

CUTANEOUS LUPUS ERYTHEMATOSUS: BETTER TREATMENTS, BETTER OUTCOMES

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Dermatology
Society
Meeting,
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2022

DISCLOSURES

- Investigator - Daavlin Corporation, Biogen Incorporation, Pfizer Incorporated
- Consultant - EMD Serono, Bristol Meyers Squibb, Horizon Therapeutics, Biogen Incorporated
- Royalties – MAPI Research Trust

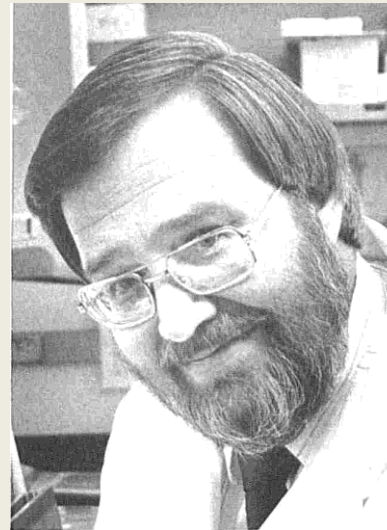
OUTLINE

- **Cutaneous Lupus at University of Texas Southwestern Medical Center**
- **Current Treatments for CLE**
- **Outcome Measures in CLE**
- **Clinical Trials in CLE**

**CLE AT UNIVERSITY
OF TEXAS
SOUTHWESTERN
MEDICAL CENTER**

CUTANEOUS LUPUS AT UNIVERSITY OF TEXAS SOUTHWESTERN

- **Classification of Cutaneous Lupus Erythematosus³**
 - Acute
 - Subacute
 - Chronic
- **Subacute Cutaneous Lupus Erythematosus¹**
 - Case series of 27 patients
 - Associated with anti-Ro antibody²



**James Gilliam,
MD**



**Richard
Sontheimer, MD**

¹Sontheimer RD et al, Arch Dermatol 1979; 115:1409-15

²Sontheimer RD et al, Ann Intern Med 1982; 97:664-71

³Gilliam JN et al, J Amer Acad Dermatol 1981; 4:471-475

MEDICAL GRAND ROUNDS
PARKLAND MEMORIAL HOSPITAL

May 1, 1975

CLINICAL SYNDROMES
WITHIN THE SPECTRUM OF LUPUS ERYTHEMATOSUS

by

JAMES N. GILLIAM, M.D.



Courtesy of Lela Lee, MD

UNIVERSITY OF TEXAS SOUTHWESTERN CUTANEOUS LUPUS REGISTRY

- Established in 2008
- Longitudinal observational study of patients with CLE
- Purpose: To advance the clinical care of cutaneous lupus patients through improvements in diagnosis, prognosis, and management



**UT
Southwestern
Medical Center**



**Parkland
Health**

UNIVERSITY OF TEXAS SOUTHWESTERN CUTANEOUS LUPUS REGISTRY

- **358 patients with CLE**
- **303 Females (84.6%)**
- **1036 total visits**

Race/Ethnicity	N	%
Black Non-Hispanic	182	50.8%
White Non-Hispanic	118	33.0%
White Hispanic	38	10.6%
Asian	17	4.7%
Mixed	3	0.8%

DATA AND SPECIMEN COLLECTION

- **Patient History**
- **Clinical Data**
- **Blood samples**
- **Skin biopsies**
- **Photographs**

UTSW CLE REGISTRY AREAS OF FOCUS

- Relationship between CLE and SLE
- Disease course and patterns of CLE patients
- Outcome measures in CLE
- Immunology of CLE

CURRENT TREATMENTS FOR CLE

TREATMENT ALGORITHM FOR CUTANEOUS LUPUS

Limited

- Photoprotective methods
- Topical Steroids/
Immunomodulators
- Intralesional Steroids (2.5-10 mg/cc)

Modest/ Refractory Limited

- Prednisone (up to 0.5 mg/kg/day) for rapid symptom reduction
- Hydroxychloroquine (200 mg QD-BID) (based on weight)
- Quinacrine (100 mg QD)
- Chloroquine (125-250 mg QD) (based on weight)

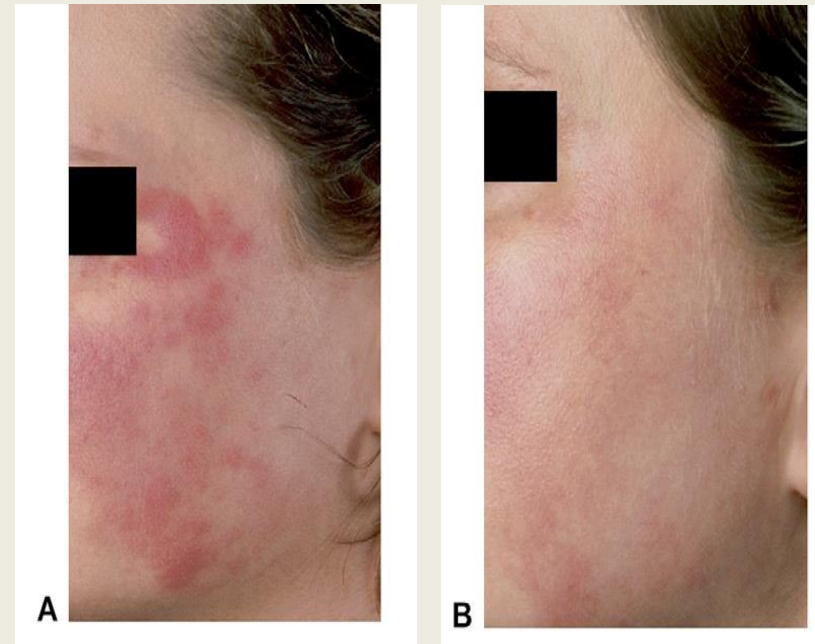
TREATMENT ALGORITHM FOR CUTANEOUS LUPUS

**Diffuse/
Refractory
Modest**

- Prednisone (up to 1 mg/kg/day)
- Mycophenolate mofetil (1000-1500 mg BID)
- Methotrexate (7.5-25 mg QWK)
- Azathioprine (2-3 mg/kg/day)
- Thalidomide (25-100 mg qHS), lenalidomide (2.5-10 mg qHS)
- Dapsone (25-100 mg BID)

