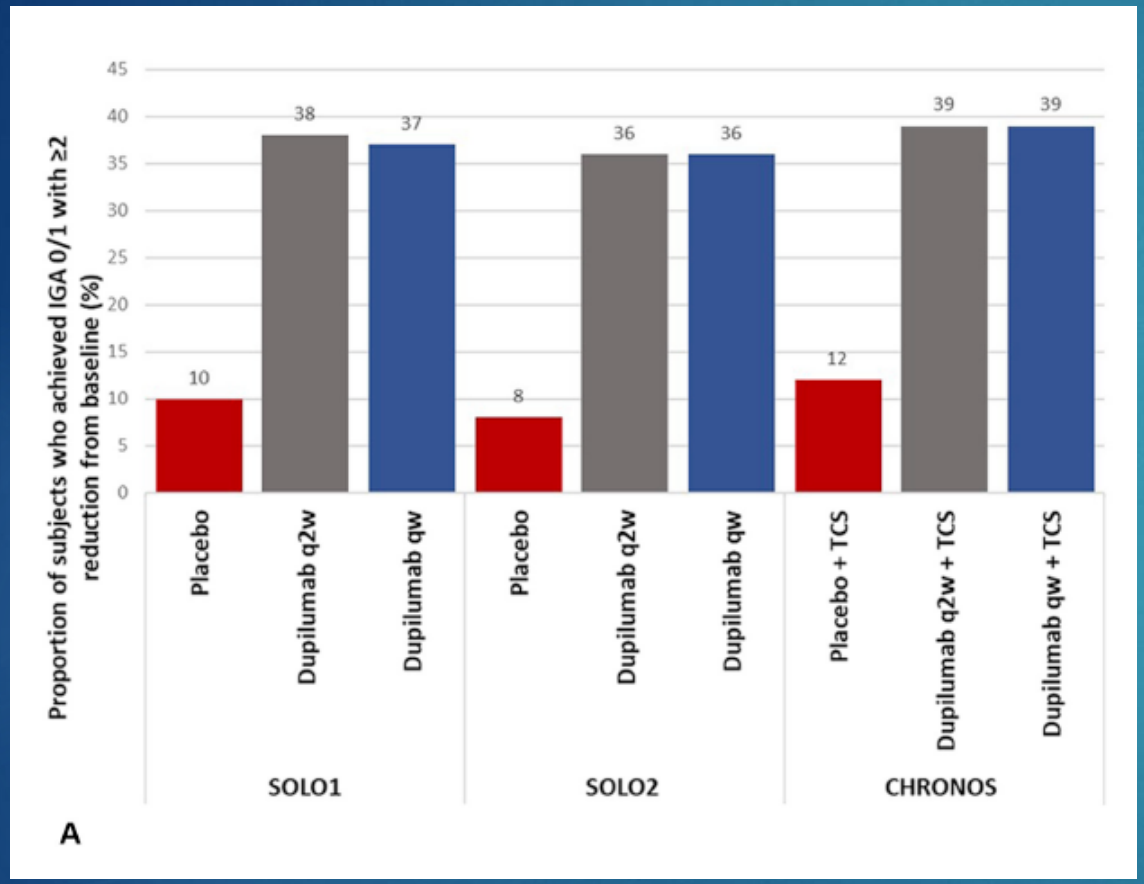


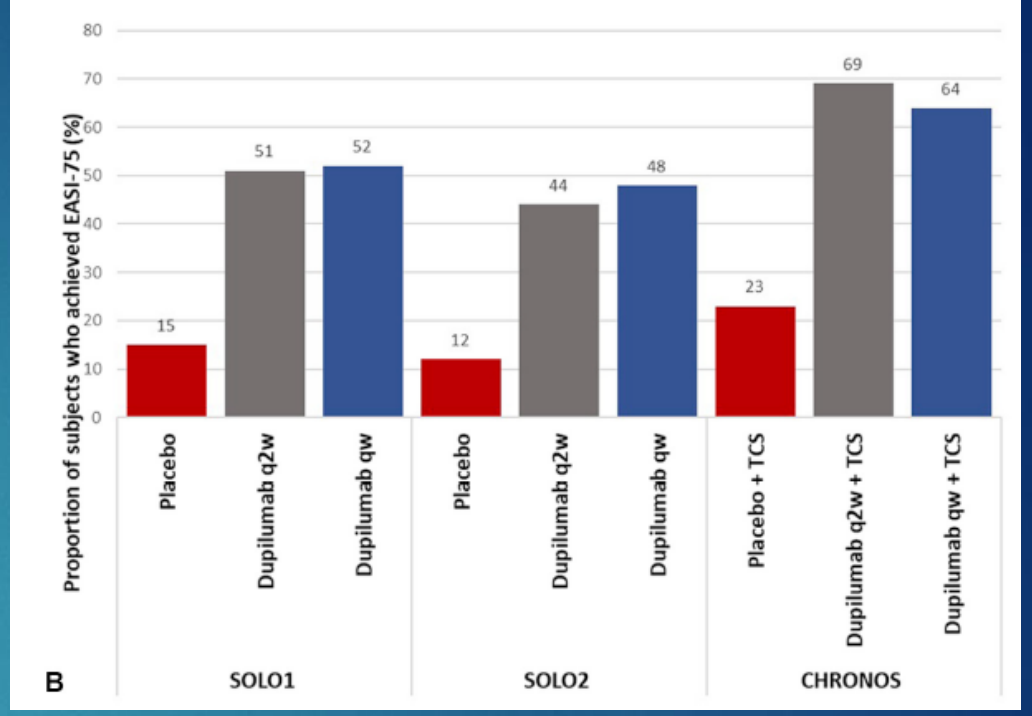


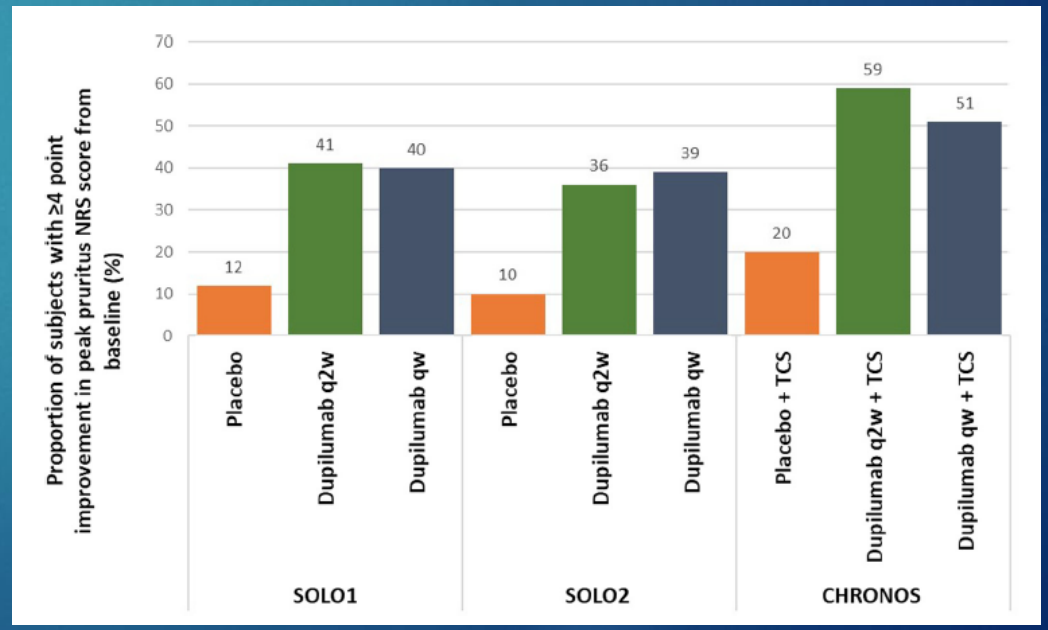
QOW = QW

Dupilumab: A review of its use in the treatment of atopic dermatitis

Melinda J. Gooderham, MD, MSc, FRCPC,[a,b,c] H. Chih-ho Hong, MD, FRCPC,[b,d] Panteha Eshtiaghi, HBSc,[e] and Kim A. Papp, MD, PhD, FRCPC[b]
Peterborough, Waterloo, and Kingston, Ontario, and Vancouver, British Columbia, Canada







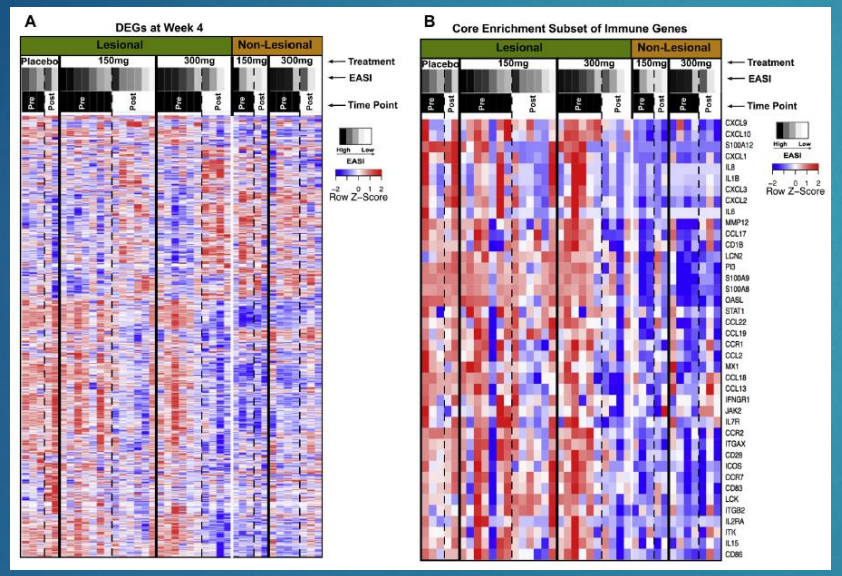
Dosing: 600 mg (SubQ) initially; then 300 mg QOW
Main Side Effects:

- **Injection site reactions** 10-20% vs Placebo 7-8%
- **Conjunctivitis** 7-12% vs Placebo 2%

Atopic dermatitis and skin disease

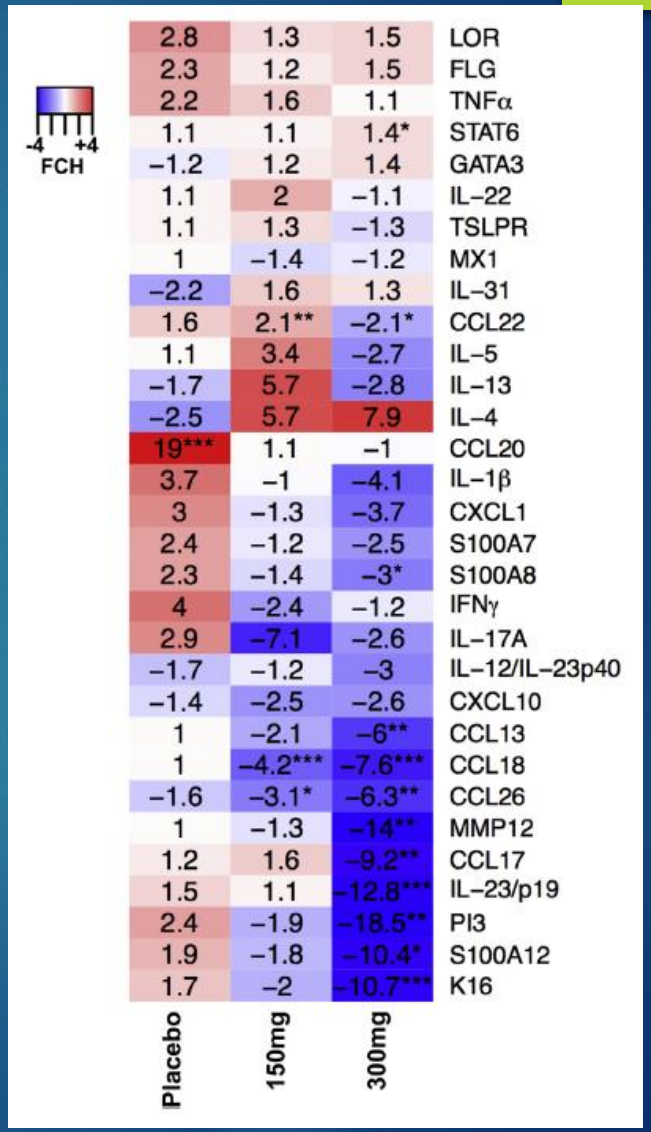
Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis

Jennifer D. Hamilton, PhD,[a]* Mayte Suárez-Fariñas, PhD,[b]* Nikhil Dhingra, BS,[b] Irma Cardinale, MSc,[b] Xuan Li, PhD,[b] Ana Kostic, PhD,[a] Jeffrey E. Ming, MD, PhD,[c] Allen R. Radin, MD,[a] James G. Krueger, MD,[b] Neil Graham, MD,[a] George D. Yancopoulos, MD, PhD,[a] Gianluca Pirozzi, MD, PhD,[c] and Emma Guttman-Yassky, MD, PhD[b,d] *Tarrytown and New York, NY, and Bridgewater, NJ*



- Gene expression profiles of inflammatory genes at baseline vs. after dupilumab therapy
- **Inflammatory genes strongly downregulated after dupilumab therapy**

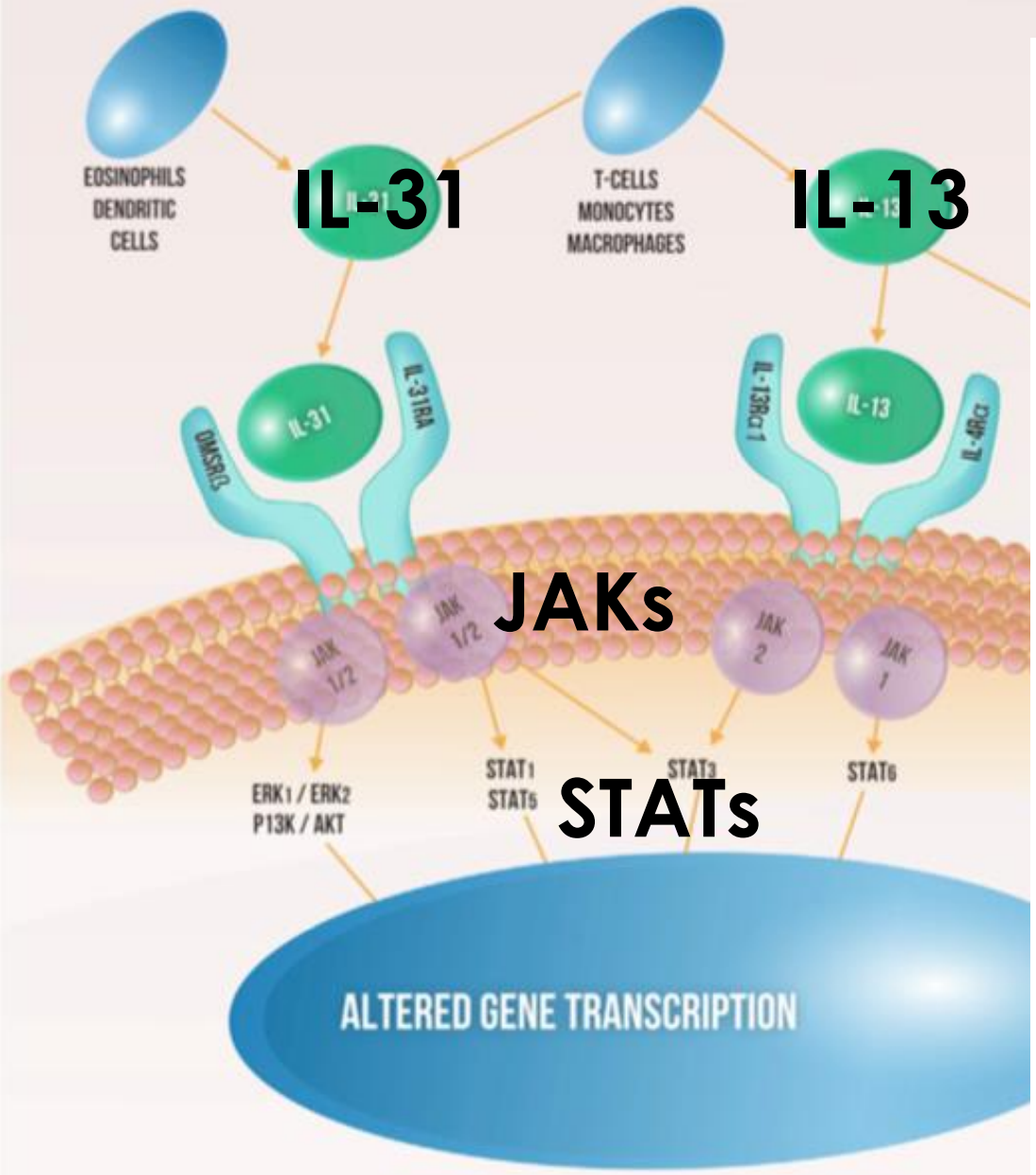
Red → Blue Transition



Dupilumab Trials for Children

- Efficacy and Safety of **Dupilumab** in Patients ≥12 to <18 Years of Age, With Moderate-to-Severe Atopic Dermatitis
- Safety, Pharmacokinetics and Efficacy of **Dupilumab** in Patients ≥6 Months to <6 Years With Severe Atopic Dermatitis (Liberty AD PRESCHOOL)
- Study to Investigate the Efficacy and Safety of **Dupilumab** Administered With Topical Corticosteroids (TCS) in Participants ≥6 to <12 Years With Severe Atopic Dermatitis (AD)

OTHER TARGETS IN THE PIPELINE?



Monoclonal antibodies against interleukin 13 and interleukin 31RA in development for atopic dermatitis

Carsten R. Hamann, MD, and Jacob P. Thyssen, MD, PhD, DMSc
Hellerup, Denmark

Table I. Monoclonal antibodies against IL-13 and IL-31RA in development

Trade name	Target	Trial	Patient population	Results
Tralokinumab	IL-13	Placebo-controlled 12-week phase 2B trial[7]	204 patients with moderate-to-severe AD	Significant reductions in EASI scores, increased % of patients achieving a IGA of 0-1, decreased pruritus
Lebrikizumab	IL-13	Placebo-controlled 12-week phase 2B trial (TREBLE)[8]	209 patients with moderate-to-severe AD	Significant reductions in EASI and SCORAD scores
Nemolizumab	IL-31RA	Placebo controlled 12-week phase 2 trial[9]	264 patients with moderate-to-severe AD	Significant reductions in pruritus and EASI scores, improvement in DLQI and sleep quality
BMS-981164	IL-31	Placebo controlled, 16-week phase 1 trial[10]	Healthy subjects and patients with moderate-to-severe AD	Not published

TRALOKINUMAB:IL-13 Ab

NIH U.S. National Library of Medicine
ClinicalTrials.gov

NCT02347176, NCT03131648, NCT03160885, NCT03363854

	Placebo	Tralokinumab Dose 1	Tralokinumab Dose 2	Tralokinumab Dose 3
Participants Analyzed [Units: Participants]	41	45	47	48
Percentage of Participants Achieving 50 Percent (%) Reduction From Baseline in Eczema Area and Severity Index (EASI) at Week 12 [Units: Percentage of participant]	61.0	64.4	72.3	75.0

EASI-50

Monoclonal antibodies against interleukin 13 and interleukin 31RA in development for atopic dermatitis

Carsten R. Hamann, MD, and Jacob P. Thyssen, MD, PhD, DMSc
Hellerup, Denmark

- **EASI scores** at baseline (**24.8 to 27.3**)
- After 2 week period TCS, 300 mg of tralokinumab vs. placebo given QOW
- The aEASI scores from baseline
  - **-15.7 (tralokinumab)**
  - -10.8 (placebo) (***P* = .011**)[7]

LEBRIKIZUMAB: IL-13 Ab

ELSEVIER

Journal of the American Academy of Dermatology

Available online 17 January 2018

In Press, Accepted Manuscript

Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE)

Data from this study have been presented at the European Academy of Dermatology and Venereology in Vienna, Austria on October 1st, 2016.

