

# **Lupus Skin Teleconference**

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# Overview

- **Epidemiology**
- **Clinical classification**
- **Diagnosis, Causes**
- **Development of a disease severity measure (CLASI)**
- **Systematic epidemiologic, translational, and clinical studies**
- **Approaches to therapy**

## Incidence of Cutaneous LE

- 156 patients with newly diagnosed CLE (100 females and 56 males)
- Incidence: 4.3 (95% CI 3.62-4.98) per 100,000
- Prevalence: 73.24 (95% CI, 58.29-88.19) per 100,000
- 19% progression to SLE
- Incidence of cutaneous lupus about as frequent as SLE

*Durosaro et al, Arch Dermatol 145:249, 2009*

# **Challenges of Current ACR Classification**

## **Criteria for SLE: Issues of case definition of Cutaneous LE vs SLE**

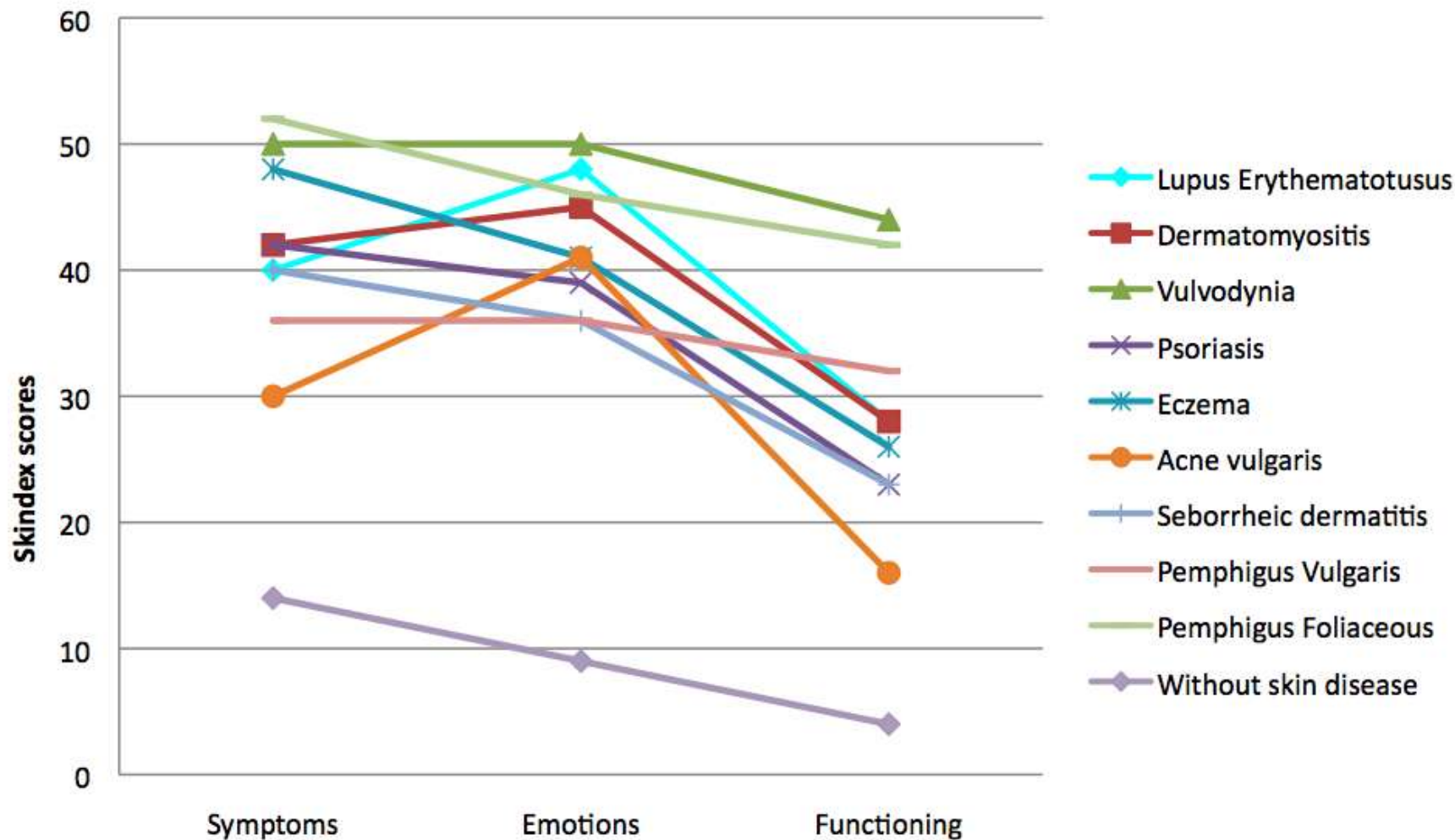
- **Butterfly rash**
- **Discoid lupus**
- **Photosensitivity: Definition unclear**
  - **Better to have specific terminology for types of skin lesions induced**
- **Oral ulcers: Overlap with Discoid LE**