RCT HAVE SHOWN BENEFICIAL EFFECTS OF TOPICAL MEDICATIONS IN CLE

- Tacrolimus 0.1% ointment¹
 - RCT of 30 CLE patients - tacrolimus 0.1% ointment or vehicle BID x 12 weeks
 - Significant improvement seen in tacrolimus-treated lesions at day 28 and 56
- Pimecrolimus vs. betamethasone²
 - RCT of 10 patients with facial DLE on either cream for 8 weeks BID
 - Pimecrolimus - 86% decrease in disease severity
 - Betamethasone - 73% decrease in disease severity
 - No difference



Baseline

**Day 28
(tacrolimus)**

¹Kuhn A et al, J Amer Acad Dermatol 2011; 65:54-64

²Barikbin B et al, Clin Exp Dermatol 2009; 34:776-780

RCT OF ACITRETIN AND HYDROXYCHLOROQUINE SHOWED BOTH CAN HELP TREAT REFRACTORY CLE

- **Acitretin 50 mg QD vs.
hydroxychloroquine 400 mg QD x 8
weeks in 58 CLE patients**
 - **Overall skin improvement seen in 46%
acitretin and 50% hydroxychloroquine patients**
 - **No significant difference between medications**

LIMITATIONS

- **Small sample size**
- **Unvalidated outcome measures for skin severity**
- **Lack of patient-reported outcome measures**

OUTCOME MEASURES IN CLE

EMERGING OUTCOME MEASURES IN CLE

- **Skin disease severity scores**
 - **Cutaneous Lupus Disease Area and Severity Index (CLASI)**
 - **Cutaneous Lupus Activity Investigator Global Assessment (CLA-IGA)**
- **Patient-reported outcome measures**
 - **Cutaneous Lupus Erythematosus Quality of Life (CLEQoL)**

CUTANEOUS LUPUS DISEASE AREA AND SEVERITY INDEX (CLASI)

- Validated skin severity measure in CLE
- Scores for disease activity and damage
- Activity (maximum - 70 points)
 - Erythema
 - Scale/Hypertrophy
 - Acute Hair loss/non-scarring alopecia
 - Mucous membrane lesions
- Damage (maximum - 80 points)
 - Scarring/scarring alopecia
 - Dyspigmentation

Activity

Cutaneous Lupus Erythematosus Disease Activity and Severity Index (CLASI)

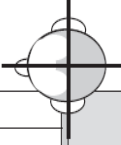
Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

Ex t e n s i v e	activity			damage		
	Anatomical Location	Erythema	Scale/Hypertrophy	Dyspigmentation	Scarring/Atrophy/Panniculitis	Anatomical Location
		0-absent 1-pink; faint erythema 2-red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentation	0 ... absent 1 ... scarring 2 ... severely atrophic scarring or panniculitis	
	Scalp				See below	Scalp
	Ears					Ears
	Nose (incl. malar area)					Nose (incl. malar area)
	Rest of the face					Rest of the face
	V-area neck (frontal)					V-area neck (frontal)
	Post. Neck &/or shoulders					Post. Neck &/or shoulders
	Chest					Chest
	Abdomen					Abdomen
	Back, buttocks					Back, buttocks
	Arms					Arms
	Hands					Hands
	Legs					Legs
	Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	Dyspigmentation
0-absent; 1-lesion or ulceration	Report duration of dyspigmentation after active lesions have resolved (verbal report by patient ... tick appropriate box) <input type="checkbox"/> Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains) <input type="checkbox"/> Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

Recent Hair loss (within the last 30 days/as reported by patient)		NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both
1-Yes 0-No		
Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.		
Alopecia (clinically not obviously scarred)	Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant	0-absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score

(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score

(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

Damage

Albrecht J, Werth VP, et al J Invest Dermatol 2005; 125:889-894

Figure 1
Cutaneous LE Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion



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Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 ... absent 1 ... scarring 2 ... severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
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Hands					Hands
Legs					Legs
Feet					Feet

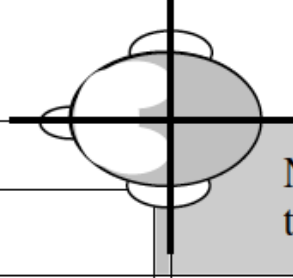
Mucous membrane

Dyspigmentation

Mucous membrane lesions (examine if patient confirms involvement)	Report duration of dyspigmentation after active lesions have resolved (verbal report by patient ... tick appropriate box)
0-absent; 1-lesion or ulceration	<input type="checkbox"/> Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains) <input type="checkbox"/> Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

ALOPECIA IN CLASI

Alopecia



Recent Hair loss
(within the last 30 days / as reported by patient)

1-Yes
0-No

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)

0-absent
1-diffuse; non-inflammatory
2-focal or patchy in one quadrant;
3-focal or patchy in more than one quadrant

Scarring of the scalp (judged clinically)

0- absent
3- in one quadrant
4- two quadrants
5- three quadrants
6- affects the whole skull