Eric L. Simpson MD [a, *], Carsten Flohr MD, PhD [b, *], Lawrence F. Eichenfield MD [c], Thomas Bieber MD, PhD, MDRA [d], Howard Sofen MD [e], Alain Taïeb MD [f], Ryan Owen PhD [g], Wendy Putnam PhD [g], Marcela Castro MD [g], Kendra DeBusk PhD [g], Chin-Yu Lin PhD [g], Athina Voulgari PhD [h], Karl Yen MD [i], Theodore A. Omachi MD [g]

Show more

https://doi.org/10.1016/j.jaad.2018.01.017

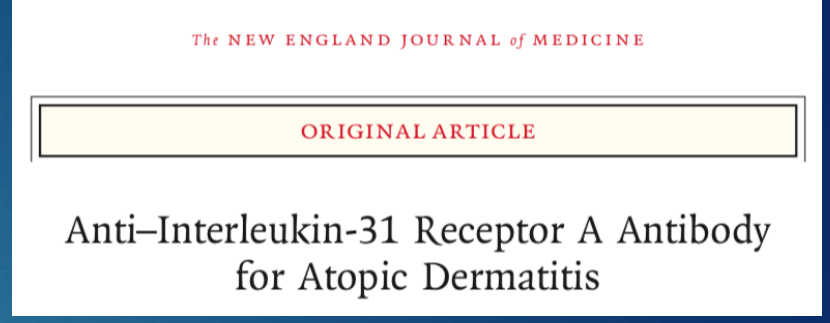
Results

- 209 patients received study drug
- At Week 12, significantly more patients achieved **EASI-50** with lebrikizumab 125 mg Q4W (**82.4%; p=0.026**) versus placebo (62.3%)

Conclusion

Lebrikizumab 125 mg Q4W led to significant improvement in patients with moderate-to-severe AD, when added to TCS, and was well tolerated.

NEMOLIZUMAB: IL-31RA Ab

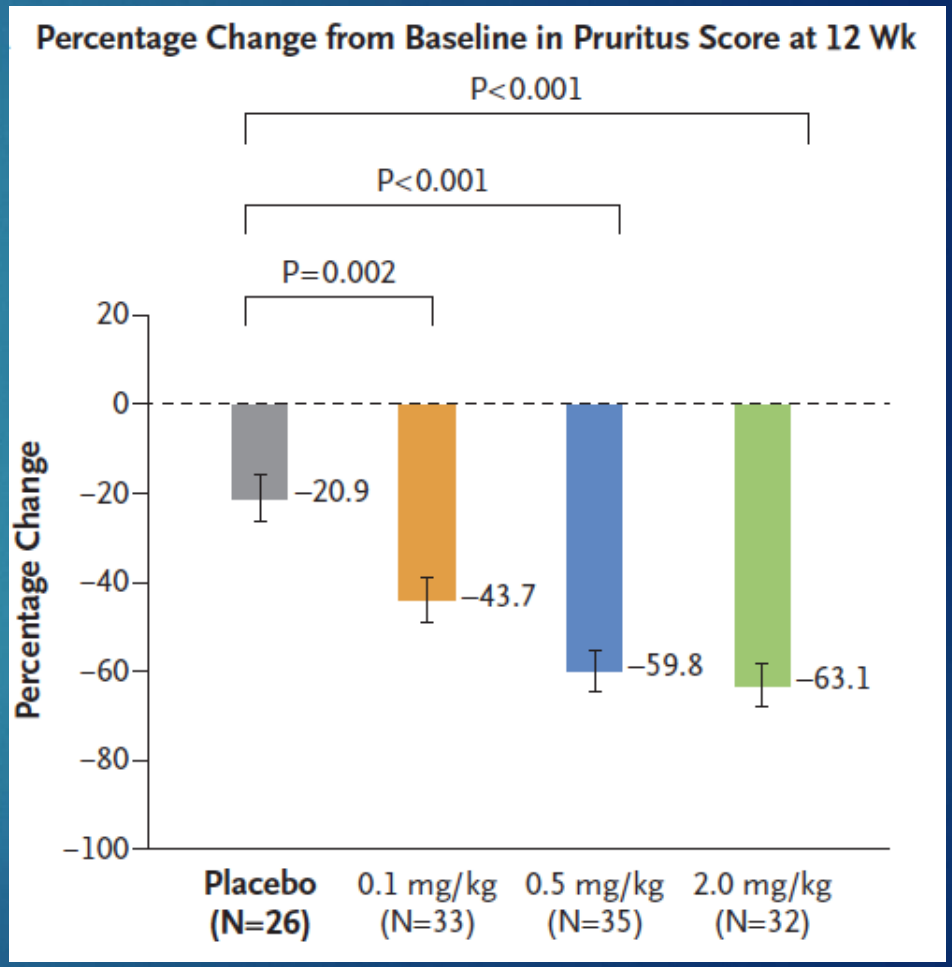


What we know about IL-31

- Th2 cytokine highly expressed in lesions of AD
- Staphylococcal superantigen rapidly induces IL-31 expression in AD pts
- IL-31R is expressed by keratinocytes, eosinophils, activated macrophages, cutaneous C nerve fibers, and dorsal root ganglia[1,2]
- Establishing a link between *S. Aureus* and pruritus

Nemolizumab (Phase 2, RCT)

- A humanized monoclonal antibody against the IL-31RA which significantly reduces pruritus in pts with moderate to severe AD[3]
- **EASI score reduction** from baseline was
  - −23.0±7.5% with 0.1 mg per kilogram
  - **−42.3±7.3%** with 0.5 mg per kilogram,
  - −40.9±7.5% with 2.0 mg per kilogram
  - **−26.6±8.1%** with placebo[3]



1. **MM Neis, B Peters, A Dreuw, et al.**: Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. *J Allergy Clin Immunol.* 118:930-937 2006 17030248
2. **SR Dillon, C Sprecher, A Hammond, et al.**: Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice.*Nat Immunol.* 5:752-760 2004 15184896
3. **T Ruzicka, JM Hanifin, M Furue, et al.**: XCIMA Study Group. Anti-interleukin-31 receptor a antibody for atopic dermatitis. *N Engl J Med.* 376:826-835 2017 28249150

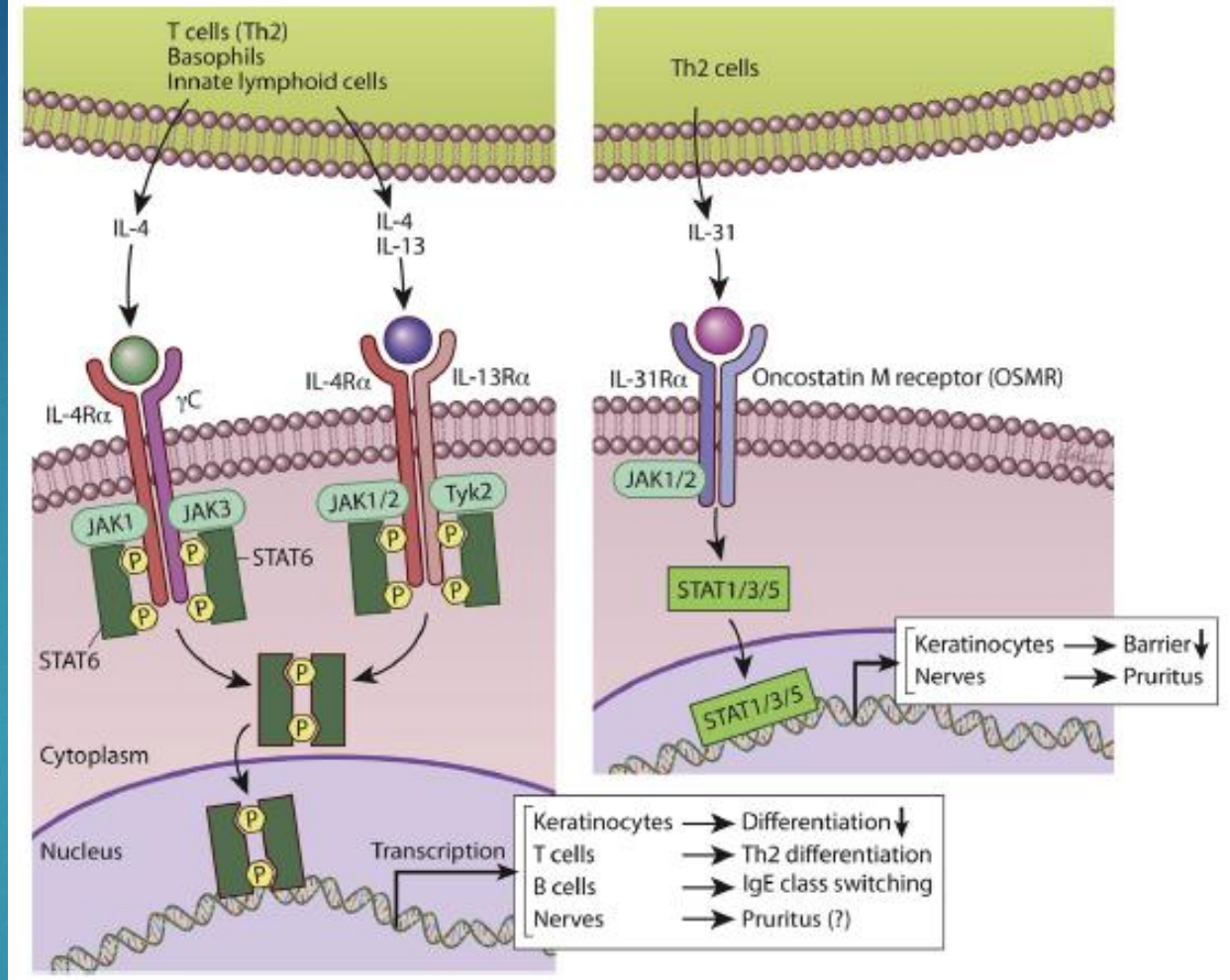
Emerging therapies for atopic dermatitis: JAK inhibitors

David G. Cotter, MD, PhD, David Schairer, MD, and Lawrence Eichenfield, MD
San Diego, California

Table I. Investigational JAK inhibitors for atopic dermatitis

Drug	Company	Formulation	Target	Enrollment	Phase	Primary outcome	Title	ClinicalTrials.gov identifier*	Status
Baricitinib (LY3009104)	Eli Lilly	Oral	JAK1, JAK2	124 adults	2	Proportion of patients with EASI score of 50 at wk 16	A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Evaluate the Safety and Efficacy of Baricitinib in Patients with Moderate-to-Severe Atopic Dermatitis	NCT02576938	Completed
Baricitinib								**completed**	
PF-04965842	Pfizer	Oral	JAK1	268 adults	2	Proportion of patients achieving IGA score for clear or almost clear and >2-point improvement from baseline at wk 12	A Phase 2b Randomized, Double-Blind, Placebo-controlled, Parallel, Multicenter, Dose-Ranging, Study to Evaluate the Efficacy and Safety Profile of PF-04965842 in Subjects with Moderate-to-Severe Atopic Dermatitis	NCT02780167	Completed
PF-04965842 200mg PO Daily						44% IGA 0 or 1		**completed**	
ABT-494 (upadacitinib)	Abbvie	Oral	JAK1	167 adults	2	Mean percentage change in EASI score at wk 16 (study length is 88 wk)	A Phase 2b Multicenter, Randomized, Placebo-Controlled, Double-Blind Dose-Ranging Study to Evaluate ABT-494 (Upadacitinib) in Adult Subjects with Moderate-to-Severe Atopic Dermatitis	NCT02925117	Active
Upadacitinib 30mg PO Daily						50% IGA 0 or 1			
INCB018424 (ruxolitinib in phosphate cream)	Incyte	Topical	JAK1, JAK2	20 pediatric patients (age 12-17 y)	1	Participants with treatment-emergent adverse events (secondary outcome: plasma concentrations of INCB018424 on d 1, d 15, and d 29)	An Open-Label, Pilot Pharmacokinetic Study of INCB018424 Phosphate Cream in Pediatric Subjects with Atopic Dermatitis	NCT03257644	Recruiting
Ruxolitinib									
INCB018424 (ruxolitinib in phosphate cream)	Incyte	Topical	JAK1, JAK2	300 adults	2	Mean percentage change from baseline in EASI score at wk 4 in subjects treated with 1.5% INCB018424 bid compared with subjects treated with vehicle cream bid	A Phase 2, Randomized, Dose-Ranging, Vehicle-Controlled and Triamcinolone 0.1% Cream-Controlled Study to Evaluate the Safety and Efficacy of INCB018424 Phosphate Cream Applied Topically to Adults with Atopic Dermatitis	NCT03011892	Recruiting
Ruxolitinib									
JTE-052/ LEO124249	Pharmaceutical Division, Japan Tobacco Inc/LEO Pharma	Topical	JAK1, JAK2, JAK3, and TYK2	327 adults	2	Change in m-EASI score at wk 4	Efficacy and Safety of Topical JTE-052, a Janus Kinase Inhibitor, in Japanese Adult Patients with Moderate-to-Severe Atopic Dermatitis: A Phase 2, Multicentre, Randomised, Vehicle-Controlled Clinical Study	JapicCTI-152887	Completed
JTE-052								**completed**	

bid, Twice daily; *EASI*, Eczema Area and Severity Index; *IGA*, Investigator's Global Assessment; *JAK*, Janus kinase; *m-EASI*, modified Eczema Area and Severity Index; *TYK2*, tyrosine kinase 2.
*JTE-052 is a Japanese study.

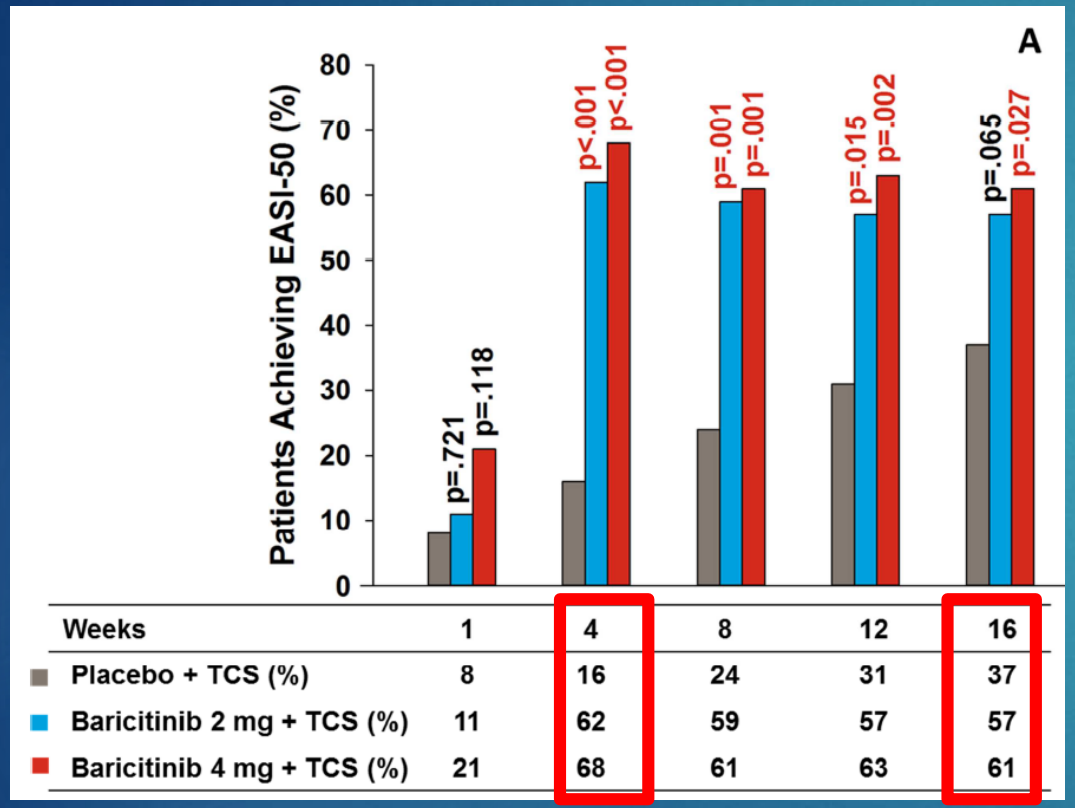


Janus Kinase–Signal Transducer and Activator of Transcription (JAK-STAT) pathway is an intracellular signaling pathway in which many different proinflammatory cytokines (eg, IL-4, IL-5, IL-13, and IL-31) elicit their pathophysiologic functions[1]

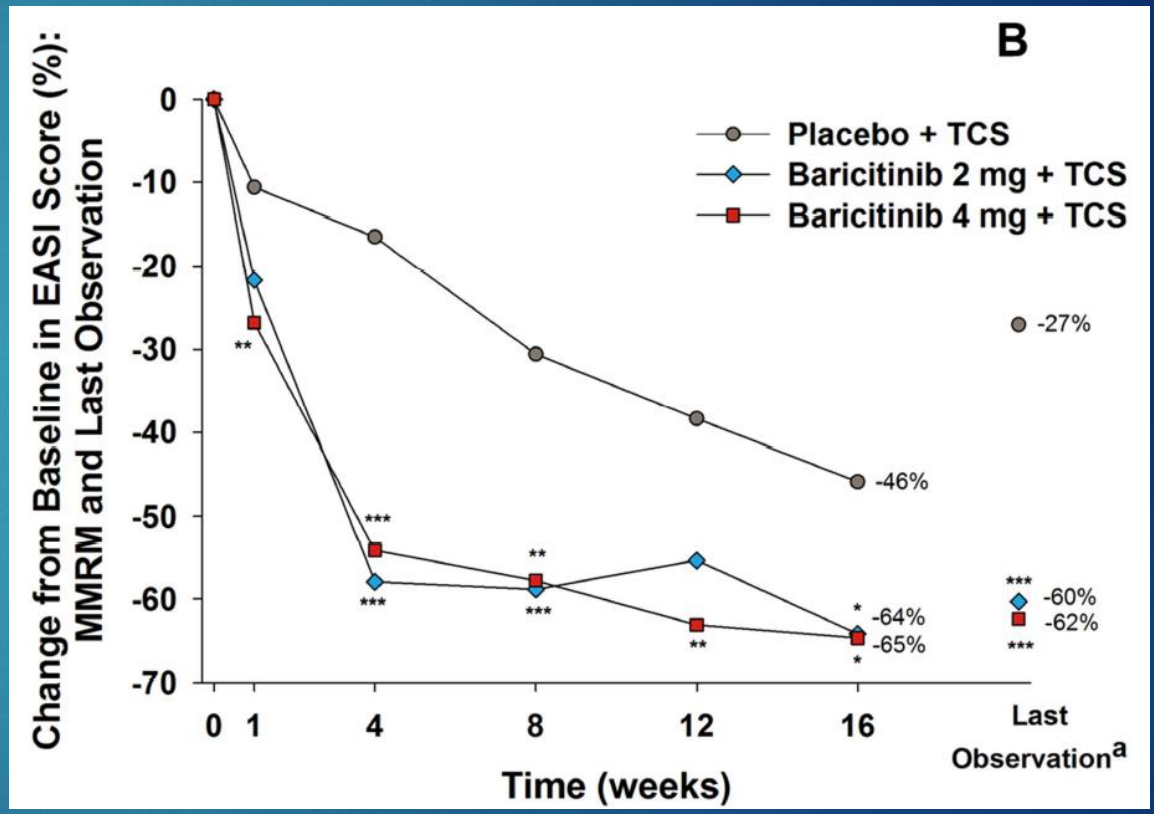
Paller AS, Kabashima K, Bieber T. Therapeutic pipeline for atopic dermatitis: End of the drought? J Allergy Clin Immunol. 2017 Sep;140(3):633-643

1. Villarino AV, Kanno Y, O'Shea JJ. Mechanisms and consequences of Jak-STAT signaling in the immune system. Nat Immunol 2017;18:374-84.

Baricitinib: Percentage of patients achieving EASI-50 (A) and percentage change from baseline in EASI score (B)



Weeks	1	4	8	12	16
Placebo + TCS (%)	8	16	24	31	37
Baricitinib 2 mg + TCS (%)	11	62	59	57	57
Baricitinib 4 mg + TCS (%)	21	68	61	63	61



Guttman-Yassky E et al. Baricitinib in adult patients with moderate-to-severe atopicdermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlledmultiple-dose study. J Am Acad Dermatol. 2018 Feb 1. pii: S0190-9622(18)30129-4. doi: 10.1016/j.jaad.2018.01.018. [Epub ahead of print] PubMed PMID: 29410014.

CLINICAL TRIAL

BJD
British Journal of Dermatolo

Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study*

H. Nakagawa,[1] O. Nemoto,[2] A. Igarashi[3] and T. Nagata[4]

[1]Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan
[2]Kojinkai Sapporo Skin Clinic, Hokkaido, Japan
[3]Division of Dermatology, NTT Medical Center Tokyo, Tokyo, Japan
[4]Pharmaceutical Division, Japan Tobacco Inc., 4-1, Nihonbashi-Honcho 3-chome, Chuo-ku, Tokyo, Japan

Linked Comment: Bissonnette. *Br J Dermatol* 2018; **178**:321.