# ACR Dermatologic Criteria for SLE

- **Many dermatologic criteria**
  - **Can meet SLE criteria with only dermatologic criteria or with no significant systemic disease**(*Parodi and Rebora, Dermatol 194:217, 1997*)

*Albrecht J, Berlin JA, Braverman IM, Callen JP, Connolly MK, Costner MI, Dutz J, Fivenson D, Jorizzo JL, Lee LA, McCauliffe DP, Sontheimer RD, Werth VP. Dermatology position paper on the revision of the 1982 ACR criteria for SLE. Lupus, 2004.*

# QoL (Skindex): Cutaneous Lupus vs Other Diseases



*Klein R, et al, JAAD, 2011*

## **QoL in Skin lupus**

- **Cutaneous lupus has a large impact on emotional quality of life**
- **Impact on emotional function is worse than hypertension, recent heart attack, or type II diabetes**

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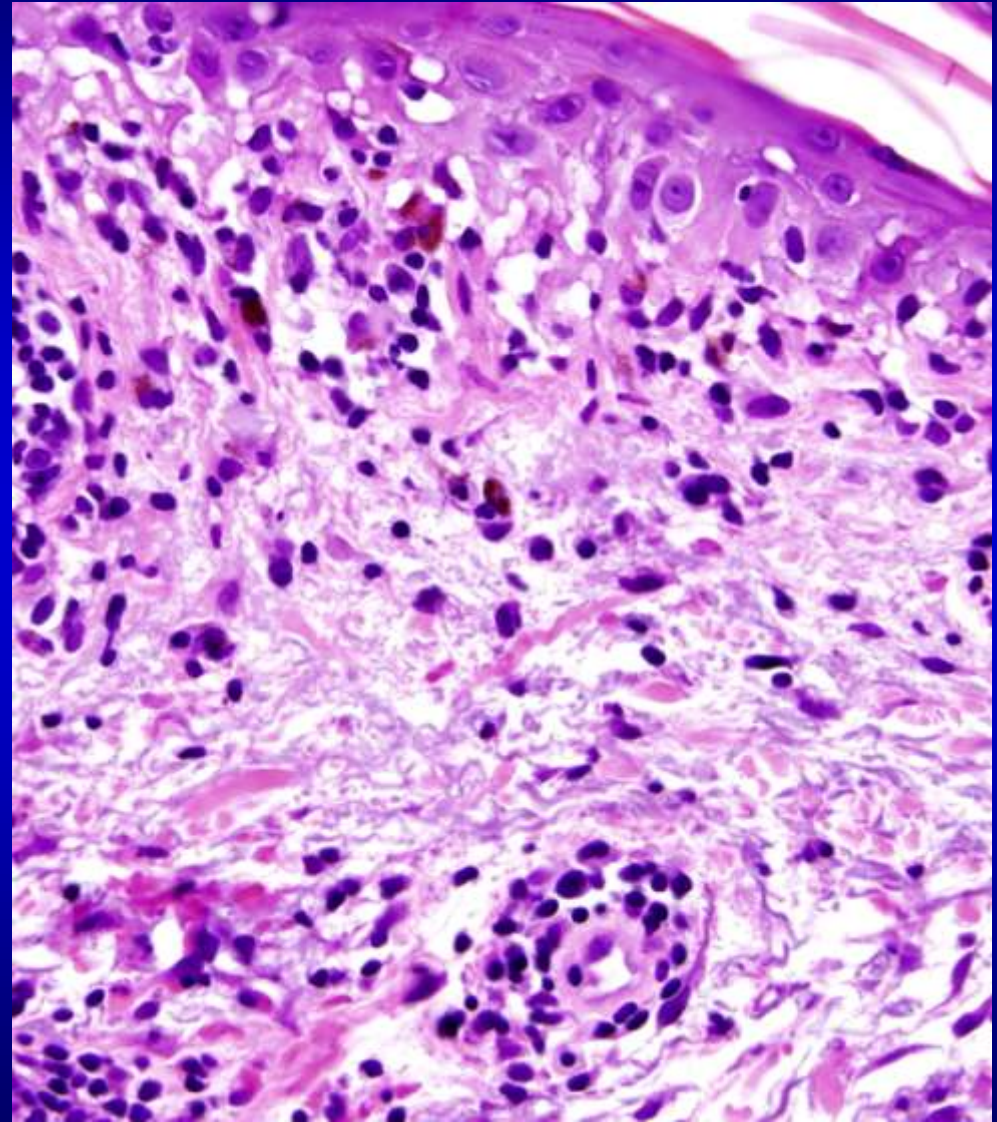
# Cutaneous LE