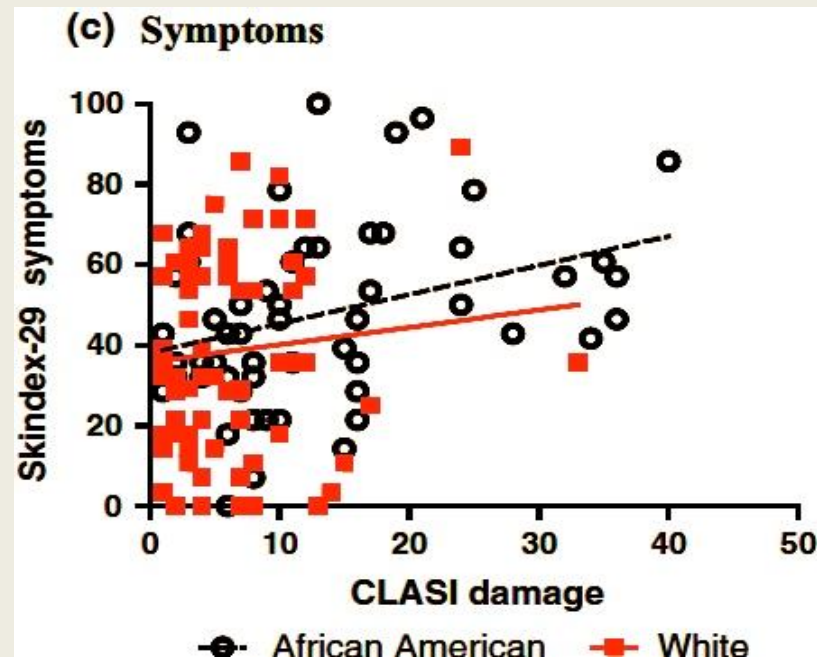
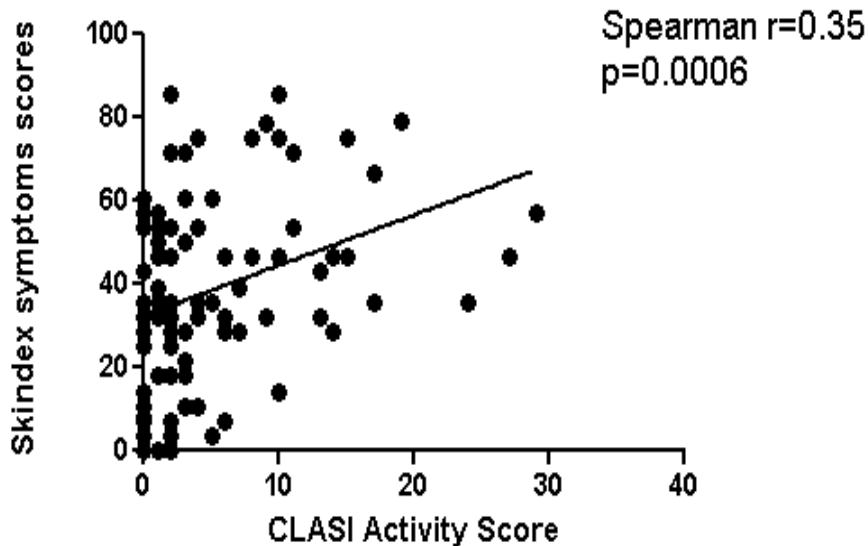
Total Activity Score

(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy,

Total Damage Score

(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation,

CLASI ACTIVITY SCORES NOT CLASI DAMAGE SCORES CORRELATE WITH QUALITY OF LIFE



Vasquez R, Werth VP, Chong BF, et al, Br J Dermatol 2013; 168:145-53
Klein R, Werth VP, et al J Am Acad Dermatol. 2011; 64: 849-58
Verma SM, Werth VP, et al, Br J Dermatol 2014; 170:315-321

Natural history of disease activity and damage in patients with cutaneous lupus erythematosus

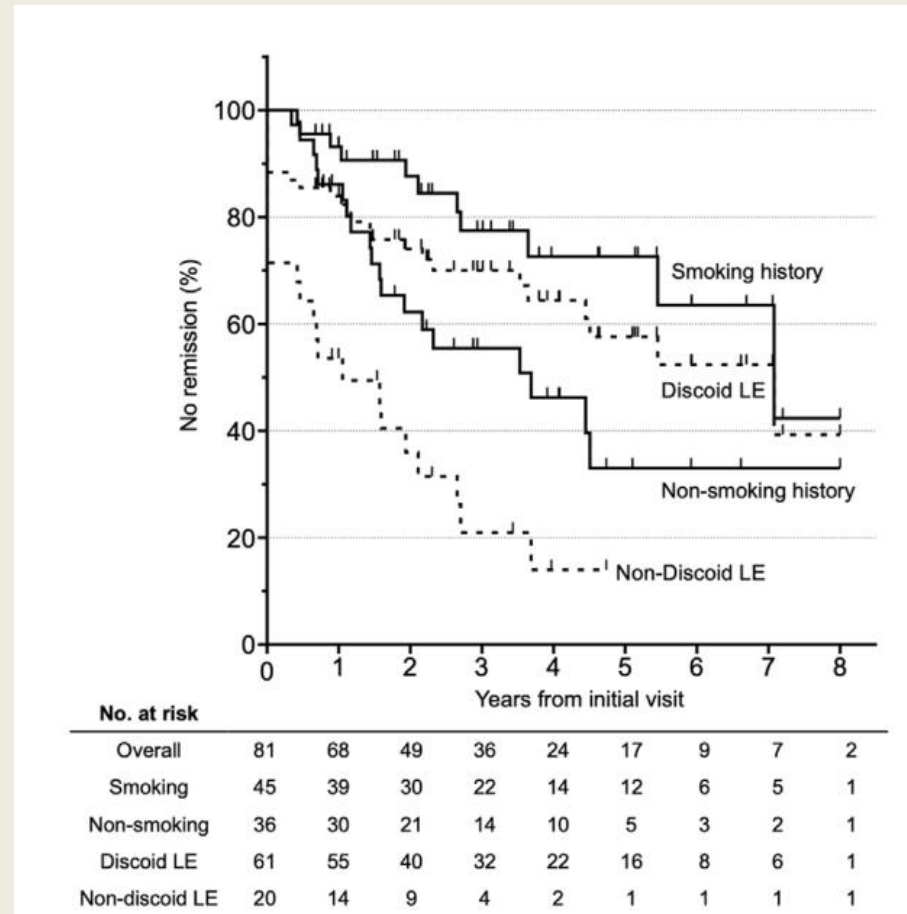
Khor Jia Ker, MRCP,^{a,b} Noelle M. Teske, MD,^c Rui Feng, PhD,^d
Benjamin F. Chong, MD, MSCS,^c and Victoria P. Werth, MD^{b,e}
Singapore, Singapore; Philadelphia, Pennsylvania; and Dallas, Texas

- Observation study of 83 patients with CLE at UTSW and Penn followed for at least two years
- Most patients had improved (37.3%) or stable (45.8%) disease activity trends
- Clinical factors associated with improved disease activity and damage

Improved Disease Activity	Improved Disease Damage
Baseline CLASI activity score ≥ 10	Baseline CLASI damage score ≥ 10
Baseline CLASI damage score ≥ 10	
Minority race	
Disease duration ≤ 1 year	