Summary

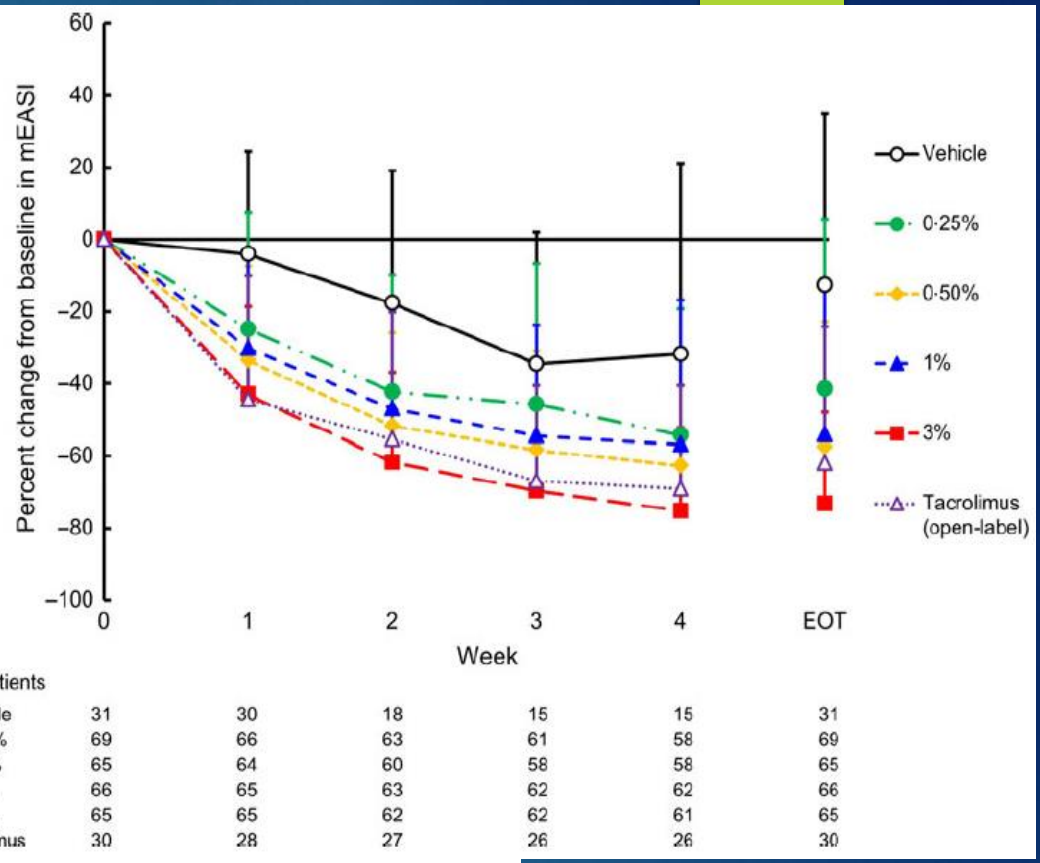
Background JTE-052 is a novel Janus kinase inhibitor presently under clinical development for the topical treatment of atopic dermatitis (AD).

Objectives To evaluate the efficacy and safety of JTE-052 ointment in Japanese adult patients with AD.

Methods Patients with moderate-to-severe AD were randomized (2: 2: 2: 2: 1: 1) to receive JTE-052 ointment at 0·25%, 0·5%, 1% or 3%, the vehicle ointment or tacrolimus 0·1% ointment (reference) twice daily for 4 weeks. The primary efficacy end point was the percentage change in modified Eczema Area Severity Index (mEASI) score from baseline at the end of treatment (EOT). Secondary efficacy end points included change from baseline in the pruritus numerical rating scale (NRS) score.

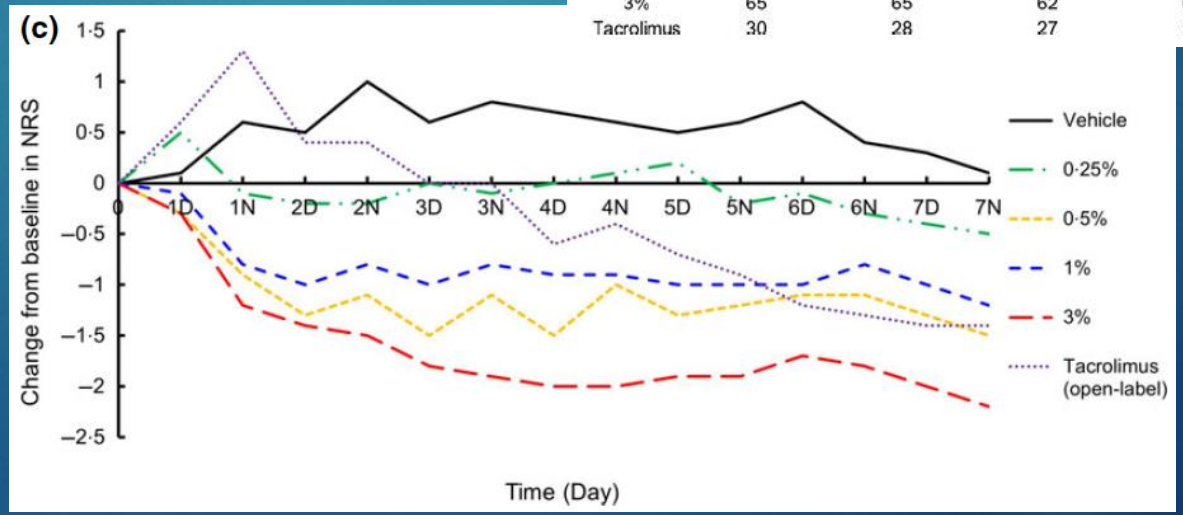
Results In total, 327 patients were enrolled. At EOT, the least-squares mean percentage changes from baseline in mEASI score for JTE-052 at 0·25%, 0·5%, 1% and 3% and the vehicle ointment were −41·7%, −57·1%, −54·9%, −72·9% and −12·2%, respectively. All JTE-052 groups showed significant reductions of mEASI score vs. the vehicle group ($P < 0·001$ for all). In the tacrolimus group, the mean percentage change in mEASI score was −62·0%. The JTE-052 groups also showed significant improvement in other parameters; notably, the pruritus NRS score was reduced as early as day 1 night-time. JTE-052 ointment at doses up to 3% was safe and well tolerated.

Conclusions Topical JTE-052 markedly and rapidly improved clinical signs and symptoms in Japanese adult patients with moderate-to-severe AD, with a favourable safety profile. The study results indicate that topical JTE-052 is a promising therapeutic option for AD. The trial registration number is JapicCTI-152887.



No. of patients

Vehicle	31	30	18	15	15	31
0·25%	69	66	63	61	58	69
0·5%	65	64	60	58	58	65
1%	66	65	63	62	62	66
3%	65	65	62	62	61	65
Tacrolimus	30	28	27	26	26	30



T-cell inhibitors for atopic dermatitis

W. James Tidwell, MD,[a,b] and Joseph F. Fowler, Jr, MD[b]
La Jolla, California, and Louisville, Kentucky

Mechanism of Action Pathway

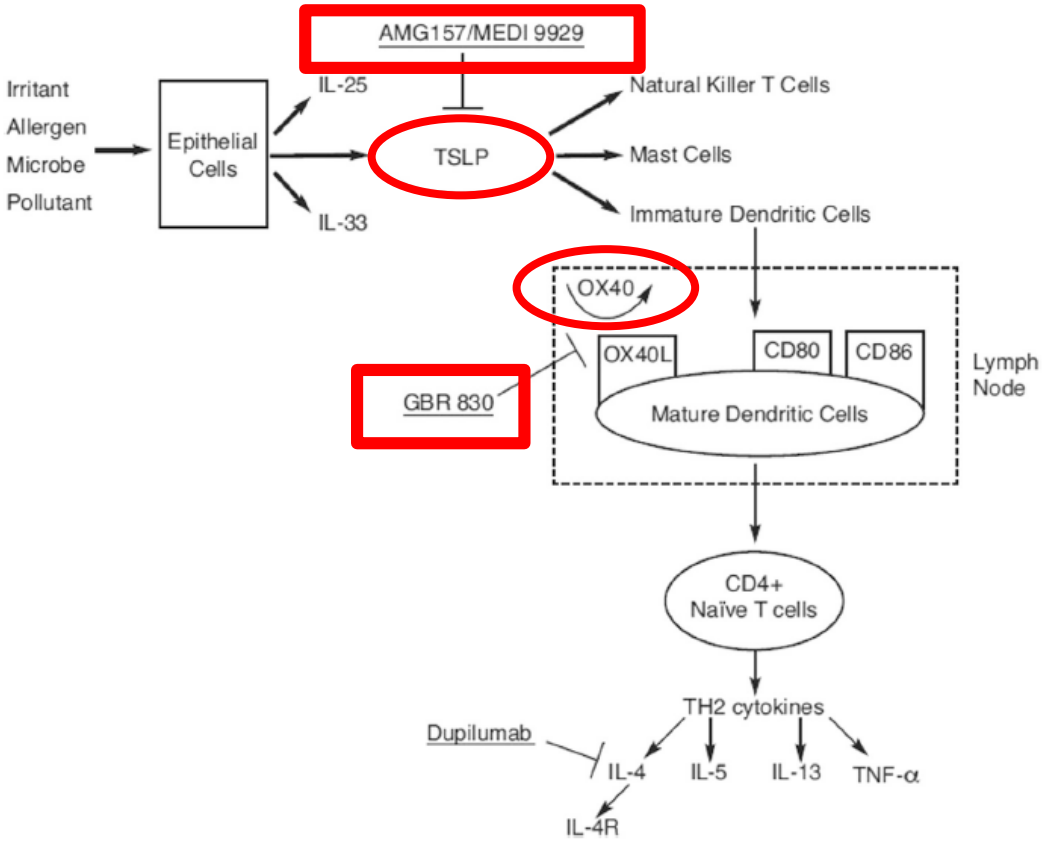


Fig 1. Mechanism of action for thymic stromal lymphopoietin (TSLP) and OX40 in inducing a T helper 2 (Th2) cytokine inflammatory response related to the development of atopic dermatitis.

Table I. Summary of T-cell inhibition drugs AMG157-MEDI9929 and GBR 830

Drug	Target	Name of antibody	Phase of development
AMG157/MEDI9929	TSLP	Tezepelumab	Phase 2
GBR 830	OX40	Not yet named	Phase 2

TSLP is highly expressed in acute and chronic lesions of AD, but not in the nonlesional skin of patients with AD or in unaffected individuals[1]

OX40 is a member of the TNF receptor superfamily. TSLP-activated dendritic cells express OX40L and are activated in the lymph nodes by OX40 → Th2 inflammatory cytokine production

1. **SF Ziegler, D Artis**: Sensing the outside world: TSLP regulates barrier immunity. *Nat Immunol.* 11:289-293 2010 20300138

THE FUTURE IS BRIGHT

THANK YOU!

Alopecia Areata
A brief review and up-to-date information on treatment

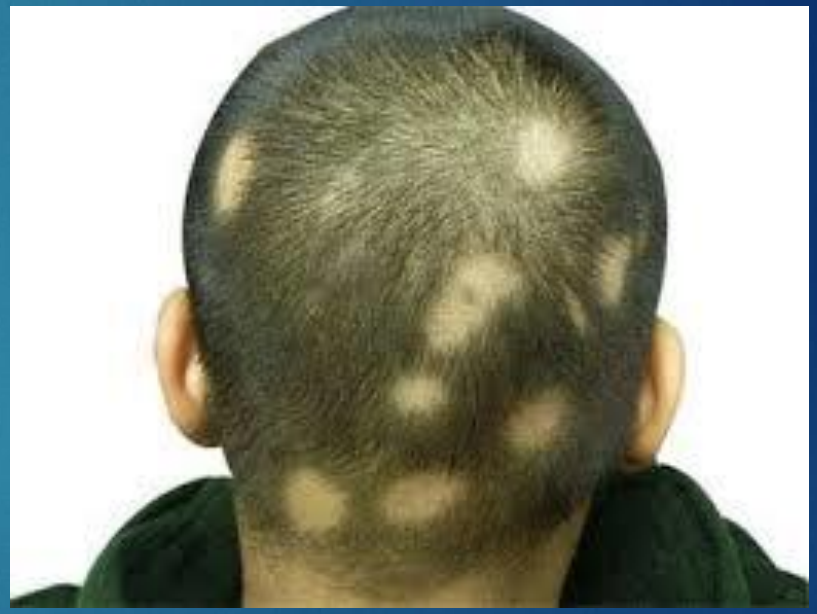
NADY HIN, DO, PGY-3

DR. BRAD GLICK, DO, MPH, FAOCD, FAAD

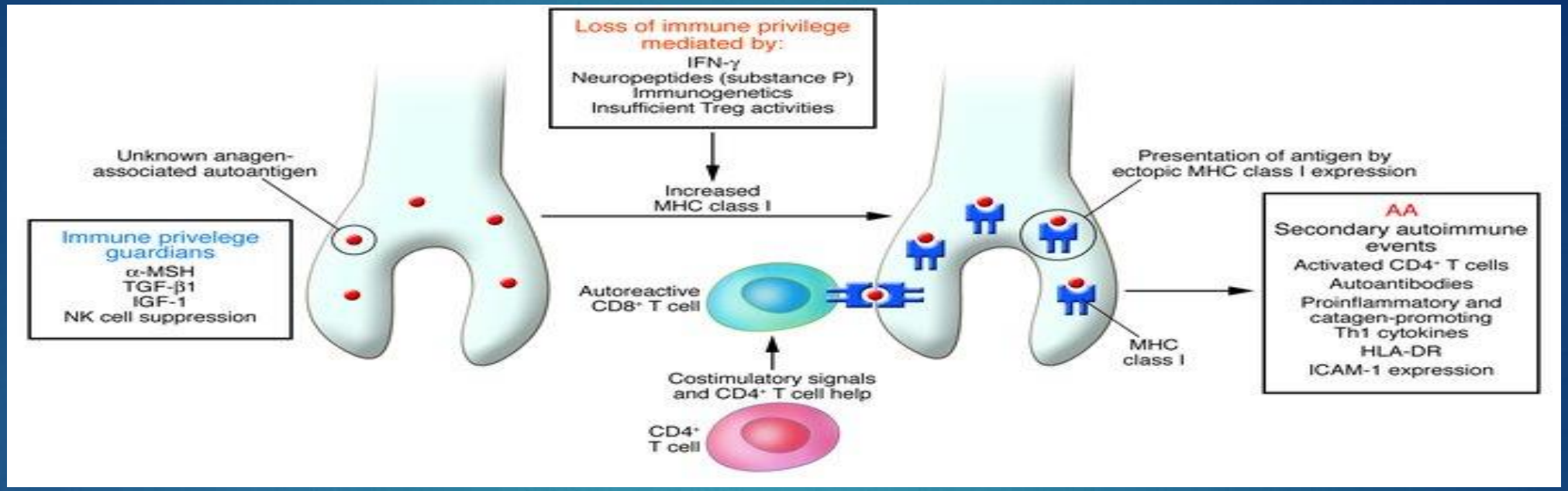
LARKIN COMMUNITY HOSPITAL PALM SPRINGS CAMPUS – LECOMT/OPTI

Introduction – Alopecia Areata

- **Non-scarring** hair loss
- **Third** most common form of hair loss
  - 0.1-0.2% of US
  - Average lifetime risk of 1.7-2.1%
- Males = Females
- Onset: Mean Age 30
  - 60% present by age 20
- Spontaneous resolution rates : 8-68%
  - Tosti et Al(2006)
    - **2/3 with <25% scalp involvement** had complete resolution for mean of 17 yrs w/o tx
    - **34.6% of 51-75% hair loss recovered** or developed milder disease w/o tx



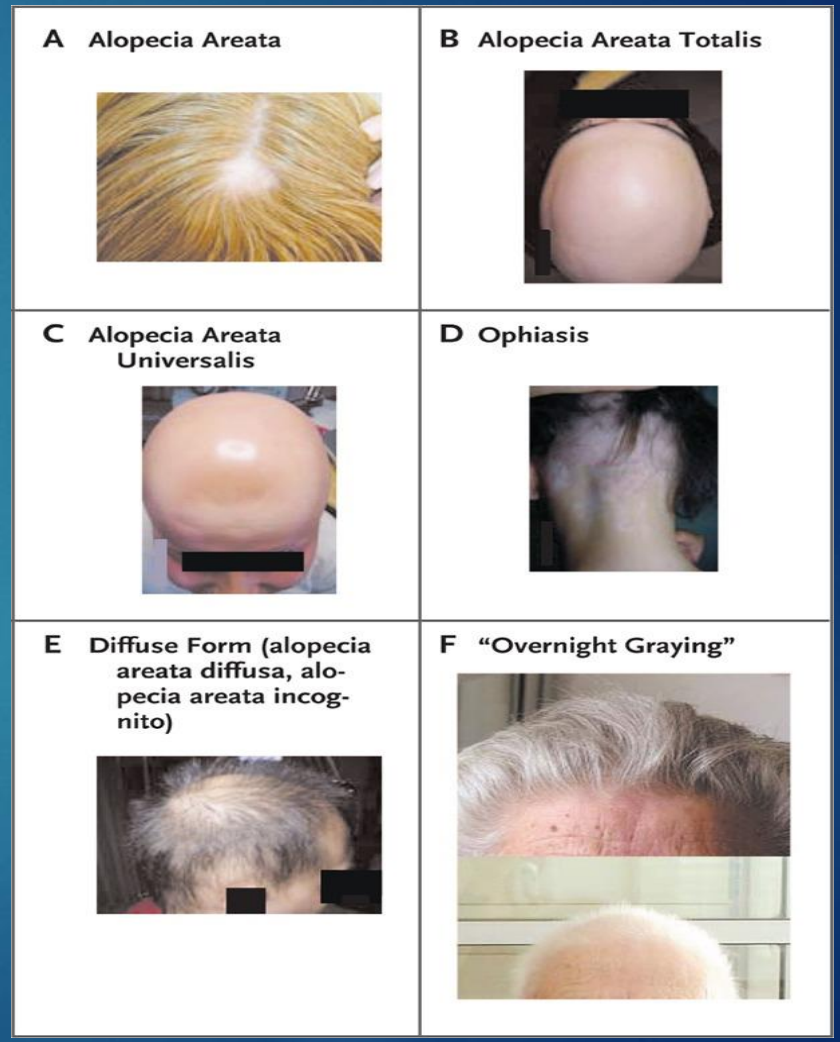
Pathogenesis



- Likely Autoimmune, due to T-lymphocyte interaction with follicular antigens
- Current thought:
  - Loss of immune privilege by Anagen bulb
- Evidence for such:
  - Oligoclonal and autoreactive T-lymphocytes are present in peribulbar inflammatory infiltrate

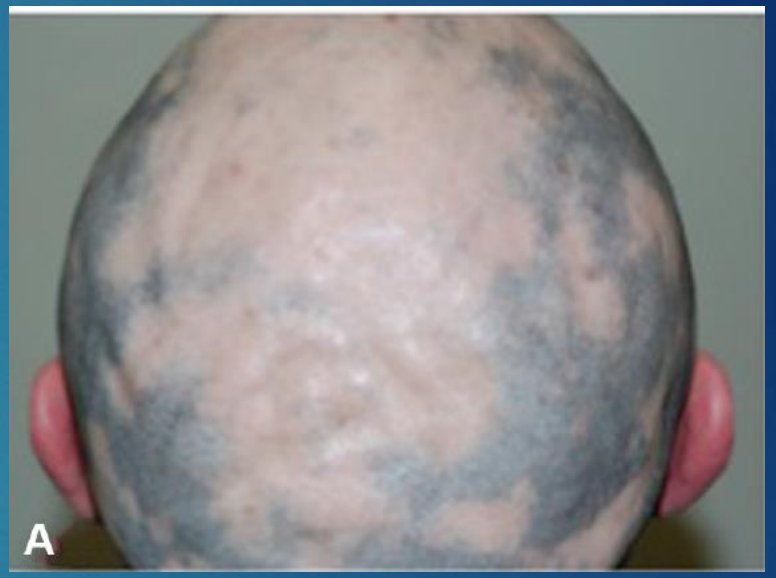
Clinical – Presentations

- Clinical presentations include:
  - Alopecia Areata - Patch
  - Alopecia Totalis
  - Alopecia Universalis
  - Ophiasis Pattern
  - Sisaipho Pattern
  - Acute Diffuse and Total Alopecia (ADTA)



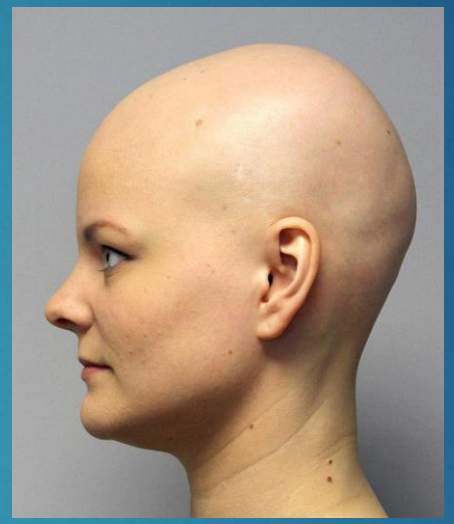
Alopecia Areata - Patch

- Clinically, sudden onset of well-demarcated round or oval patches of non-scarring hair loss
- Location : **Scalp is MC**
  - **In Men: Beard**
- Pull Test (+)
- Worst prognostic factors:
  - **Younger age at initial presentation**
  - **Severity at Onset**
  - **Family history**
  - **Ophiasis Subtype**