- **LE-specific**
  - **Skin biopsy shows LE-specific histology**
  - **Diagnosis of LE can be confirmed regardless of if ACR criteria for SLE are present**
- **LE-nonspecific**
  - **Not histopathologically distinct for LE and/or may be seen as a feature of another disease process**

# LE-nonspecific Skin Lesions

- **Chronic Cutaneous LE**
  - **DLE: localized, generalized, hypertrophic**
  - **Lupus panniculitis**
  - **Tumid LE**
- **Subacute Cutaneous LE**
- **Acute cutaneous LE**

# DLE



# Skin Disease in Lupus Erythematosus

- Inflammatory skin disease found in up to 70% of patients with SLE (*Patel and Werth, Derm Clin 19:583,2000*)



SLE



Vasculitis

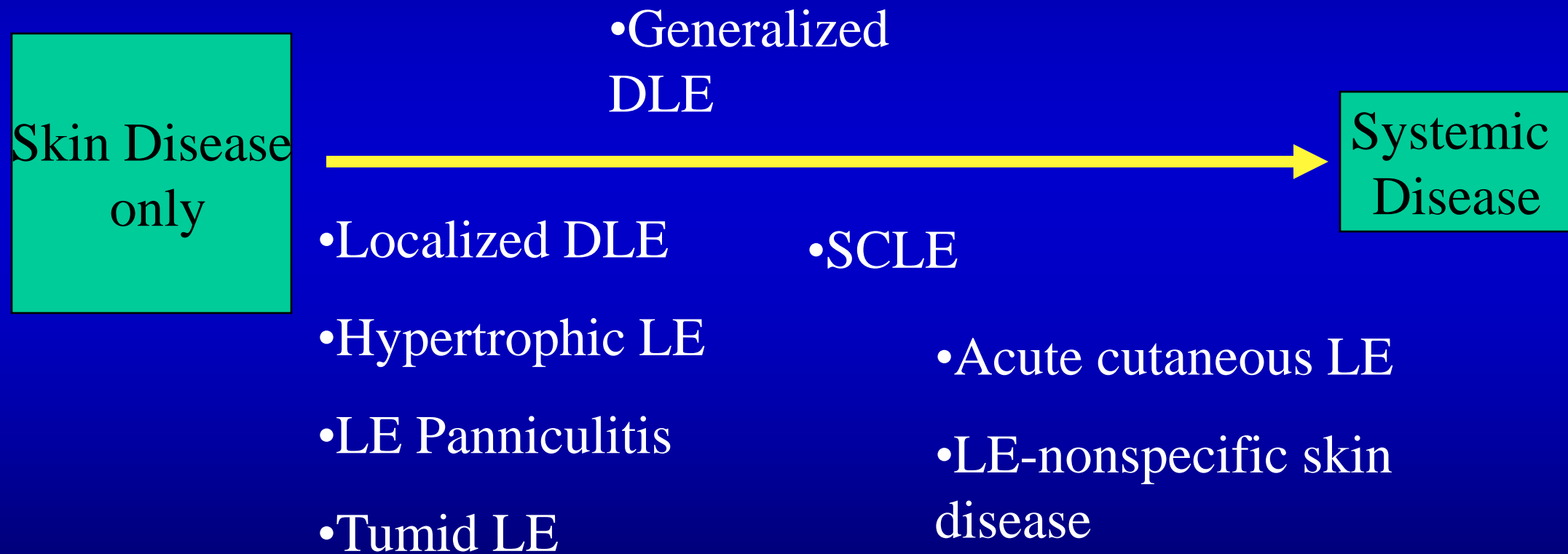


EBA

## LE-nonspecific Skin Lesions

- Usually in the active phase of the disease
- Those with LE-nonspecific lesions had increased disease activity when compared to those with only LE-specific lesions and to those with both kinds of lesions(*Aecevic et al, Lupus 10:364, 2002*).