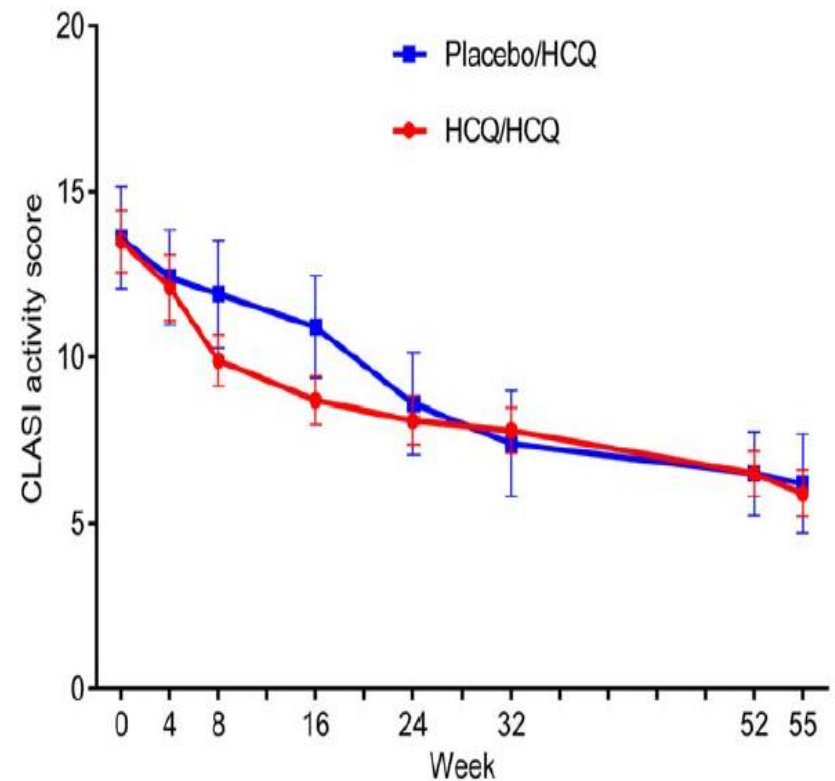
ABSENCE OF DLE AND NON-SMOKERS ARE MORE LIKELY TO HAVE CLE DISEASE REMISSION

- 97 patients with CLE
- 46% achieved disease remission (CLASI-A=0)
 - Absence of DLE
 - Lifetime non-smokers
- 63% experienced disease recurrence (CLASI-A>0)



HYDROXYCHLOROQUINE IMPROVES CLE

- RCT of 103 patients with CLE
 - Hydroxychloroquine (HCQ) vs. placebo for 1st 16 weeks, then ALL treated with 36 weeks of HCQ
 - HCQ - CLASI-A score improvement of 4.6 ($p < 0.0001$)
 - Placebo - CLASI-A score improvement of 3.2 ($p = 0.002$)
 - HCQ-treated patients achieved secondary endpoints
 - Improvement in physician global assessment scores



LENALIDOMIDE IS A THALIDOMIDE ANALOG USED TO TREAT CLE

- Lenalidomide – thalidomide analog
- Open-label trial of 5 refractory CLE patients
 - 5 mg QD x 6 weeks
 - 10 mg QD in non-responders, 5 mg QOD in responders
- CLASI activity scores improved from 21.4 (baseline) to 8.6 (week 12)



CUTANEOUS LUPUS ACTIVITY INVESTIGATOR GLOBAL ASSESSMENT (CLA-IGA)

- **5-point Likert scale that evaluates severity of signs of CLE disease activity**
 - Erythema
 - Scale
 - Elevation
 - Follicular involvement
 - Secondary changes

CLA-IGA

Cutaneous Lupus Activity Investigator's Global Assessment (CLA-IGA)

0- Clear	<p>Erythema - none Scale - none Edema/infiltration - none Follicular involvement: <i>follicular plugging / follicular hyperkeratosis – absent</i> Secondary Change: no vesicles, erosion, crusting</p>
1- Almost clear	<p>Erythema – faint Scale - minimal Edema/infiltration - minimal (barely palpable) Follicular involvement: <i>follicular plugging / follicular hyperkeratosis – minimal and diffuse</i> Secondary Change: no vesicles, erosion, crusting</p>
2- Mild	<p>Erythema – pink/mild Scale – thin, patchy Edema/infiltration – mild, palpable, barely visible Follicular involvement: <i>follicular plugging / follicular hyperkeratosis (recent) in one quadrant of scalp</i> Secondary Change: mild superficial erosion, crusting present; no vesicles</p>
3- Moderate	<p>Erythema - red erythema Scale – thick, patchy Edema/infiltration – moderately raised, palpable, visible Follicular involvement: <i>follicular plugging / follicular hyperkeratosis in more than one quadrant of scalp</i> Secondary Change: moderate, superficial erosion, crusting; no vesicles</p>
4- Severe	<p>Erythema – violaceous/bright red erythema Scale – thick, confluent Edema/infiltration – thick, raised, easily palpable, easily visible Follicular involvement: <i>follicular plugging / hyperkeratosis in more than two quadrants of scalp</i> Secondary Change: Marked erosion, crusting and/or vesicular change present</p>

QUALITY OF LIFE MEASURES USED IN CLE TRIALS ARE FOR GENERIC SKIN DISEASES

- DLQI – Dermatology Life Quality Index
- **SKINDEX**
- SF-36 – Short-Form 36

SKINDEX-29+3 MEASURES IMPACT OF SKIN DISEASE ON QUALITY OF LIFE IN CLE



- 29 questions
- 3 domains
 - Symptoms (physical burden)
 - Emotions (psychological effects)
 - Functioning (changes to daily life)
- 4th domain (lupus-specific subscale) - 3 questions (SKINDEX-29+3)

CLEQOL IS A DISEASE-SPECIFIC QUALITY OF LIFE QUESTIONNAIRE FOR CLE

QUALITATIVE AND OUTCOMES RESEARCH

BJD
British Journal of Dermatology

Validation and reliability of a disease-specific quality-of-life measure in patients with cutaneous lupus erythematosus

M.E. Ogunsanya ¹, S.K. Cho,² A. Hudson² and B.F. Chong ²

¹College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73117, U.S.A.

²Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX 75390, U.S.A.