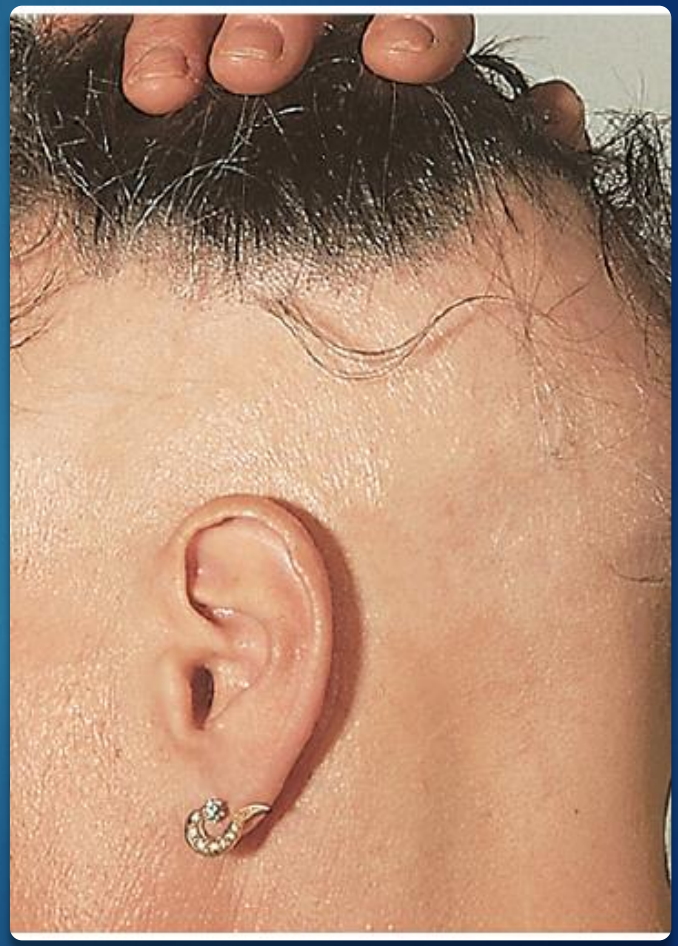
Alopecia Totalis / Universalis

- Advanced forms of Alopecia Areata
  - **5% progression rate** from Patch AA
  - Alopecia Totalis
    - Loss of all scalp hair
  - Alopecia Universalis
    - Loss of all **scalp and body hair**



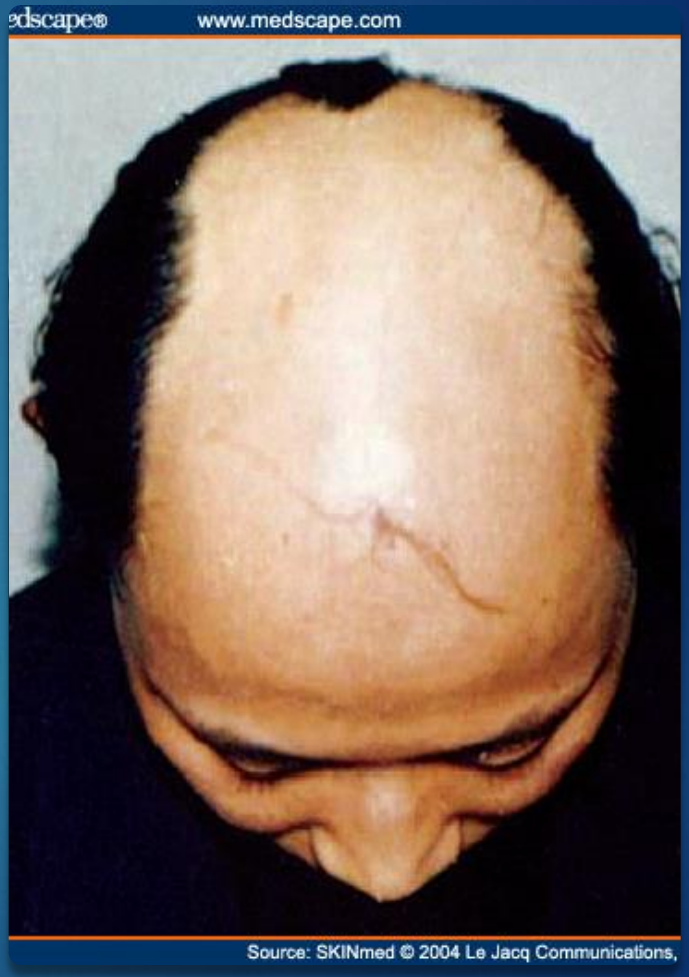
Alopecia Areata - Ophiasis

- Band-like alopecia
  - Occipital hairline extending towards temples
- Rarely can present at frontal hairline
  - Can be confused with Frontal Fibrosing Alopecia
- **Worst Prognosis** of all clinical subtypes



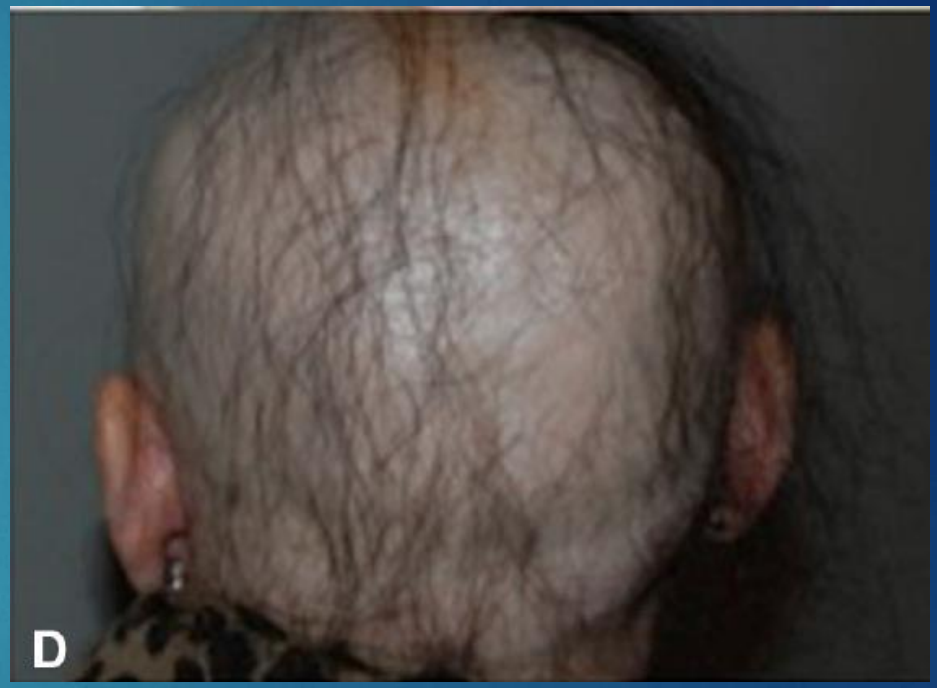
Alopecia Areata - Sisaipho

- Opposite configuration of Ophiasis subtype
- Hair loss centrally but sparing hairs at margin of scalp
  - Can be confused with androgenetic alopecia

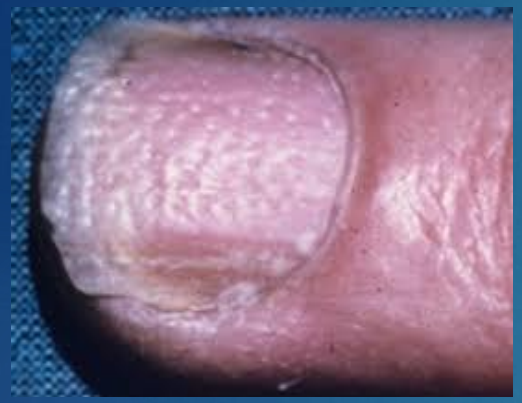


Acute Diffuse and Total Alopecia (ADTA)

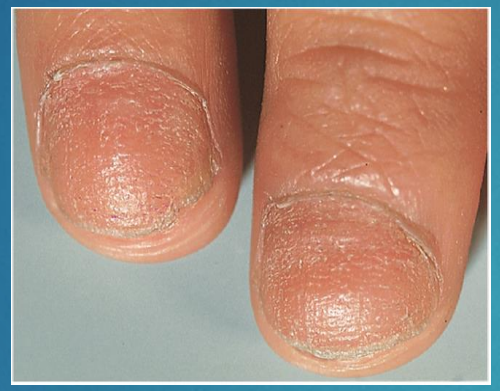
- More common in **women**
- Sudden and diffuse hair loss that lasts around **3 months** followed by **rapid regrowth over 4-9 months**
- **Favorable Prognosis** but it may recur in future



Nail Changes



Nail Pitting (MC)



Trachyonychia

Longitudinal Ridging

Red Lunulae

Comorbidities

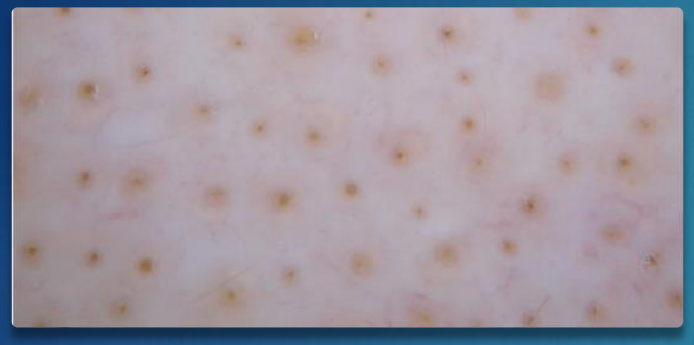
- Higher incidence noted in patients with:
- Atopic Dermatitis (MC)
  - **Higher risk of severe AA phenotype**
- Autoimmune Diseases (SLE, Thyroiditis, DM, Myasthenia Gravis, Vitiligo)
  - Patel et al(2017) conducted a retrospective analysis of 298 patients with AA
    - **Thyroid abnormalities discovered in 20% of the pediatric patients**
    - Screening should be done in those with thyroid symptomology
- Vitamin D Levels
  - Tsai et al (2018)
  - Retrospective analysis showed **association with severity**
  - Meta-analysis of studies **show association between Vit D deficiency and AA**

Characteristic	AA, n = 584
Gender	
Female	400 (68.50%)
Male	184 (31.50%)
Mean age ± SD, y	35.54 ± 19.28
Type of alopecia	
AA	553 (94.7%)
Alopecia totalis	12 (2.05%)
Alopecia universalis	19 (3.25%)
Atopy	
Allergic rhinitis	100 (17.12%)
Eczema	83 (14.20%)
Asthma	79 (13.50%)
Autoimmune disorders	
Thyroid	110 (18.80%)
Diabetes mellitus	21 (3.60%)
Psoriasis	15 (2.56%)
RA	8 (1.37%)
SLE	7 (1.20%)
Psychological problem (physician diagnosed)	
Anxiety	80 (13.70%)
Depression	86 (14.72%)
Sleep problems	64 (11.00%)
Deficiency	
Vitamin D	228 (39.00%)
Anemia	98 (16.80%)
Iron	43 (7.36%)
Gastrointestinal disease	
IBS	5 (0.86%)
IBD	10 (1.71%)
Celiac	5 (0.86%)

Diagnosis

- Pull Test
  - Sign of active disease
- Trichoscopy
  - See Next Slide
- Biopsy
  - Peribulbar lymphocytic infiltrate

Trichoscopy



Yellow Dots

Infundibula with Sebum and Keratin

Exclamation Mark Hairs

Broken hair with a thick pigmented tip

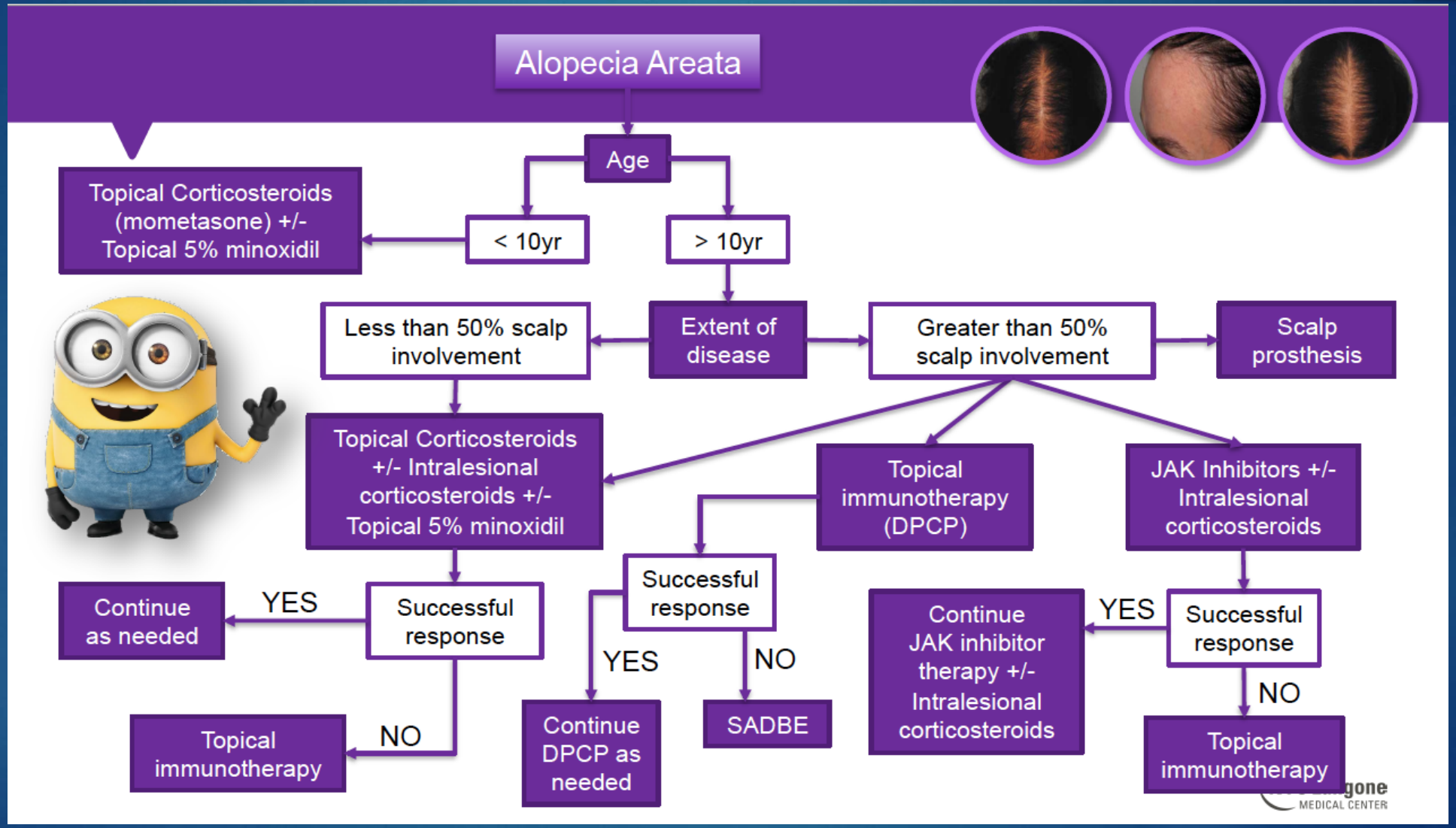
Black Dots

Destroyed hairs in hair follicle opening

Treatment

- AA is often **self limiting**
- Current first line treatments
  - Corticosteroids (Topical and Intralesional)
  - Minoxidil (5%)
  - Topical Immunotherapy
- Newer Treatments
  - JAK Inhibitors
  - PRP
- Others
  - Immunomodulators
  - Anti Inflammatories
  - Targeted Therapies
  - Devices (Lasers, Cryotherapy)

But Where Do I Start?

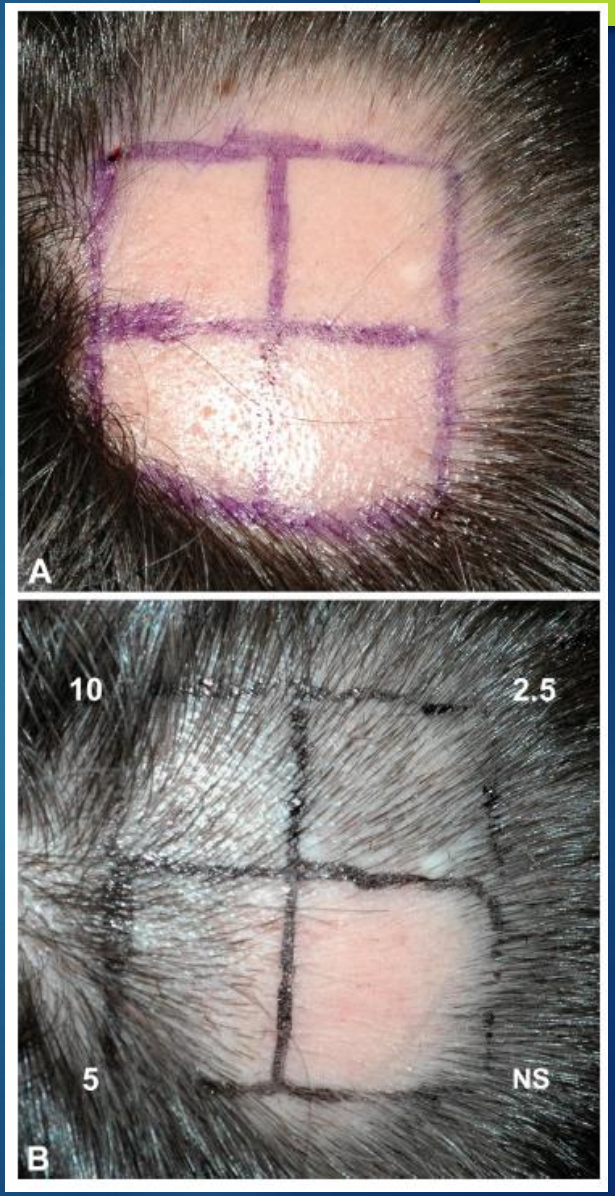


Current Treatments Generally considered first-line

- Corticosteroids
  - Topical and Intralesional
- Minoxidil 5%
- Contact Immunotherapy
  - With Anthralin

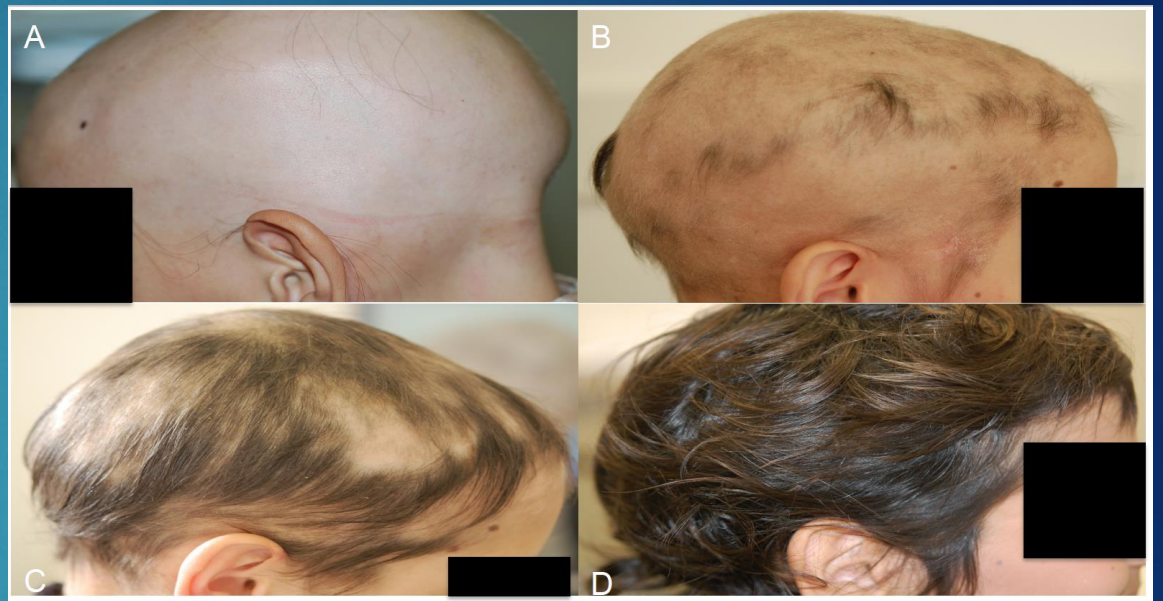
Treatment – First Line

- Corticosteroids
  - Intralesional - First line for limited disease
    - Chu et Al (2015)
      - Recommend: **low concentration, higher volume**
      - **2.5mg/CC was as effective as 5-10mg/cc**
  - Topical
    - Clobetasol vs Mometasone (for pediatric patients)
    - Tosti et al (2006)
      - **Clobetasol foam** in Double Blind RCT, greater regrowth in 89% vs 11%
  - Monitor for side effects such as skin atrophy
- Minoxidil 5%
  - Insufficient as monotherapy
    - In long term studies, mild hair growth without statistical significant
  - Use for maintenance with other treatments



Treatment – First Line

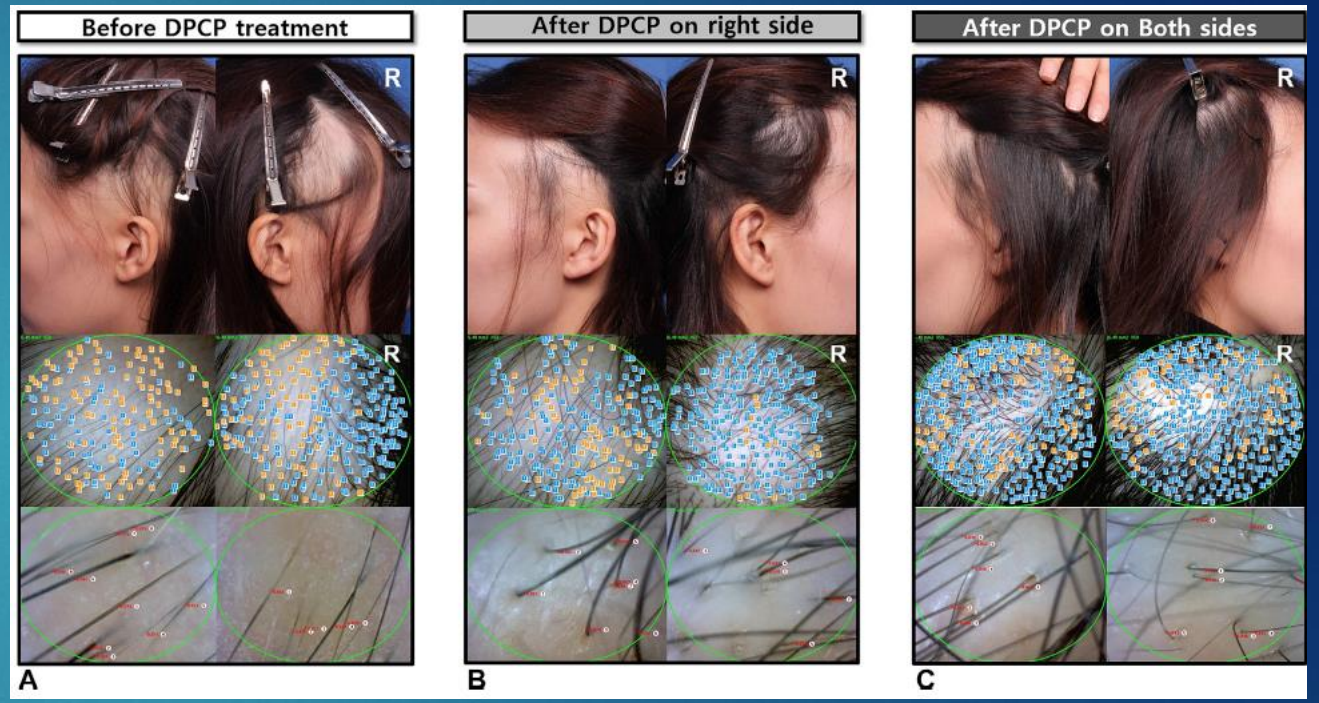
- **Contact Immunotherapy**
  - Anthralin Cream, DPCP Solution, Squaric Acid, topical anthralin
  - Usually at alopecia treatment centers
- **Overall:**
  - ~50-70% rate response rate with some responses occurring after 1-2 years
  - Remission for >1 year
  - DPCP with Anthralin 0.5% ointment
  - Reserved for AU, AT
  - Issues: High dropout rates, level of evidence poor
- Chiang et al (2014) - 50 case review using **DPCP**
  - 71% of AT, 56% of AU had >50% regrowth
  - **15% of responders did not respond until 1-2 years**
- Durdu et al (2015), Vedak et al (2015)
  - DPCP + Anthralin 0.5% ointment
  - **88% vs 54.5% had >50% terminal hair regrowth after 30 weeks**
- Kuin et al (2015)
  - 11 Studies with 500 patients, no RCTs, 10 ½-head studies with no tx, variety of AA severity
  - **~50% response rate overall, remission >1 year**
  - High dropout rates, level of evidence poor



12 year old female AA patient noted on initial exam to have sparse hairs only on the top of the scalp, treated with 1.5% DPCP.

Treatment – First Line

- High Dropout Rates
  - Often due to expected SE
  - Patient compliance is a strong factor in decreased relapse rates (Duh)
- Choe et al (2018)
  - Retrospective analysis, 159 pts
  - Modified DPCP treatment protocol with **subclinical sensitization**
    - Sensitized with 0.1% and tx with 0.01% QWeekly
  - Sensitization with an eczematous reaction may not be required for successful contact immunotherapy
  - **46 (28.9%) complete response, 59 (37.1%) partial response**



New and More Recent Treatments

- JAK Inhibitors
- Platelet Rich Plasma (PRP)

Treatment – What's New-Ish? JAK Inhibitors

- **JAK – STAT Pathway**
  - Cytokine binding
  - JAK receptors dimerize, phosphorylated, recruit STAT molecules to activate target gene transcription
  - Mediates downstream IL-15 signaling of T-cells
- **Baseline lab monitoring** : CBC, CMP, Lipids, HIV, Quant-Gold, CXR
- Avoid in : Hx of Malignancy, Tb, Hepatitis
- Cost: $2000-$5000 per month

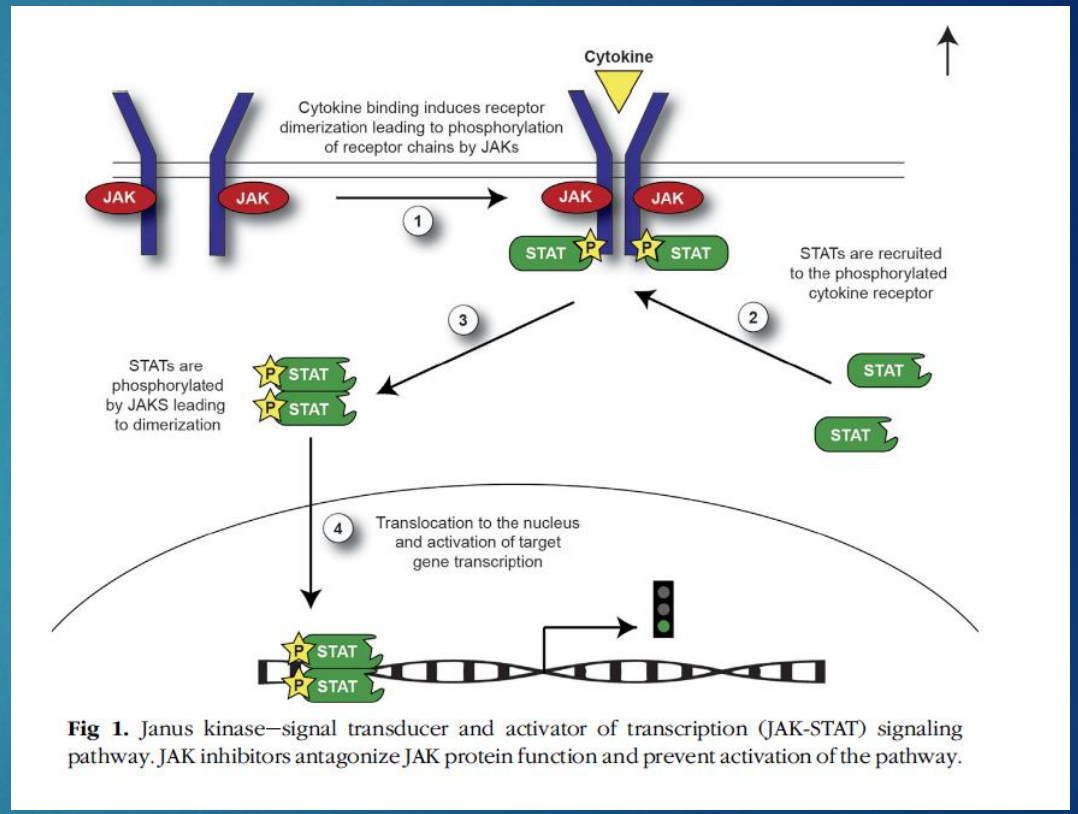


Fig 1. Janus kinase–signal transducer and activator of transcription (JAK-STAT) signaling pathway. JAK inhibitors antagonize JAK protein function and prevent activation of the pathway.

Treatment – JAK Inhibitors

- Tofacitinib (JAK1/3)
  - **Dose: 5-10mg BID, or 11mg ER QD**
    - **Shapiro : Recommends 15mg QD + Intralesional Corticosteroids**
- Ruxolitinib (JAK1/2)
  - **20mg BID**
- Oclacitinib (JAK 1)
- Issues:
  - **Relapse once taken off medication**
  - **Adverse Effects**
  - Higher doses have unknown safety profile
  - Topical route safer but unknown benefit
  - Long term likely necessary
  - Longer duration and extent often has poorer response

Table II. Correlation between characteristics of alopecia areata patients (n = 32) treated with tofacitinib and percentage of hair regrowth at last visit

	Hair regrowth, %	
Duration of current episode	−0.434	.013*
Age at onset of first episode	0.370	.037*
Duration of disease since first onset	−0.436	.013*
Age	0.059	.834
Body mass index (n = 29)	−0.248	.194
Initial Severity of Alopecia Tool score	−0.170	.351
Tofacitinib duration	0.487	.005*
Total tofacitinib dose	0.098	.595

*P value <.05.

Treatment – JAK Inhibitors

Authors	Drug	Dose	%pts with SALT 50	timeline
Mackay-Wiggan, J., et al. (2016)	Ruxolitinib	20 mg BID	75% (n=9/12)	4-6 mos
Kennedy Crispin, M., et al. (2016)	Tofacitinib	5 mg BID	32% (n=21/66)	3 mos
Liu, L. Y., et al. (2017)	Tofacitinib	5-10 mg BID +/- pulsed pred	58% (n=37/65)	4-18 mos
Craiglow BG, et al (2017)	Tofacitinib (in adol, n=14)	5 mg BID	n/a (71% pts mean SALT88)	2-16 mos
Park H-S, et al (2017)	Tofacitinib	5 mg BID	56.3% (n=18/32)	3 mos

Treatment – JAK Inhibitors

- Kennedy Crispin et al (2016) – Tofacitinib (5mg BID)
  - 66 pts with AA, AT, AU
    - **>66% showed regrowth** by 3 months (32% had >50% SALT)
    - **Relapse by 8.5 weeks**
    - AE: 25% with Infxn (UTI/URI)
- Liu et al (2016) – Tofacitinib (5-10mg BID) + Syst. Corticosteroids
  - 90 pts with AA, AT, AU
  - Pulsed oral CST 300 mg monthly x 3 months
    - **77% achieved clinical response (55% had >50% regrowth)**
- Liu et al (2018) – Topical 2% tofacitinib ointment BID
  - 10 patients, 24 weeks
    - **3/10 experienced hair regrowth with Salt improvement of 34.6%**

Kennedy Crispin et al. "Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata." JCI Insight 2016

Fig 1. Alopecia areata patient 1 before (**A**) and after 4 months (**B**) and 6 months (**C**) of treatment with tofacitinib 2% ointment. Ointment was applied only to the right half of the scalp for the first 2 months, at which time hair regrowth was evident only in the area of drug application. Subsequently, ointment was applied to the entire scalp. At month 4, there was more hair on the right scalp than on the left scalp. By month 6, hair growth was prominent on both sides.

Treatment – JAK Inhibitors (adolescents)

- Craiglow et al (2017) – Tofacitinib 5mg BID
  - **10/14 pts with Salt 20-100%**
    - Mean SALT improvement over **2-16 months of 88%**
    - Mild AE, no treatment interruptions
- Castelo-Soccio (2017) – Tofacitinib 5-10mg BID
  - **8 patients age 12-19 with AU**
    - **All pts had >50% hair regrowth**
    - 1st 3 months – slow growth, rapid thereafter
    - No AE or infections noted
- Bayart et al (2017) – Tofacitinib and Ruxolitinib 1% and 2% topical
  - 6 patients, 3AU, 2AT, 1AA
  - **Ruxolitinib (1 success, 1 fail)**
    - 75% eyelash regrowth
  - **Tofacitinib (3 success, 1 fail)**
    - 20% medial eyebrow regrowth
    - 20% 1 month, 80% 1 year
    - Fail with verabase cream, 95% regrowth with liposomal base of scalp

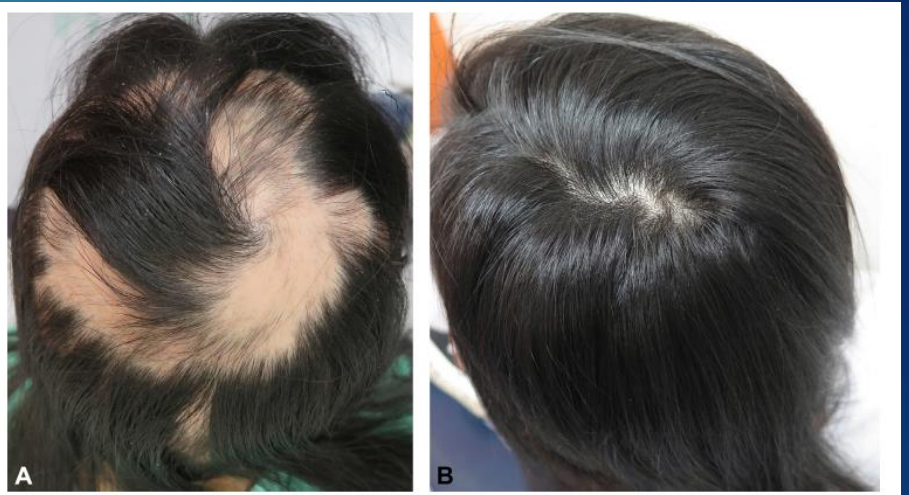


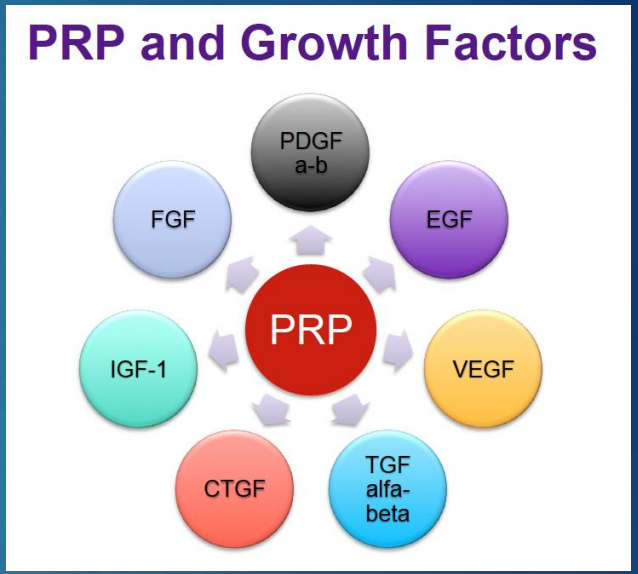
Fig 1. Alopecia areata with patient 4 after 2 months of treatment with 2% tofacitinib in VersaBase cream (**A**) and after 6 months of treatment with 2% tofacitinib in liposomal base (**B**).

Treatment – JAK Inhibitors

- Mackay-Wiggan et al (2016) – Ruxolitinib
  - 12 pts
  - 20mg BID for 3-6 mos
    - **9/12 pts with marked response**
    - Average of 92% hair regrowth
  - Issue : Relapse over 3-6 months

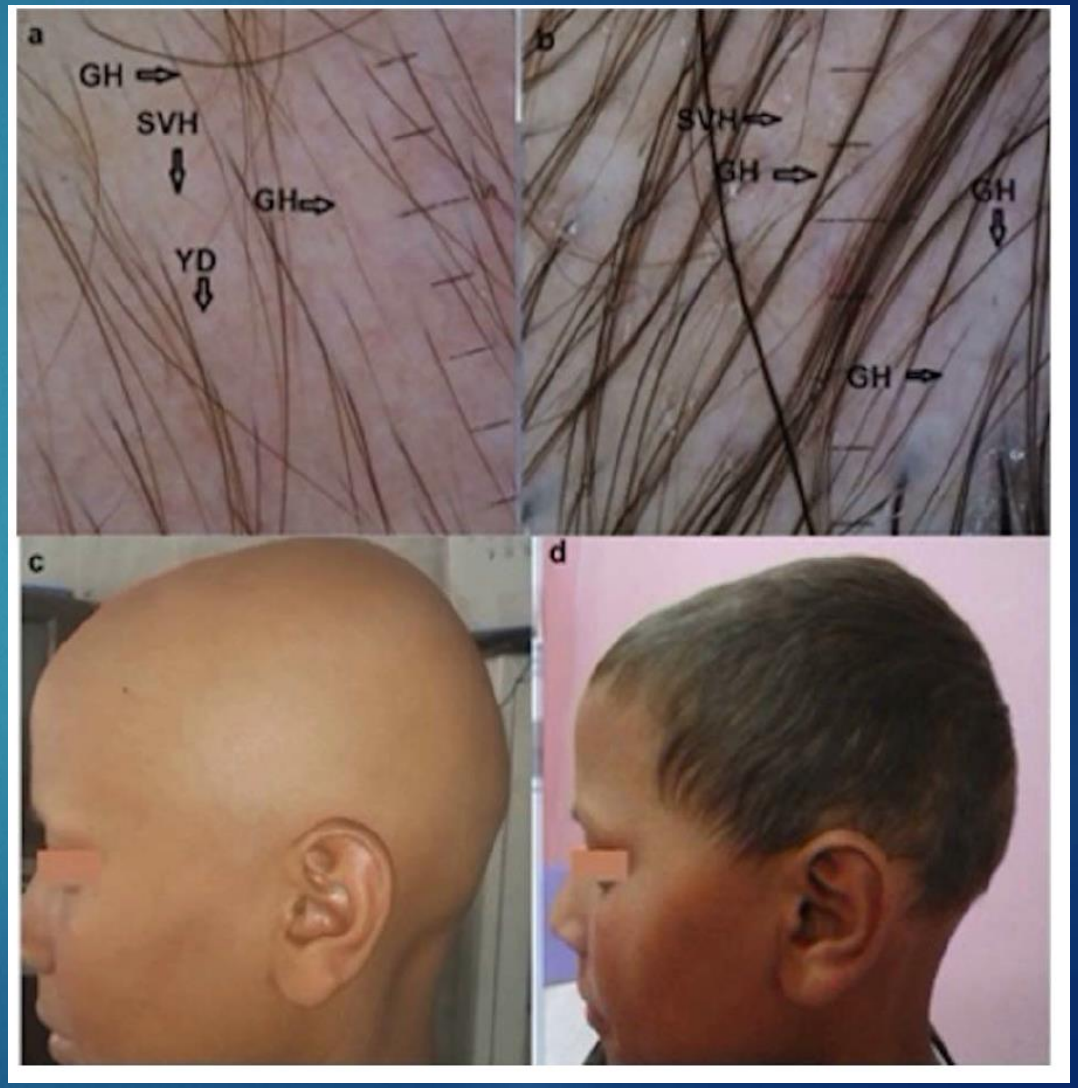
Treatment - PRP

- Advantages:
  - Ability to induce longer disease remission
  - Regrow pigmented hairs from beginning of hair regrowth
  - Safe – autologous material
  - No lab monitoring, drug interactions, side effects
- Issue : non standardized protocol
- Trink et al (2013) - Double blind placebo, half head x 3 months
  - Significant improvement monthly PRP(60%) vs ILK(27%) vs placebo
- Singh (2015) – Monthly x 6 months
  - 19/20 with regrowth



Treatment - PRP

- El Taieb et al(2017)
  - RCT, 90 patients with no treatment for 3 months before therapy.
  - 3 groups:
    - Minoxidil 5% BID vs PRP injections Q4 weeks vs Topical Panthenol BID (placebo)
  - PRP more effective than minoxidil in same treatment period
  - Showed reduction in short vellus hairs



Existing treatments with possible utility

- Immunomodulators
  - Systemic Corticosteroids
  - Mycophenolate Mofetil
  - Methotrexate
  - Cyclosporine
  - Sulfasalazine
  - Azathioprine
  - Prostaglandin Analogs
- Anti-Inflammatories
  - Simvastatin/Ezetimibe
  - Anti-histamines (Fexofenadine)
  - Low Dose Naltrexone

Treatment – Immunomodulators

- Systemic Corticosteroids
  - Shreberk-Hassidim et al (2016)
  - Pulsed recommended if deciding on this route
  - 41 Studies, various protocols with IV/IM/PO q-monthly
    - **Route was not statistically significant**
  - **RCT Study**
  - **Complete response in 40% on CST ,0% in placebo**

Table II. Summary of the response, relapse, and side effects, divided by different routes of treatment and pediatric-only studies

Rate	Total	IV or IM treatment	PO treatment	Mini-PO treatment
All studies	1078	765	170	143
Complete response*	466 (43%)	317 (41%)	83 (49%)	66 (46%)
Partial response†	235 (22%)	168 (22%)	28 (16%)	39 (27%)
No response	377 (35%)	280 (37%)	59 (35%)	38 (27%)
Relapse (% of responders)‡	188 (17%)	145 (19%)	33 (19%)	10 (7%)
Side effects	225 (21%)	140 (18%)	53 (31%)	32 (22%)
Pediatric-only studies	65	45	20	-
Complete response*	33 (51%)	22 (49%)	11 (55%)	-
Partial response†	15 (23%)	11 (24%)	4 (20%)	-
No response	17 (26%)	12 (27%)	5 (25%)	-
Relapse (% of responders)‡	29 (60%)	23 (70%)	6 (40%)	-
Side effects	8 (12%)	5 (11%)	3 (15%)	-

Data are presented as total No. of patients and percentage.
IM, Intramuscular; *IV*, intravenous; *mini-PO*, pulse corticosteroids given once weekly; *PO*, oral.
*Complete response is defined mainly as >75% of hair regrowth.
†Partial response is defined mainly as 25%-75% of hair regrowth.
‡Relapse is defined as recurrence in responders to therapy.