- Validation cross-sectional study of CLEQoL
 - SKINDEX-29 + 7 CLE-specific questions (e.g. photosensitivity, alopecia, dyspigmentation)



Ogunsanya ME, Chong BF, et al, *Int J Women Dermatol* 2018; 4:152-158

Ogunsanya ME, Chong BF, et al, *Br J Dermatol* 2019; 180:1430-1437

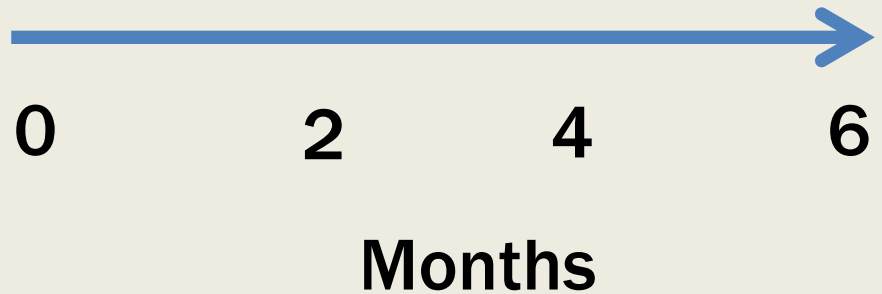
CLEQOL QUESTION EXAMPLES

Directions: These questions concern your feelings over the past 4 weeks about **the skin condition that has bothered you the most**. Check the answer that comes closest to the way you have been feeling

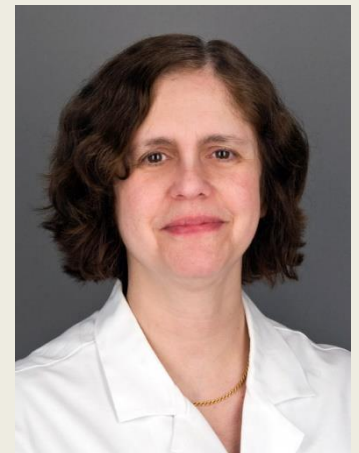
	Never (0)	Rarely (25)	Sometimes (50)	Often (75)	All the time (100)
1. My skin hurts. (SYMPTOMS)					
2. My skin condition affects how well I sleep. (FUNCTIONING)					
3. I worry that my skin condition may be serious. (EMOTIONS)					
31. I worry about going outside because the sun might flare my disease (PHOTOSENSITIVITY)					
35. My skin condition influences the clothes I wear (BODY IMAGE/COSMETIC EFFECTS)					

OBSERVATIONAL STUDY TO ESTABLISH OUTCOME MEASURES FOR CLE

- 24-week observational study of patients with skin lupus on treatments
- Goal – establish standardized outcome measures for therapeutic efficacy in CLE trials