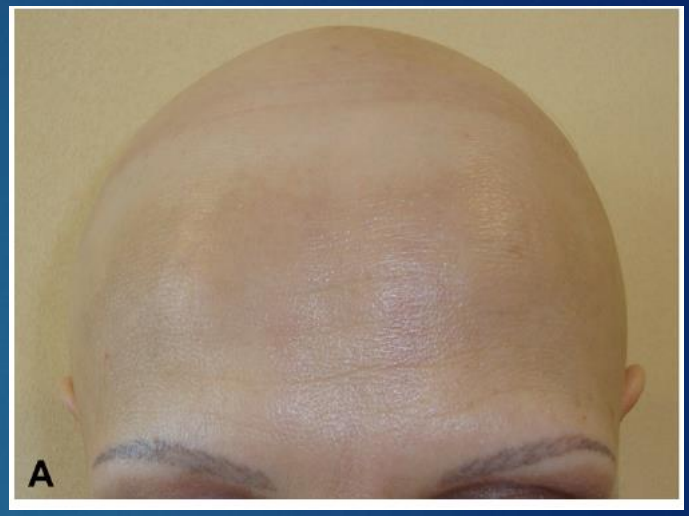
Treatment – Immunomodulators

- Mycophenolate Mofetil
  - Systemic : 500mg BID – 1500mg BID
  - Topical : 2% Cream
- Methotrexate
  - Comparative Study, MTX + Prednisone vs Prednisone alone
  - **5/14** pts had >50% hair growth with combo MTX + Prednisone
- Cyclosporine
  - **Ranges from 25-76.7% success rate >50% regrowth**
  - One uncontrolled study – 45.4% of 25 pts showed sig. regrowth
- Sulfasalazine
  - Pilot study
  - **43% of 14 pts showed complete regrowth**
    - 66% showed no signs of relapse after treatment discontinuation
    - 33% relapsed after 2.5 months

Case 2 – Successful hair regrowth in the eyebrows: (a) Previous to methotrexate; (b) 2 months after treatment; (c) 4 months after treatment

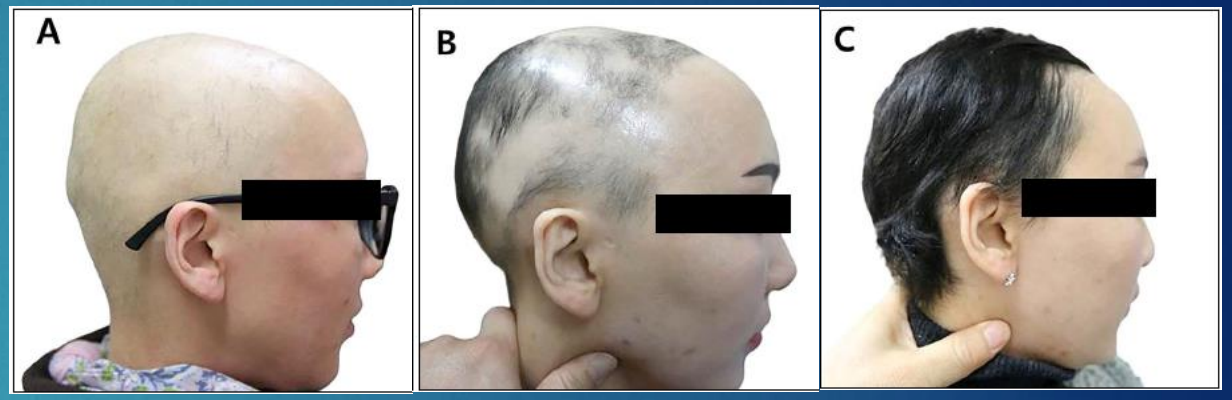
Treatment – Immunomodulators

- Azathioprine
  - Prospective Study (Vano-Galvan et al 2015)
  - **Azathioprine dosage 2.5 mg/kg/day**
  - 14 patients with AU, recalcitrant to oral CST and DPCP
  - **Response in 6/14 patients**
  - Response in 4.7 months response
  - Relapse : 2 patients after 2.5 months, remaining 4 persistent
- Prostaglandin Analogs (Lee et al, 2015)
  - Studies have wide range of variable therapeutic effect
  - Consider for eyebrows
  - Lee et al (2015)
    - Tac + Latanoprost > Tac alone
    - 45% vs 0% improvement



Treatment – Anti-Inflammatories

- Simvastatin/Ezetimibe – 40/10mg QD
  - Lattouf et al (2015)
    - 29 patients, 40-70% SALT
    - **73% responded after 16-24 weeks (>24% regrowth)**
  - Other study, 82.4% showed no improvement
  - Choi et al (2017)
    - **Non responders, 14 patient** open prospective study
    - **4 responded with 30-80% after 3 months**
- Antihistamines (Lee et al, 2017)
  - Cohort Study
  - DPCP + Fexofenadine > DPCP monotherapy
- Low-dose Naltrexone
  - 1-4.5mg QD
  - Possible use for anti-inflammatory

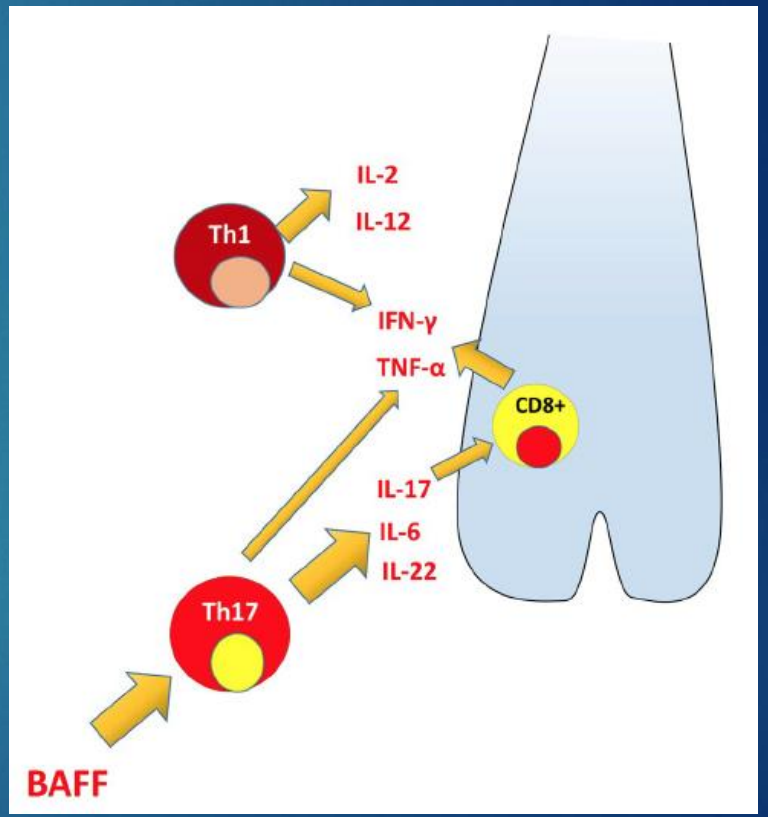


Targeted Therapies

- Ustekinumab
- Apremilast
- Secukinumab
- Abatacept

Treatment - Targeted Therapy

- Ustekinumab – 90mg Q12 weeks
  - Guttman-Yassky E Et Al (2016)
  - **3/9 pts with complete response** after 12 months, 1 had AU
- Apremilast – 30mg BID x 3-6 months (mean 4.2mos)
  - Liu et Al (2017)
  - 9 patients (1 AA, 8AU)
    - Duration of disease 23.3 years
  - **None showed improvement over 3-6 months**
- Secukinumab
  - RCT was **terminated in 2017** due to low enrollment



Treatment - Targeted Therapy

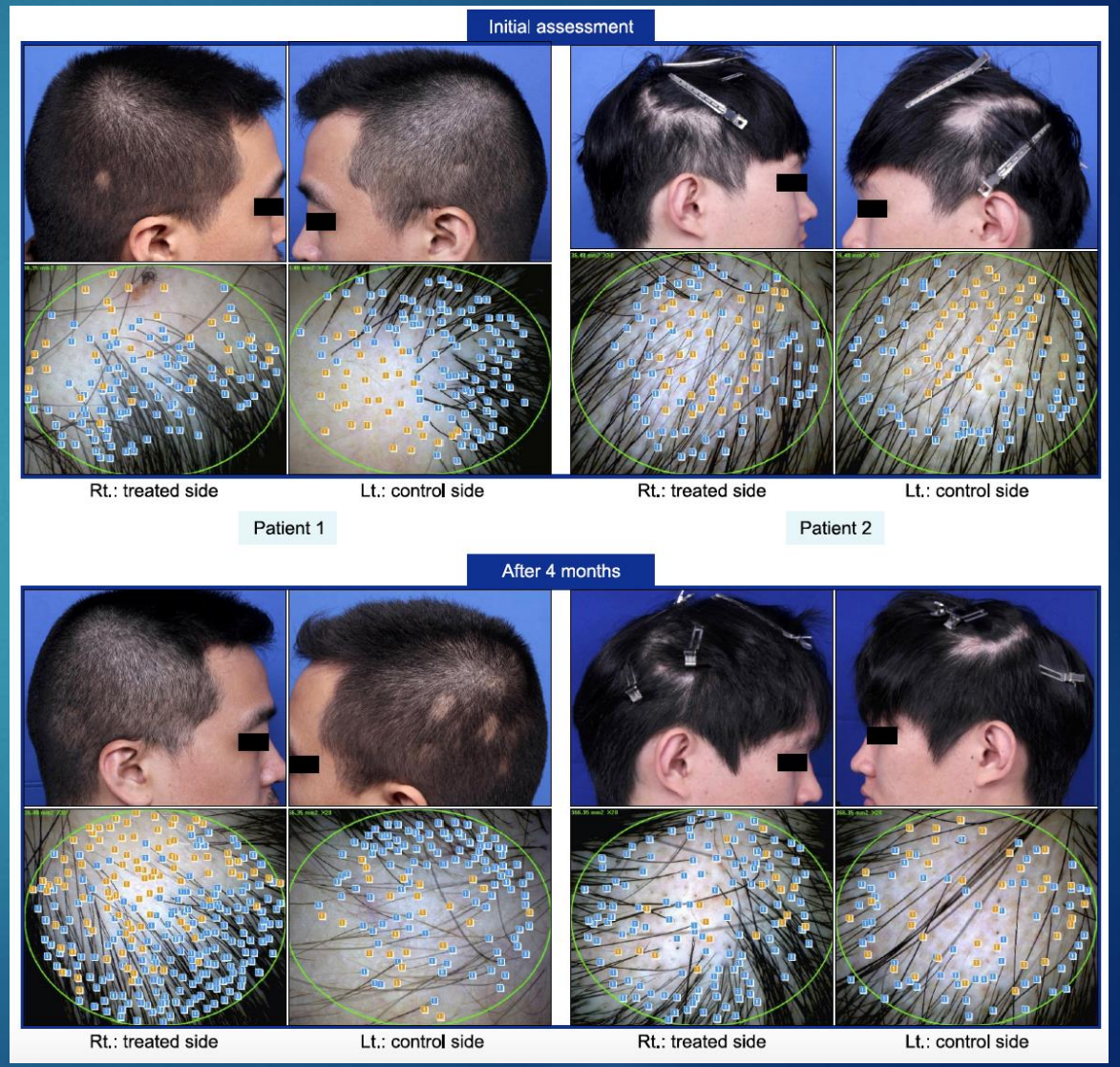
- Abatacept (CTLA4 Agonist) – 125mg SC weekly
  - Guttman-Yassky E et al (2016), Mackay-Wiggan J et al (2015), Keren a et al (2015)
  - SALT 30-100% **(3/15 improved)**
    - 1/15 pts with 98% regrowth after 6 months
    - 2/15 with 23% regrowth

Devices

- Superficial Cryotherapy
- Carboxytherapy
- Excimer Laser
- Fractional Photolasers
- Fecal Transplant.. Device?

Treatment - Devices

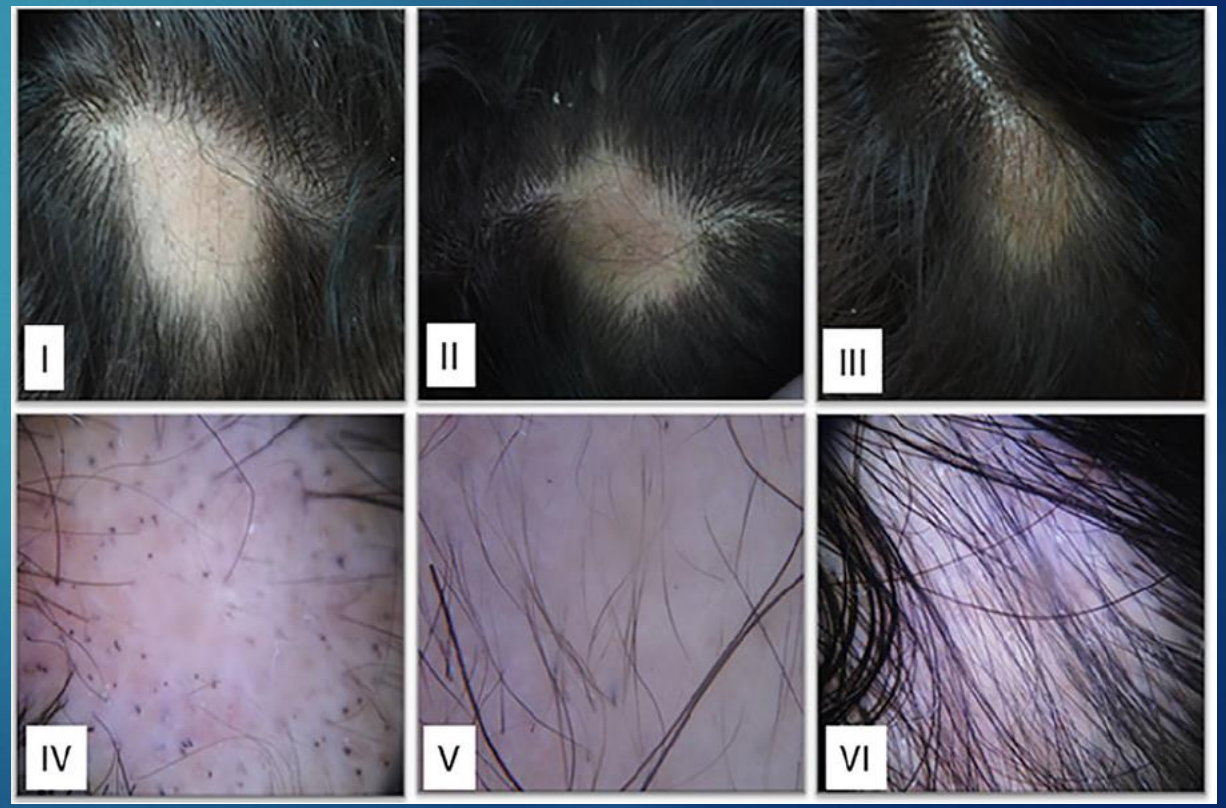
- Superficial Cryotherapy
  - Comparative Study (Faghihi and Radan 2014)
    - **80% vs 91.5% (clobetasol)**
  - Jet cryotherapy
    - 11 recalcitrant AA patients
    - **5 excellent response, 3 satisfactory response**
    - Most effective at 2 weeks or less
  - **Half head study** (Jun et al, 2017)
    - Superficial cryotherapy showed increased hair thickness and eyebrow density
    - Tx: **Each patch 3-4 times for 2-3 sec q 2 weeks**
    - **11 of 15 responded, with maintenance 1 month.**
    - Improvement by 1.6 x of terminal hair on treated side
    - **SALT score of 40% improvement vs 9.6%**
  - **Rationale: Readily available at most offices, inexpensive, no systemic side effects**



Treatment - Devices

- Carboxytherapy
  - Doghaim et al (2018)
  - **80 pts** (**40 AA**, 40 AGA), 4 groups (1a, 1b, 2a, 2b)
  - Placebo was intradermal distilled water
  - Injection: 30g Needle, 2mL CO2 per injection site
  - **Significant improvement**
    - **3 months after last session**
    - **SALT from 9 -> 5.7**
    - **Control group : 12.5 -> 16.0**
  - Before, after 6 sessions, then 3 months after last session
  - Rationale: Inexpensive

SALT score	Before treatment sessions	After treatment sessions	At the end of follow-up period	Sig. bet. periods: Before vs after	Before vs follow-up	After vs follow-up
Group I (AA patient)						
Group IA	9 (4.5-30)	8.2 (2-30)	5.7 (0-29.7)	<0.001*	<0.001*	0.011*
Group IB	12.5 (5.4-30)	11.9 (8-35.4)	16 (0-40)	0.092	0.152	0.093
U(P)	0.965	0.043*	0.040*			



Treatment - Devices

- Excimer Laser
  - **308nm Excimer**
  - Pilot study
    - 42 recalcitrant patches in 18 patients
    - Twice per week for max of 24 sessions
    - 50mJ/cm2 less than MED
    - **Complete regrowth in 13/42 lesions, excellent in 5/42**
    - Presence of Atopic Diathesis had an unfavorable prognosis
    - **Rationale**
      - Minimal side effects, ideal for pediatric patients

Treatment - Devices

- Fractional Photothermolysis
  - Yalici-Armagan et al (2016)
  - Controlled clinical trial
  - 32 subjects, 21pAA, 2AT, 1AU, 8 ophiasis
  - 3 patches on each subject
    - Control patch, **Nd:YAG patch**(2-3 sessions with 2-8 week intervals), fractional CO2 patch (3-6 sessions with 2-4 week intervals)
  - **No significant difference between baseline and final hair counts between treated patches and the control patch**
- But other studies have reported some improvement
  - Cho et al (2013)
  - 17 patients with 10,600 nm Co2
    - 30-50mJ, spot 150 spots/cm2, **8-22 sessions**
  - 12/17 reported clinical response

Treatment - Devices

- Fecal Microbiota Transplant
  - Rebello et al (2017)
  - Pt A
    - 38yoM with recalcitrant AU(Dx at 28yo), p/w C.Diff and tx with FMT. 8 weeks later, patchy hair growth on beard, arms, scalp, face.
  - Pt B
    - 20yoM with Pmhx of Crohn's and recalcitrant AU(Dx at 18yo)
    - Pt previously tx with ILK, Topical CST, Laser, Squaric Acid with no improvement
    - C. Diff tx with FMT at 20yo
      - Improved from AU to 25-49% Hair loss with body hair regrowth as well
  - But what does this mean?
    - Microbiota and the immune system

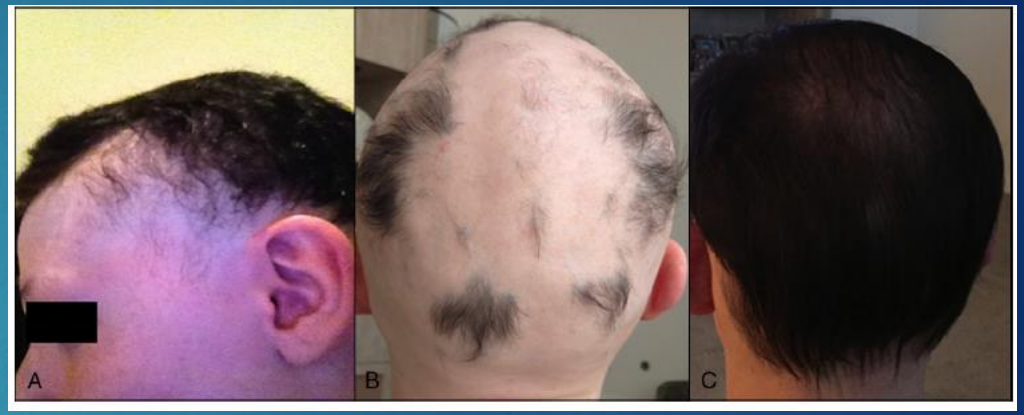


Figure 2. Hair regrowth on a 20-year-old patient's scalp after FMT. (A) The patient's scalp when he first started losing his hair at age 16. The patient's scalp (B) a few months and (C) 1.5 years after FMT.

Conclusion

- Alopecia Areata can and almost always will self resolve… eventually
- Initial treatment should follow an algorithmic approach with corticosteroids, minoxidil, immunotherapy
- Widespread and recalcitrant cases
  - JAK inhibitors, PRP, immunomodulators, and various devices
- Be aware of the comorbidities of AA
  - Thyroid Disorders
  - Vitamin D deficiency
  - Atopic Diathesis
  - Anemia

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Thank you!

Granuloma Annulare: A Brief Review and Up-to-date Information on Treatment

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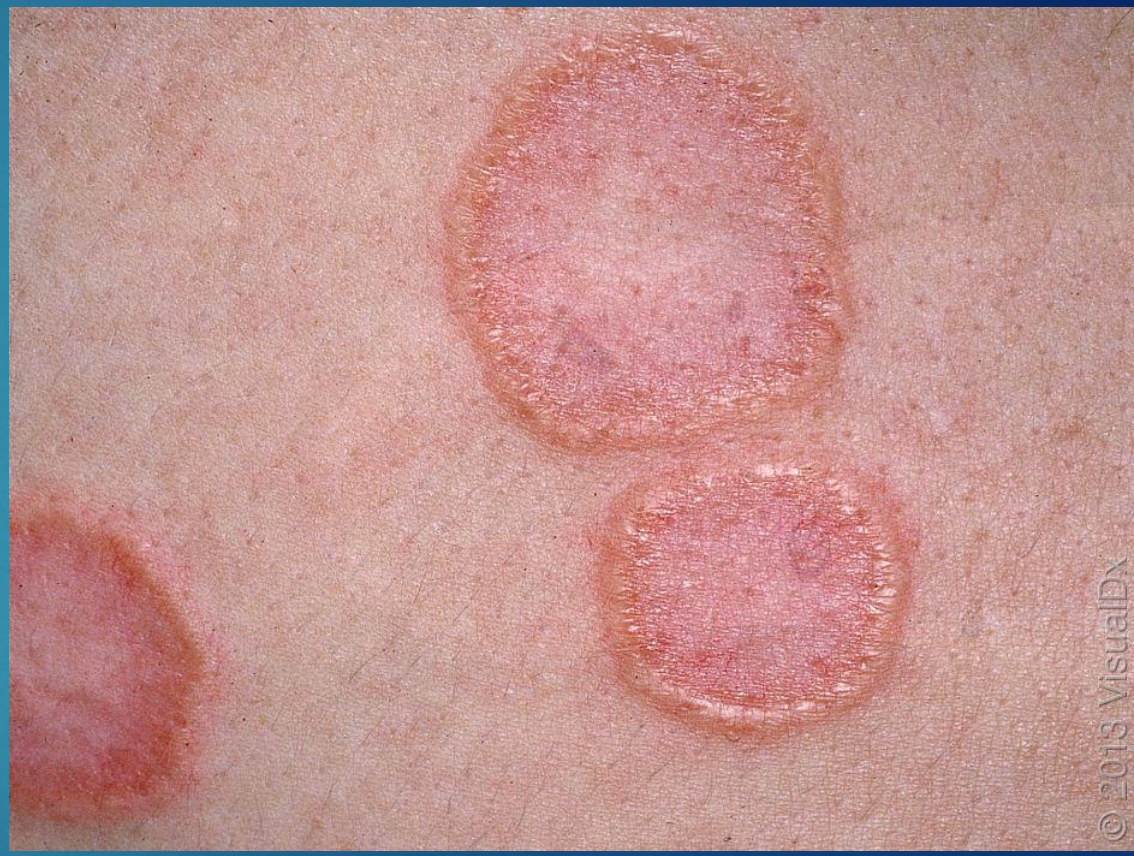
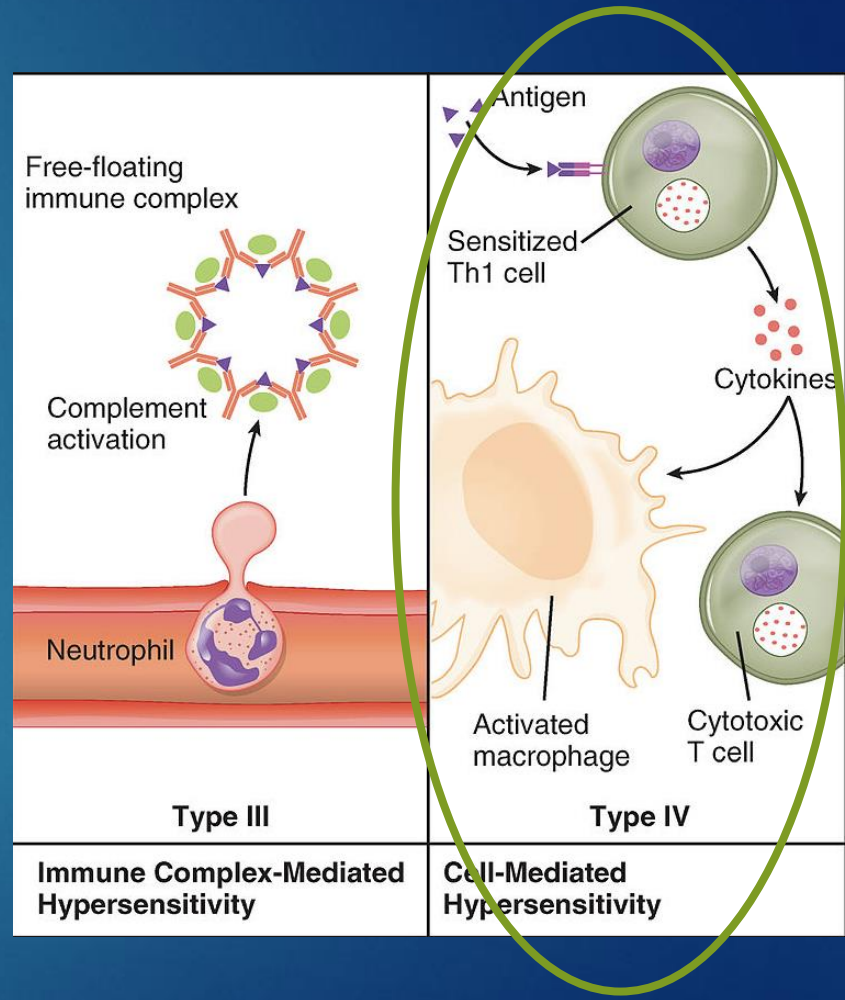
Background

- Benign, often self-limited granulomatous skin disease
- Clinically – pink annular plaques with raised border and central clearing
- Histologically – interstitial or palisading granulomas, degenerated collagen and mucin
- Most common in children and young adults
- More common in females



Pathogenesis – Mechanisms

- Unknown mechanism; theories originate from histologic findings
- Original theory – immune-mediated type III hypersensitivity reaction → vasculitis
- Recent theory – cell-mediated delayed-type IV hypersensitivity reaction to unknown antigen
  - Sensitized Th1 lymphocytes → macrophages → proinflammatory cytokines & collagen-degrading enzymes → tissue injury
- Other theories – injury to dermal elastic fibers



Pathogenesis – Inciting Factors

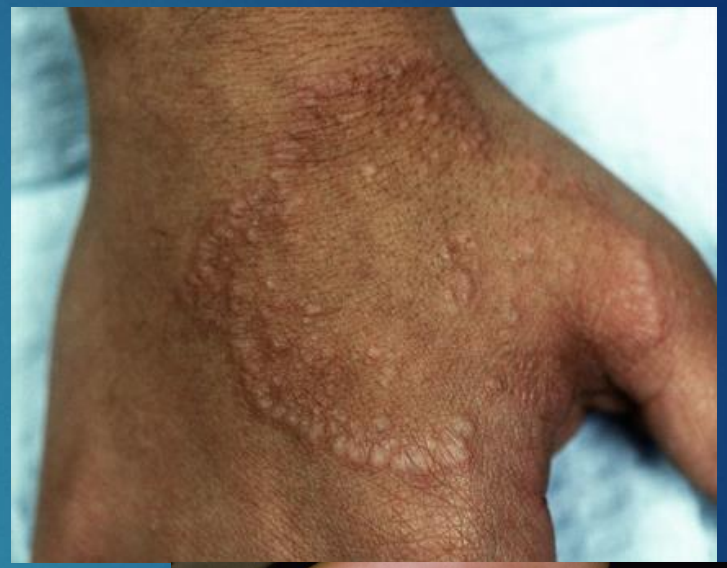
- Trauma/foreign body – insect bite, tuberculin skin testing, vaccinations, subcutaneous immunotherapy for allergies, tattoo, isomorphic response
- Infectious – viruses (Hep B, Hep C, EBV, HIV); *Borrelia* species
- Drugs – TNF-α inhibitors, allopurinol, topiramate, gold therapy
- Genetic – familial cases including identical twins, HLA-Bw35 (generalized GA)

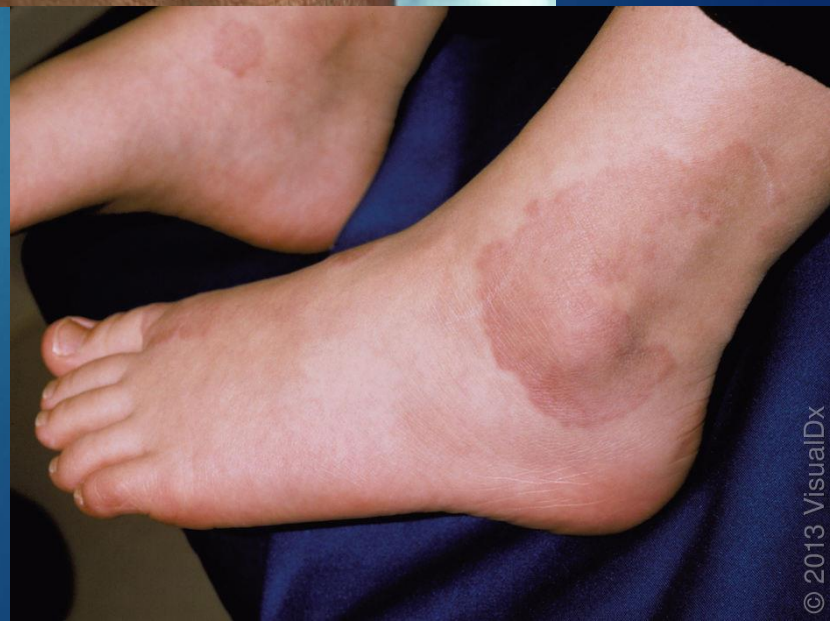
Associated Disorders

- Diabetes
  - Definitive evidence lacking and conflicting data
- Dyslipidemia
  - Evidence shows link with adult GA
- Malignancy
  - No causative relationship
  - Seen in atypical GA variants
  - Most common malignancy is lymphoma
- Thyroid disease – autoimmune
- HIV – atypical variants

Clinical – Localized GA

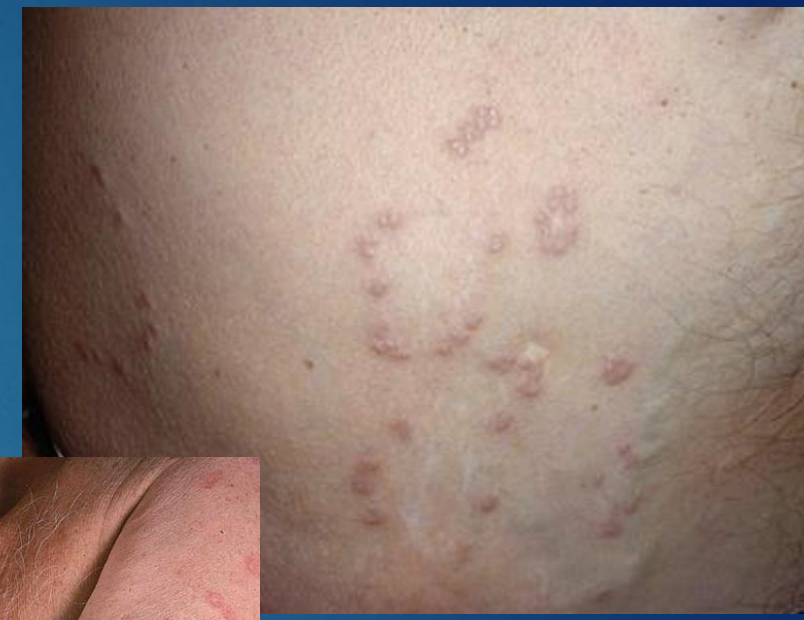
- Most common form
- Skin-colored to pink erythematous annular or arcuate plaques with raised border and central clearing
- Discrete papules at periphery
- Location – wrists, ankles, dorsal hands and feet
- Asymptomatic
- Onset – children, young adults
- ~50% patients have >1 lesion

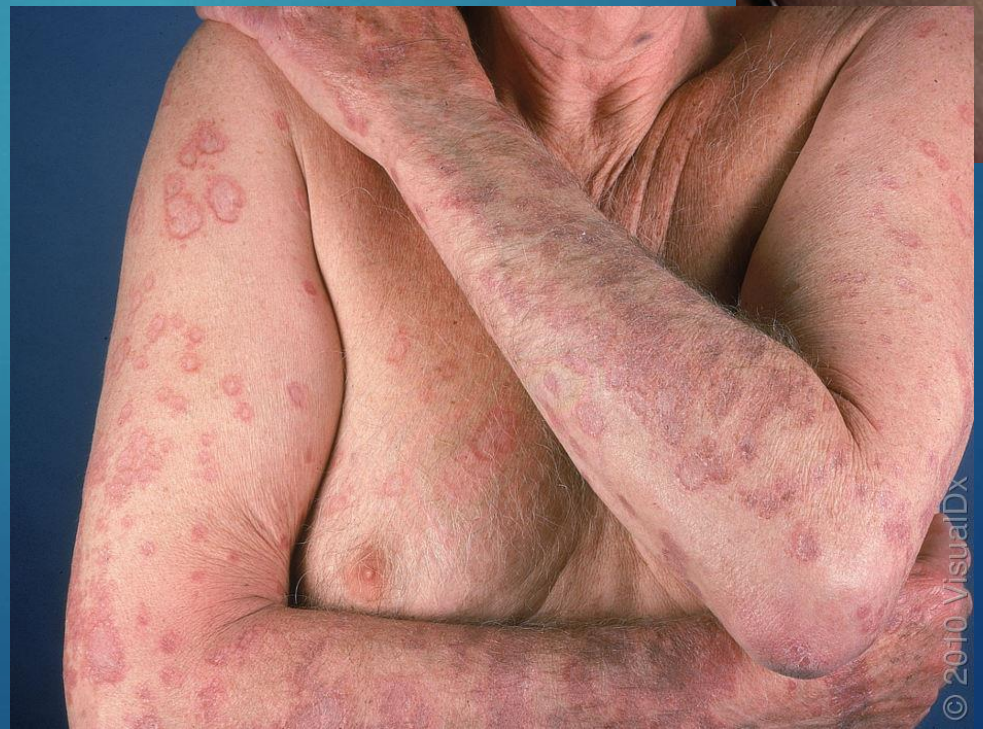




Clinical – Disseminated/Generalized GA

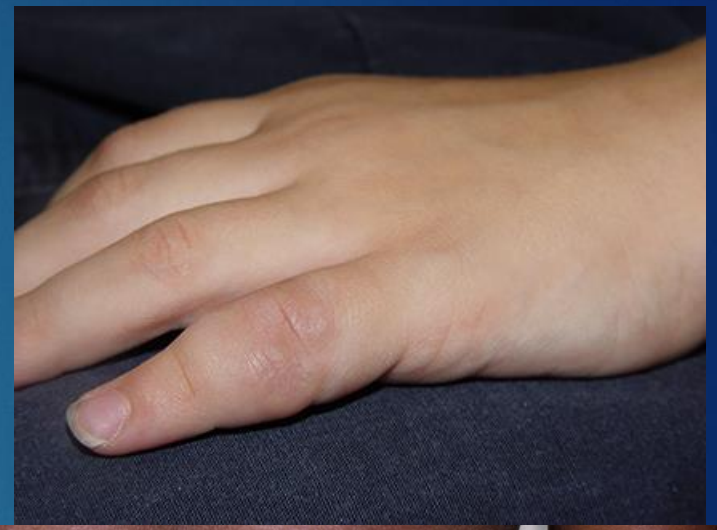
- Widespread skin-colored to pink erythematous papules and plaques of varying sizes
- Location – trunk and extremities
- Asymptomatic or pruritic
- Onset – adulthood
- Associated with HLA-B35

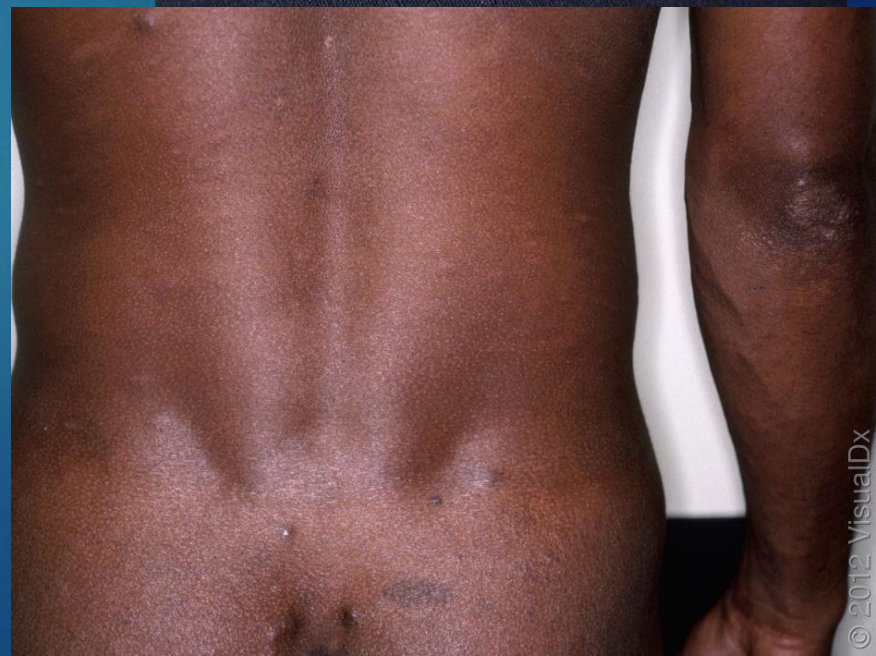




Clinical – Deep/Subcutaneous GA

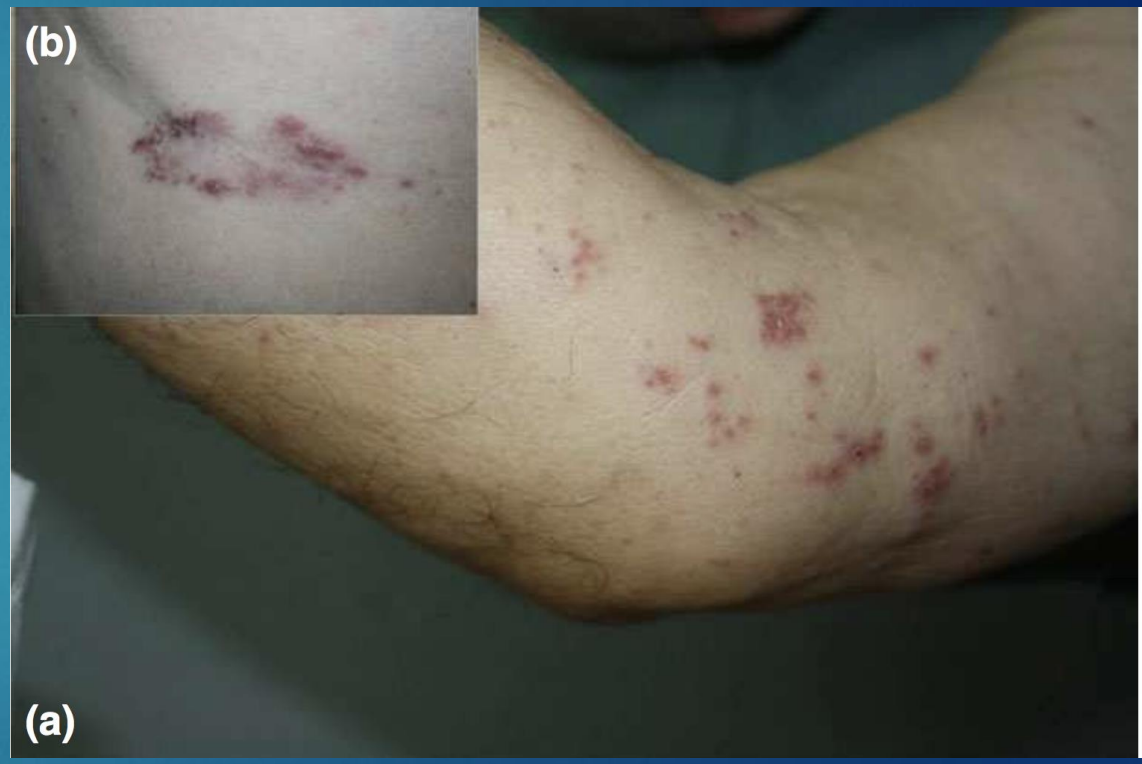
- Large skin-colored nodules, overlying skin uninvolved
- Location – scalp, buttocks, extremities
- Painless
- Onset – children <6 yo