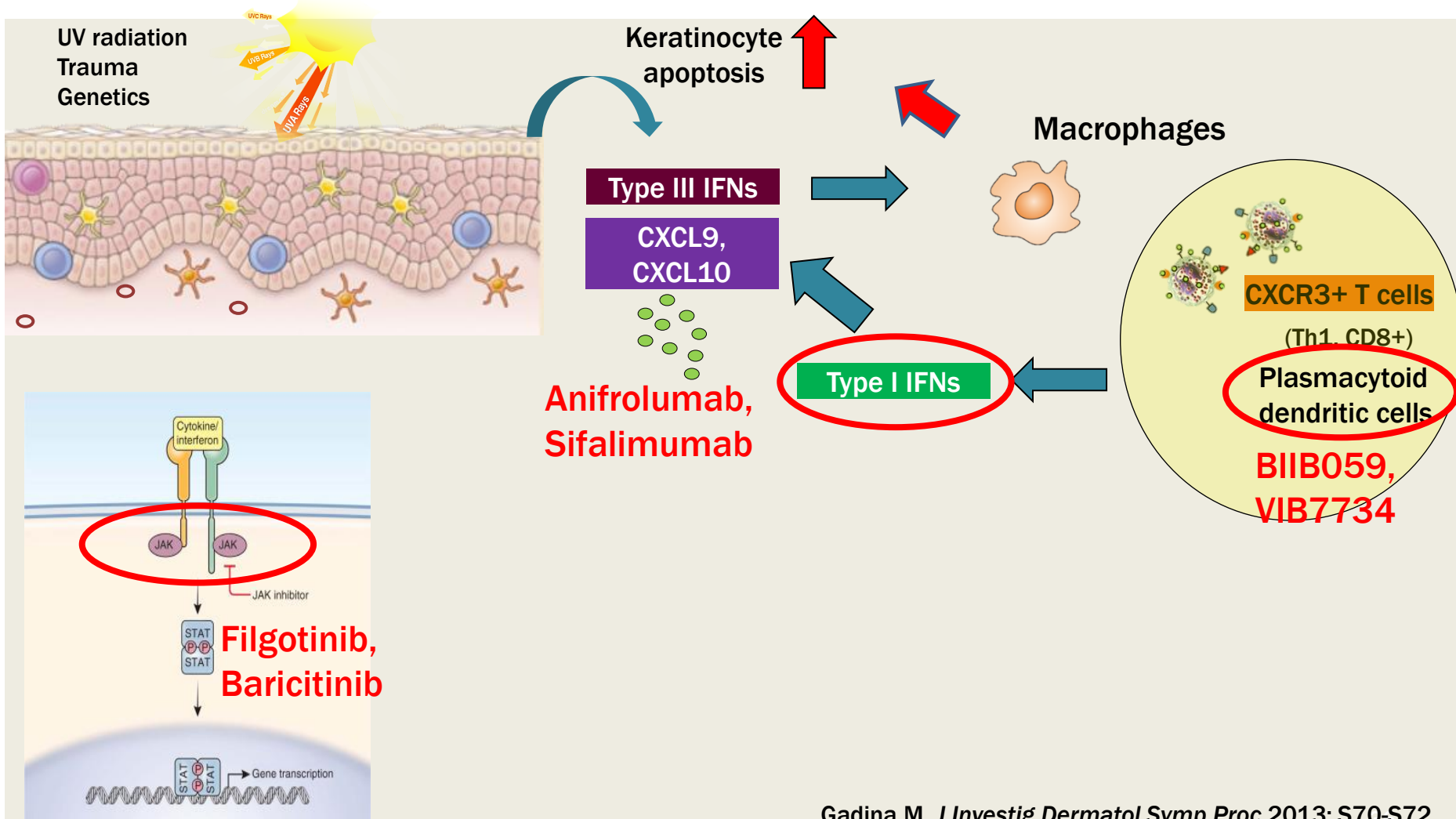


Questionnaires
Examination
Photographs



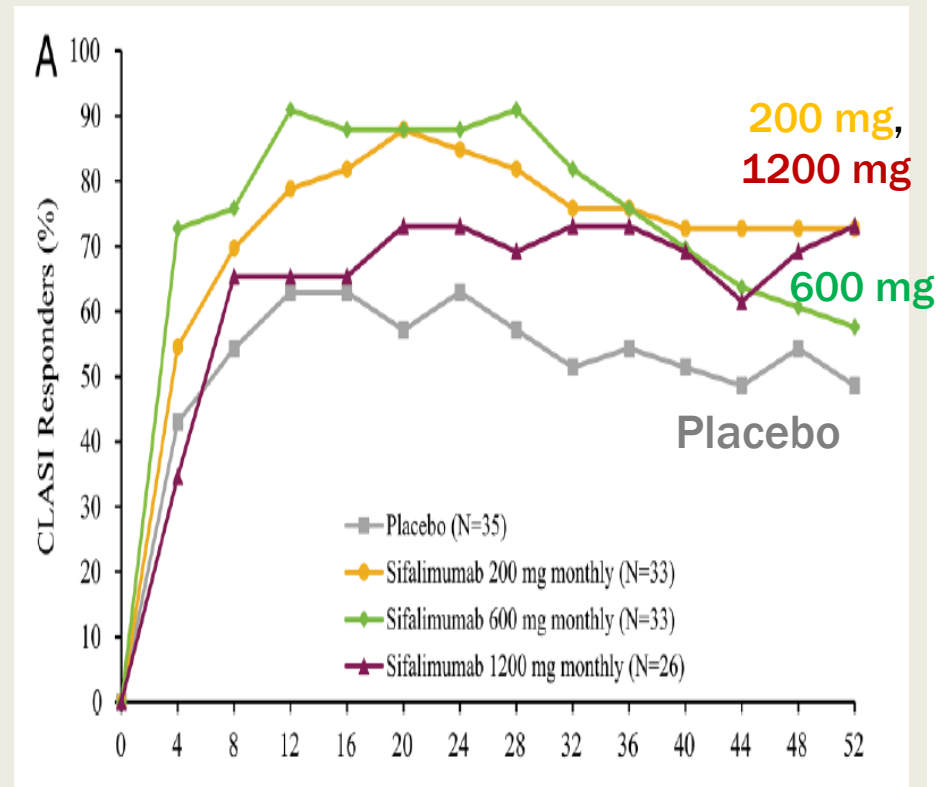
CLINICAL TRIALS IN CLE

THERAPEUTIC TARGETS IN CLE

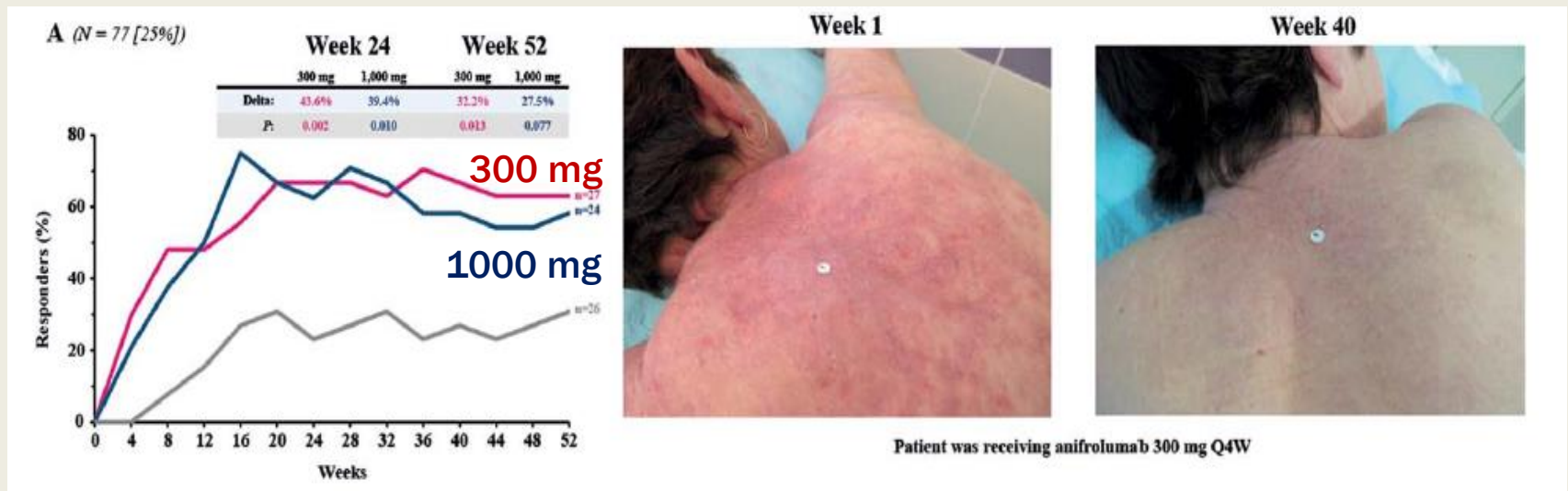


SIFALIMUMAB MAY BE EFFECTIVE FOR CLE

- Sifalimumab – anti-interferon- α mAb
- Phase IIB RCT in 431 SLE patients (127 with CLE) treated with IV sifalimumab 200 mg, 600 mg, or 1200 mg or placebo q4 weeks
 - More CLE patients on 200 mg and 1200 mg doses reached treatment response (≥ 4 CLASI-A score improvement) than placebo at week 52
 - Adverse events – SLE flares, infections



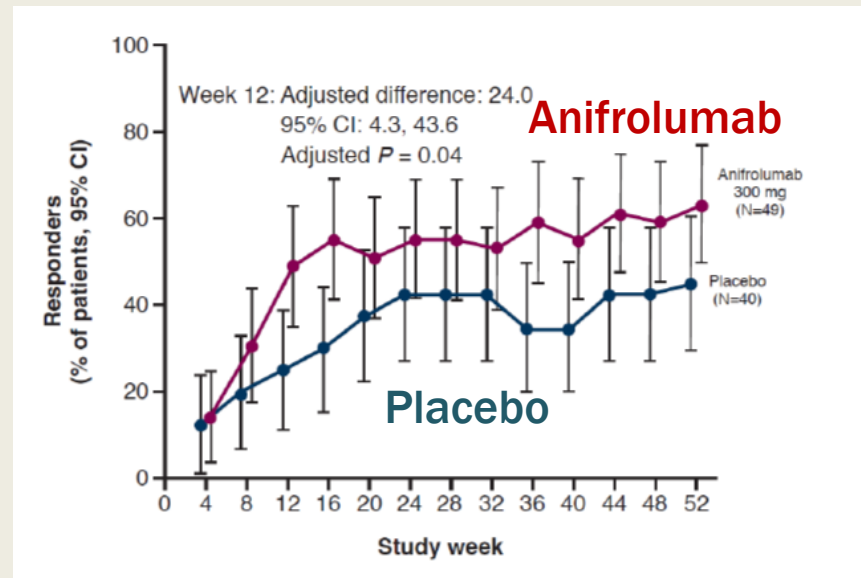
ANIFROLUMAB MAY BE EFFECTIVE FOR CLE



- Anifrolumab – type I IFN receptor antagonist
- Phase IIB of 305 SLE patients treated with IV anifrolumab 300 mg, 1000 mg or placebo q4 weeks
 - More anifrolumab-treated patients with CLE (63% (300 mg), 58.3% (1000 mg)) showed treatment response (≥50% improvement in CLASI-A) than placebo (30.8%)
 - Adverse effects – headache, infections (herpes zoster)