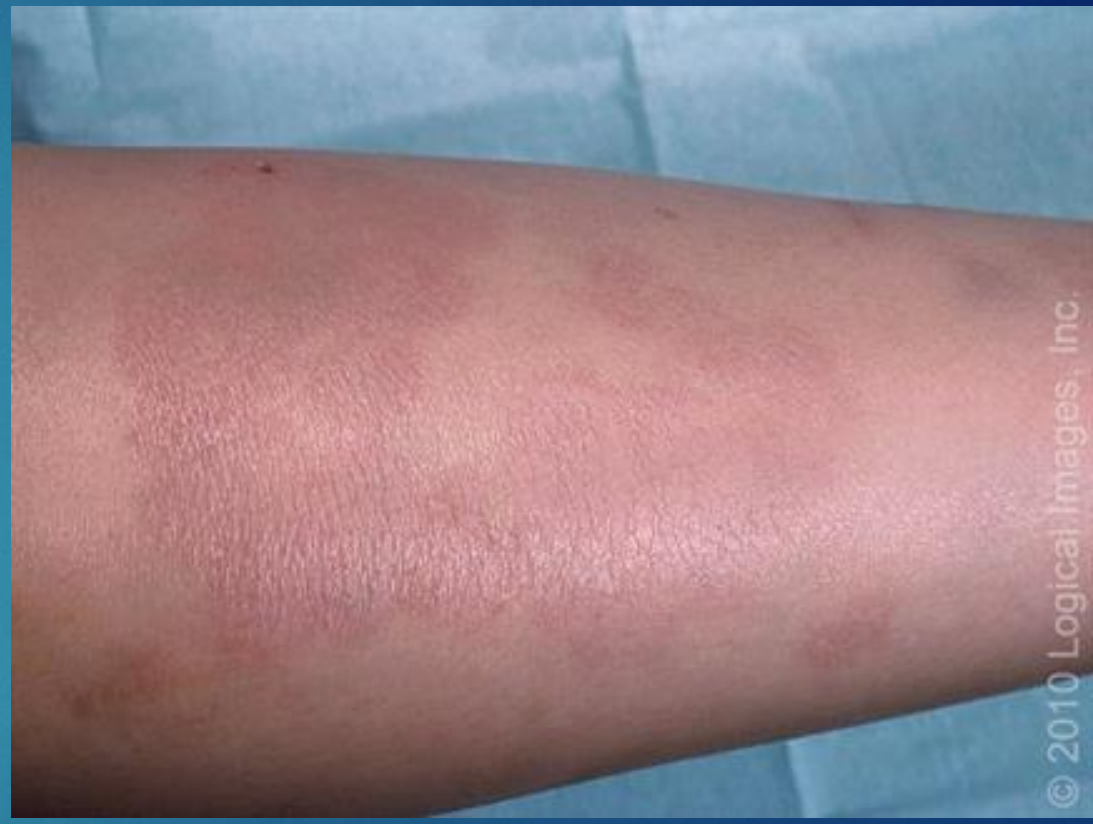
Clinical – Perforating GA

- Yellow umbilicated papules with scale crust and focal ulceration
- Location – localized on extremity or widespread
- Asymptomatic, pruritic, or painful
- Onset – children, young adults



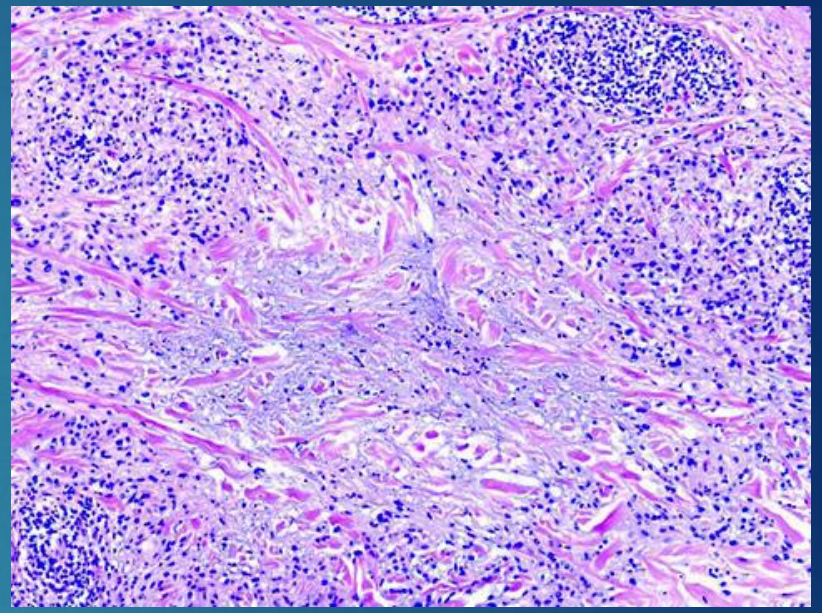
Clinical – Patch GA

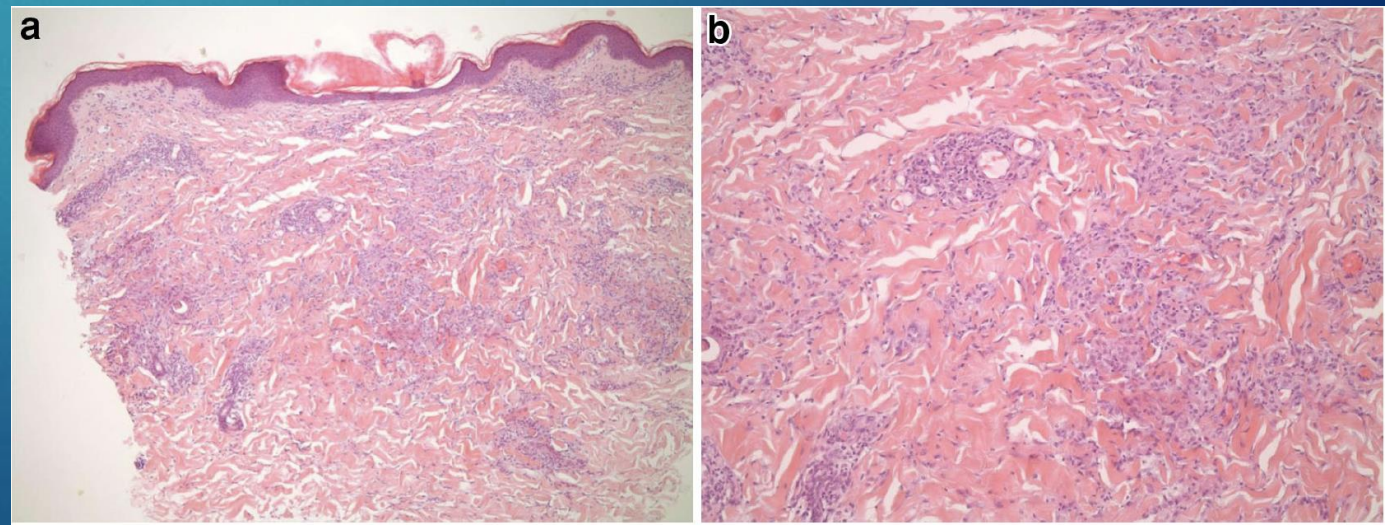
- Symmetric annular patches
- Location – proximal extremities, dorsal feet
- Onset – adults



Pathology

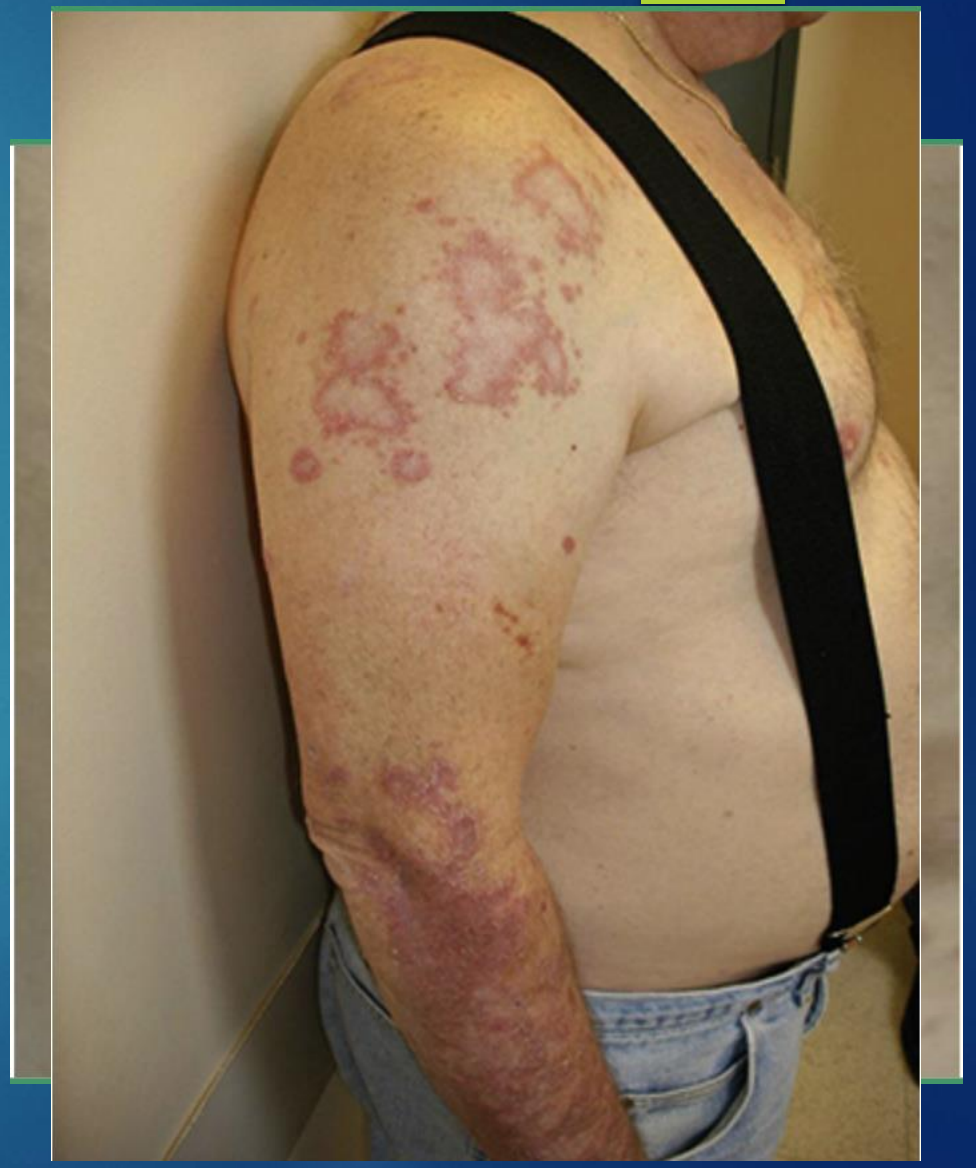
- Lymphohistiocytic infiltrate forming interstitial or palisading granulomas, degenerated collagen, and mucin
- Both patterns in localized and generalized GA
- Patch GA – interstitial
- Subcutaneous GA – palisading
- Perforating GA – transepidermal elimination of mucin and degenerated collagen fibers





Differential Diagnoses – Annular Lesions

- Annular elastolytic giant cell granuloma (actinic granuloma)
- Interstitial granulomatous dermatitis
- Tinea corporis
- Annular lichen planus
- Erythema annulare centrifugum
- Sarcoidosis
- Nodular tertiary syphilis
- Mycosis fungoides
- Borderline leprosy



Differential Diagnoses

- Generalized GA
  - Arthropod assault
  - ID reaction
  - Interstitial granulomatous dermatitis
  - Secondary syphilis
  - Eruptive xanthomas
  - Eruptive syringomas
  - Histiocytomas
- Subcutaneous GA
  - Rheumatoid nodules
  - Epithelioid sarcoma
  - Sarcoidosis
  - Deep fungal infection
  - Tendinous xanthomas
- Perforating GA
  - Reactive perforating collagenosis
  - Perforating folliculitis
  - Elastosis perforans serpiginosa
  - Calcinosis cutis
  - Perforating gout
  - Sarcoidosis
  - Molluscum contagiosum

Diagnosis and Work Up

- Clinical diagnosis
- Punch biopsy with H&E for atypical presentations
- Lipid panel in adults
- Review signs/symptoms/risk factors for diabetes, HIV
- Age-appropriate cancer screening in elderly patients with atypical presentations

Treatments – Overview

- No treatment necessary – often self-limited
- 50% localized GA resolve within 2 years
- Generalized GA more persistent – 25% courses >5 years
- Resolves without scar
- Treatment dependent on type, symptoms, cosmesis

Treatment – Localized GA

- First-line
  - High-potency corticosteroids topical +/- intralesional
    - Clobetasol 0.05% cream BID x 2-4 w
    - Triamcinolone acetonide 2.5-10 mg/cc q 6-8 w
- Others (limited evidence)
  - Cryotherapy
  - Topical calcineurin inhibitors – tacrolimus, pimecrolimus
  - Phototherapy – PUVA, UVA1, NB-UVB, PDT
  - Topical dapsone
  - Intralesional IFN-γ
  - Imiquimod

Treatments – Generalized GA

- First-line
  - High potency topical/intralesional corticosteroids
  - Topical calcineurin inhibitors
    - Tacrolimus 0.1% ointment BID x 6 w
    - Pimecrolimus 1% cream
  - Phototherapy
    - UVA1 – high cumulative doses most effective = 1770 – 1840 J/cm^2
    - PUVA – oral or bath PUVA with cumulative dose 60.4 J/cm^2
    - Narrow-band UVB – cumulative dose 47.7 J/cm^2 → 54% complete/partial response
    - Photodynamic therapy

Treatments – Generalized GA

- Systemic treatment
  - Antimalarials – first line
    - Hydroxychloroquine – 3 – 6 mg/kg/d
    - Chloroquine – 3 mg/kg/d
  - TNF-α inhibitors
    - Adalimumab – 80 mg at week 0 → 40 mg every other week SQ
    - Infliximab – 5 mg/kg at weeks 0, 2, 6 → every month IV
  - Isotretinoin – 0.5-1 mg/kg/d
  - Dapsone – 100 mg/d
  - Pentoxifylline – 400 mg TID
  - Nicotinamide – 500 mg TID
  - Cyclosporine – 3-4 mg/kg/d
  - ROM (rifampin, ofloxacin, minocycline)
  - Vitamin E oral – 400-600 IU daily
  - Fumaric acid esters – used in Europe
  - Other case reports: doxycycline, clofazimine, allopurinol, methotrexate, hydroxyurea, alkylating agents (chlorambucil), oral calcitriol, defibrotide, etretinate

Treatments – Lasers

- Pulsed dye laser
  - Localized or generalized GA
  - ~1/3 no improvement; ~1/3 some improvement; ~1/3 >50% improvement
- Fractional photothermolysis
  - Case reports – significant improvement height and diameter
- Excimer laser – complete remission ¾ patients

Study	Fluence, J/cm^2	Power density, mW/cm^2	Distance from skin, cm	Treatments (pulses per treatment)
Bronfenbrener *et al.* (2012)[12]	0.3	NR	NR	15 (5)
Nistico *et al.* (2009)[13]	Mean: 1.0	48	15	6–10 (NR)
Sniezek *et al.* (2005)[8]	585	6.75	5	NR	3 (36, 43, 42)

flattening

Treatments - Upcoming

- Radial pulse therapy – indirect mechanotherapy
  - 500 shots, pressure 2.5 bars, frequency 4 pulses/sec
  - Positive effects in all treated GA plaques

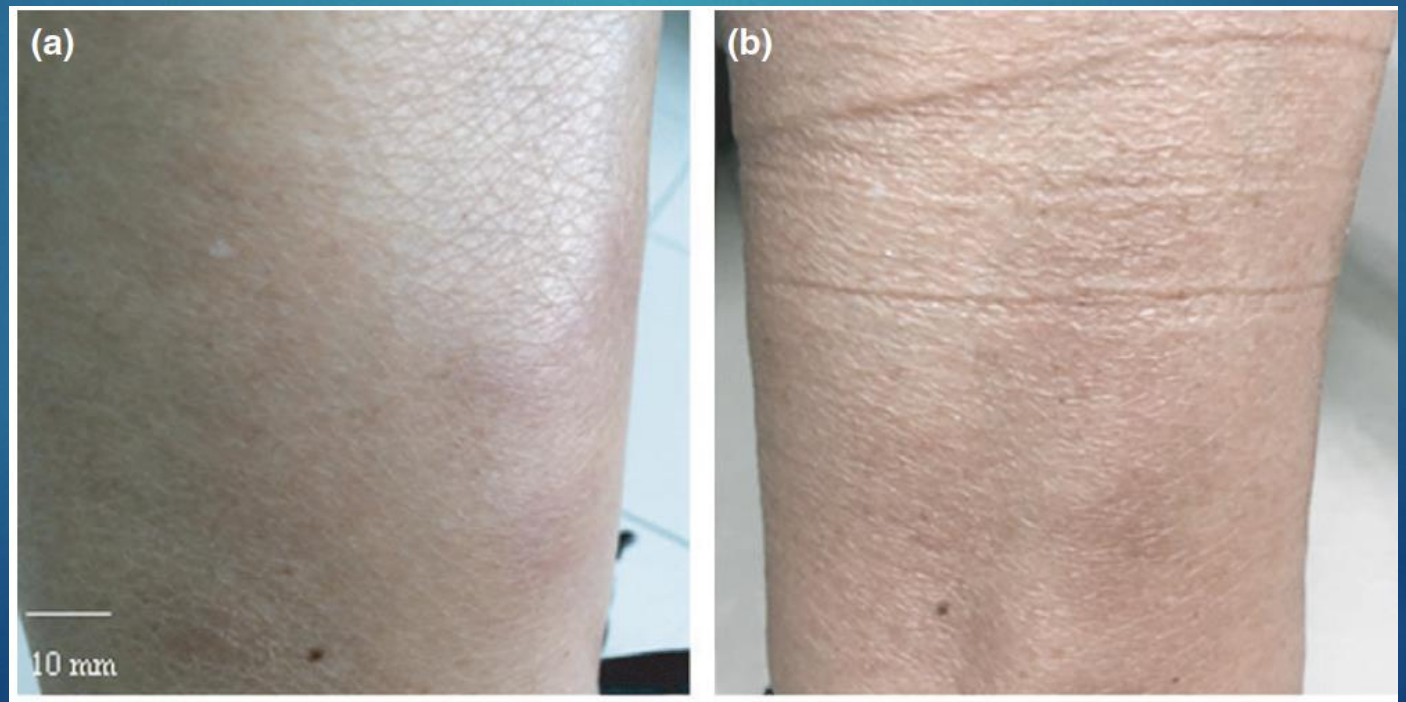
TABLE 1. Plaque characteristics and response to treatment

PLAQUE	LOCATION	DIAMETER	SHAPE	NUMBER OF RPT SESSIONS	DURATION OF TREATMENT	RESULTS
A	Left dorsal forearm	35mm	Approximately square; has raised and indurated annulare ridge	34	26 weeks	Smooth; no ridges, less erythema
B	Left dorsal forearm	5mm	Round; smooth	5	2 weeks	Extinct
C	Right dorsal forearm	44mm	L-shaped; raised and indurated open ridge	25	23 weeks	Partial smoothed ridge, less erythema
D	Right dorsal forearm	8mm	Oval; smooth	25	23 weeks	Split; demonstrated two smaller point-shaped plaques

RPT: radial pulse therapy

Treatments – Subcutaneous GA

- Treatment not indicated
- Surgical excision – recurrence common
- Local hyperthermia – case report
  - 44° C for 30 min, improvement after 10 treatments



Conclusion

- Benign, often self-limited disease
- Work up may include history/labs for diabetes, dyslipidemia, malignancy, and HIV
- Pathogenesis involves possible cell-mediated delayed type IV hypersensitivity reaction to unknown antigen
- Many treatments available from topical and light-based therapy to systemic and biologic medications
- Prospective double blind randomized control trials need to be performed for improved evidence-based treatment

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Thank you!

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