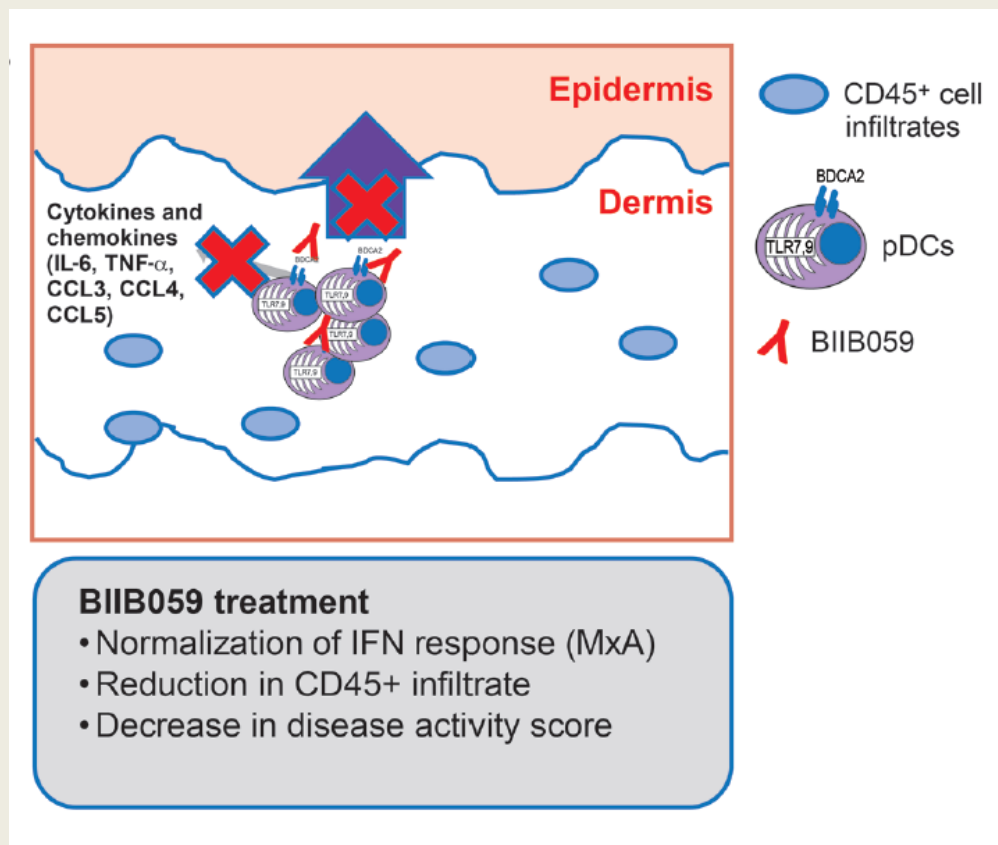
ANIFROLUMAB MAY BE EFFECTIVE FOR CLE

- Phase III of 362 SLE patients (89 with CLE) treated with IV anifrolumab 300 mg or placebo q4 weeks x 48 weeks
 - More anifrolumab-treated patients with CLE (49%) showed treatment response than placebo (25%) ($p=0.04$)
 - Adverse effects – infections (URIs, nasopharyngitis, Zoster)
- FDA approved for lupus in July 2021



ANTIBODY TARGETING PLASMACYTOID DENDRITIC CELLS (BIIB059) MAY HELP CLE

- BIIB059 – mAb targeting BDCA2 on plasmacytoid dendritic cells (pDCs)
- Phase I RCT trial of 12 patients of SLE and active CLE¹
 - 1 IV dose of 20 mg/kg
 - 6/8 patients showed clinical response in skin
- Phase II RCT trial of 132 patients with CLE²
 - Dose-related improvement seen in CLASI-A scores

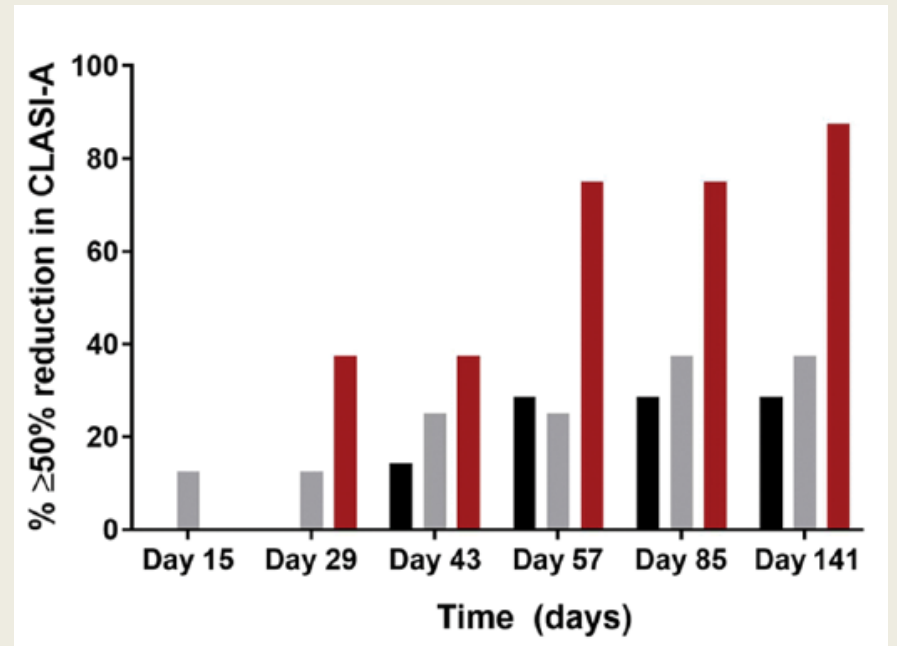


¹Furie R, et al, J Clin Invest 2019; 129:1359-1371

²Werth V et al, Ann Rheum Dis 2020; 79:120-121

ANOTHER ANTIBODY TARGETING PLASMACYTOID DENDRITIC CELLS (VIB7734) MAY HELP CLE

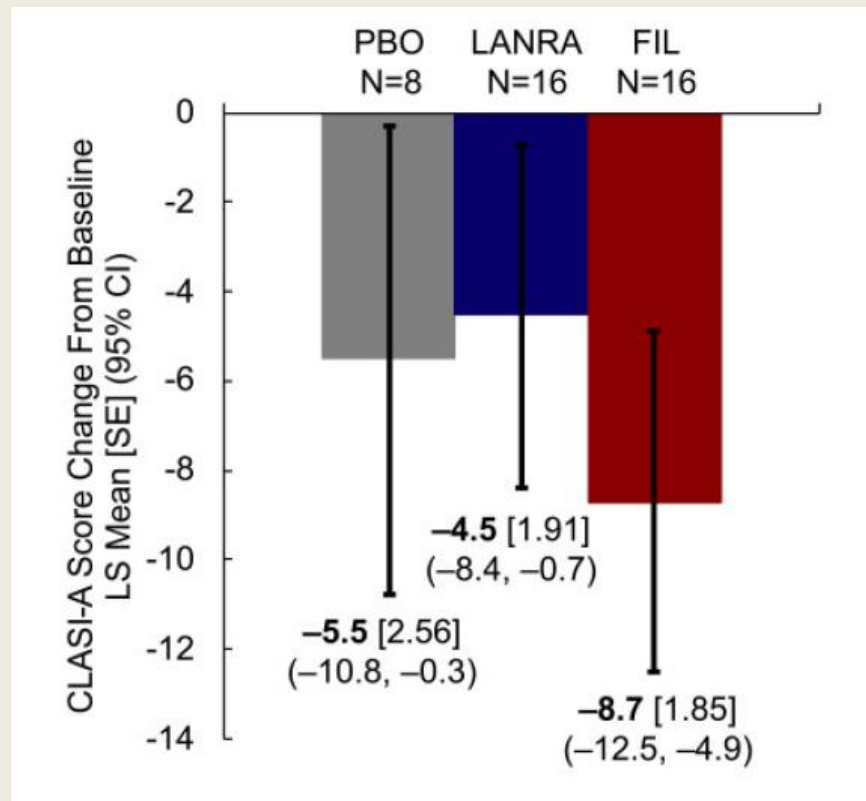
- VIB7734 – anti-ILT7 mAb which depletes pDCs and decreases IFN- α production
- Phase 1b study of 23 CLE patients
 - Decreases in blood and skin pDCs and type I IFN gene expression
 - More patients receiving 150 mg VIB7734 achieved disease response (CLASI-A score \geq 50% improvement) vs 50 mg VIB7734 and placebo at day 141



■ Placebo ■ VIB7734, 50 mg ■ VIB7734, 150 mg

JAK AND SYK INHIBITORS HAVE YET TO SHOW SIGNIFICANT IMPROVEMENT IN CLE

- Filgotinib (JAK1 inhibitor) and lanraplenib (spleen kinase (Syk) inhibitor)¹
 - Phase 2 RCT of 45 CLE patients did not meet primary endpoint goal
 - More patients with severe disease did better with filgotinib
- Baricitinib (JAK1/2 inhibitor)²
 - Phase 2 RCT study of 314 SLE patients
 - No significant improvement in CLASI-A score seen

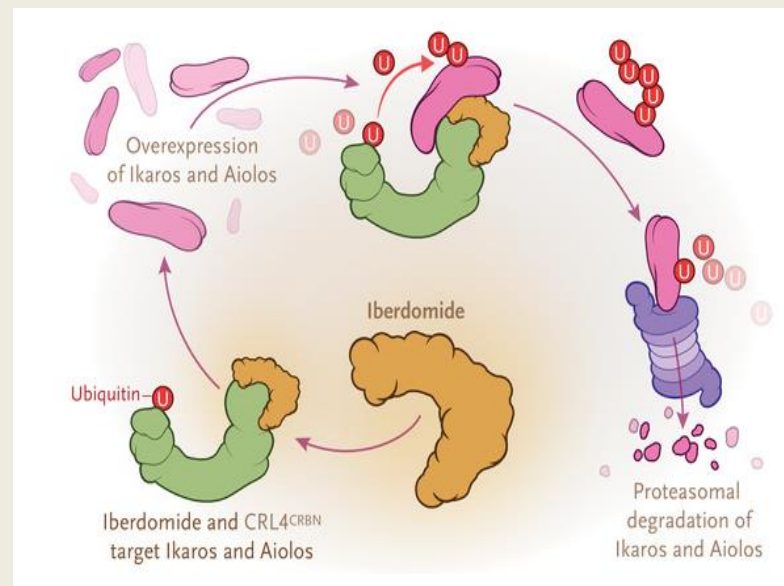


¹Werth VP et al, Rheumatology (Oxford) 2021 [epub]

²Wallace DJ et al, Lancet 2018; 392:222-31

IBERDOMIDE MAY HELP REFRACTORY CLE

- Iberdomide – cereblon modulator that degrades Ikaros and Aiolos
- Phase II study of 288 patients with SLE treated with 0.45, 0.30 or 0.15 mg or placebo daily x 24 weeks
 - 64 patients with CLE
 - 68% of 0.45 mg iberdomide patients (n=19) and 73% of 0.15 mg iberdomide (n=11) reached CLASI-A-50 vs. 50% on placebo (n=16)
- Adverse events – UTIs, URIs, neutropenia



SUMMARY

- **CLE-specific outcome measures are important in identifying promising medications in CLE.**
- **More clinical trials focused on CLE patients are emerging.**
- **Clinical trials in CLE are focusing on targets including**
 - **Type I interferons and their receptors**
 - **Plasmacytoid dendritic cells**
 - **Janus kinases**

RHEUMATOLOGIC DERMATOLOGY SOCIETY

- Specializing in rheumatic skin diseases
- Annual meeting with American College of Rheumatology meeting
 - Research
 - Clinical Pearls
 - Delphi consensus
- Residents, medical students are welcome to join!