# Prognostic Significance of Cutaneous LE



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# Diagnosis of Cutaneous Lupus

- **Clinical findings**
- **Skin pathology: biopsy**
- **Occasionally look for antibodies in skin**
- **Specific lupus antibodies: may or not be present**
  - **Anti-nuclear antibody**
  - **Anti-SSA, SSB**
  - **Anti-dsDNA**
  - **Anti-histone**



## **Diagnosis of Cutaneous Lupus**

- **Some people that have lupus antibody but don't have lupus: not a specific test**
- **If suspect systemic lupus, will check for involvement of other organs**
  - **Urinalysis**
  - **Kidney function**
  - **Blood counts (anemia, low WBC, low platelets)**
- **Many with skin lupus don't have systemic disease, but should be checked periodically**

# Diagnosis of Cutaneous Lupus

- **If skin flaring, may be good time to have other blood tests checked**
- **Should touch base with your doctor with flares**

# Drug-induced Cutaneous LE

Thiazide diuretics

Calcium channel blockers

Antifungals

Terbinafine

(Lamisil), griseofulvin

Beta blockers

oxyprenolol

NSAIDS: Piroxicam, naproxen

Antihistamines: Cinnarizine

Chemotherapy: Taxotere,

Paclitaxel

ACE inhibitors

Cilazapril, captopril

GI Acid inhibitors

Ranitidine, omeprazole

TNF- $\alpha$  inhibit. biologics

Etanercept, infliximab

Platelet inhibitor: Ticlopidine

Miscellaneous:

Interferon  $\alpha$ & $\beta$ ,

statins, procainamide, phenytoin,

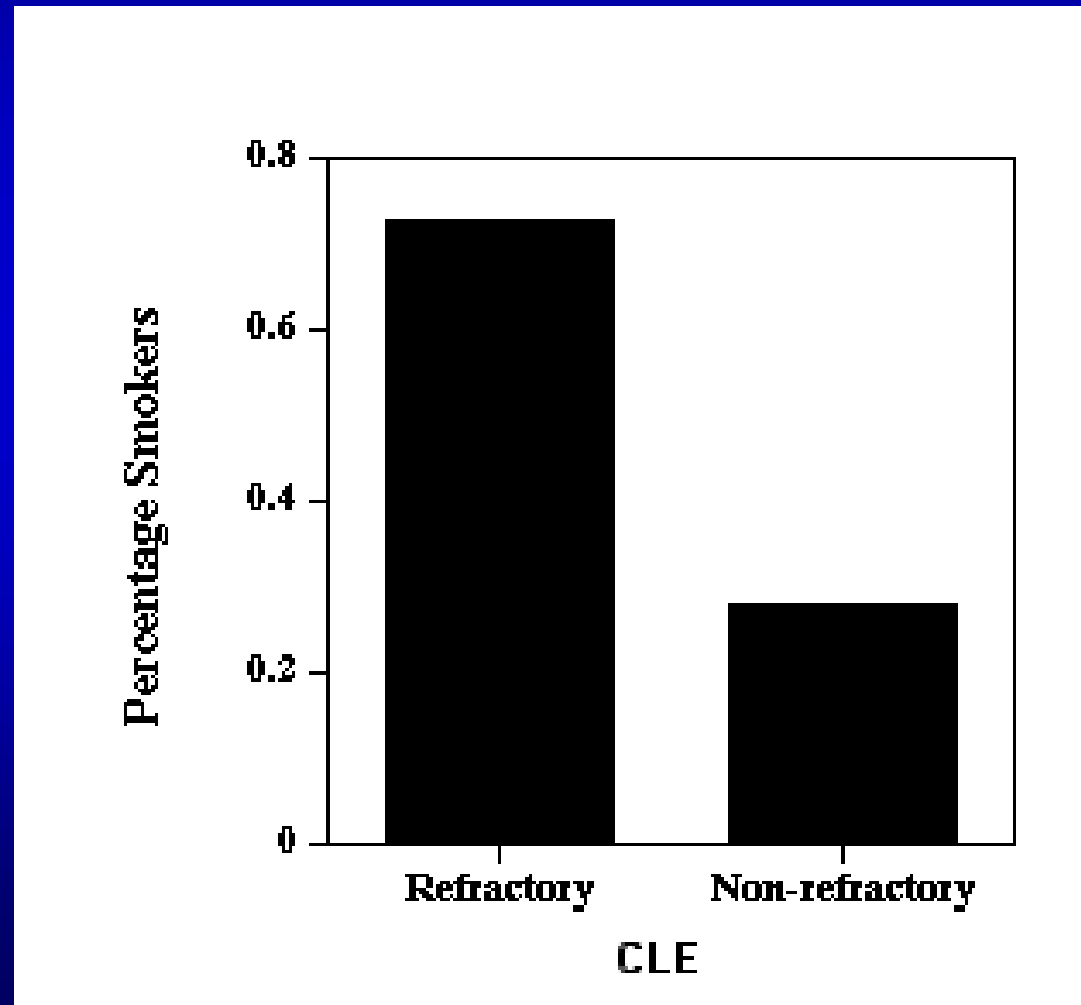
oxyprenolol, d-penicillamine,

fertilizer/pesticides

# Causes

- **Genetics**
  - **Complement deficiency**
  - **HLA types**
  - **Other genetic risks related to inflammatory pathways**
- **Smoking**
- **Ultraviolet light**

# Smoking and Refractory Cutaneous LE



**n=114**

**P=0.006**

*Moghadam-Kia  
and Werth,  
Arch*

*Dermatol, 145:  
255, 2009*

# Insights into Disease Classification

- **Dissecting differences between types of cutaneous LE (and between patients) will likely be increasingly important in learning more about causes of cutaneous lupus**

# Overview

- **Clinical**
- **Pathophysiology**
- **Development of a disease severity measure (CLASI)**
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## 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

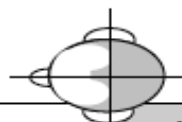
| Extent | activity                  |  |  | damage                         |  |                           |
|--------|---------------------------|--|--|--------------------------------|--|---------------------------|
|        | Anatomical Location       | Erythema   | Scale/<br>Hypertrophy                                | Dyspigmentation                | Scarring/<br>Atrophy/<br>Panniculitis  | Anatomical Location       |
|        |                           | 0-absent<br>1-pink; faint erythema<br>2- red;<br>3-dark red;<br>purple/violaceous/<br>crusted/ hemorrhagic | 0-absent;<br>1-scale<br>2-verrucous/<br>hypertrophic | 0-absent,<br>1-dyspigmentation | 0 – absent<br>1 – scarring<br>2 – severely<br>atrophic scarring<br>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) | Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)  |
| 0-absent;<br>1-lesion or ulceration                               | <input type="checkbox"/> Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)<br><input type="checkbox"/> Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled) |

### Dyspigmentation

### 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<br>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<br>1-diffuse; non-inflammatory<br>2-focal or patchy in one quadrant;<br>3-focal or patchy in more than one quadrant   |   | 0- absent<br>3- in one quadrant<br>4- two quadrants<br>5- three quadrants<br>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)

*Albrecht  
and Werth,  
JID  
125:889,  
2005*



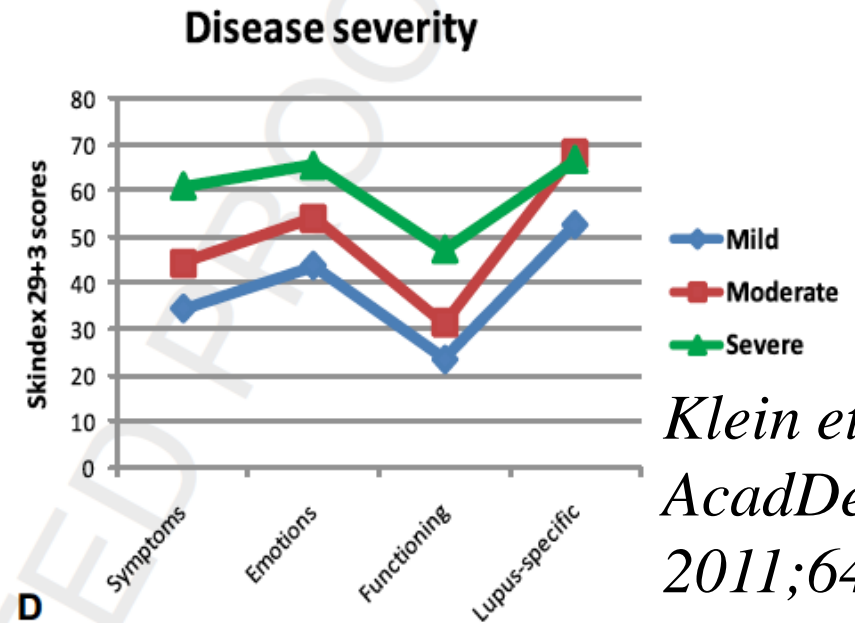
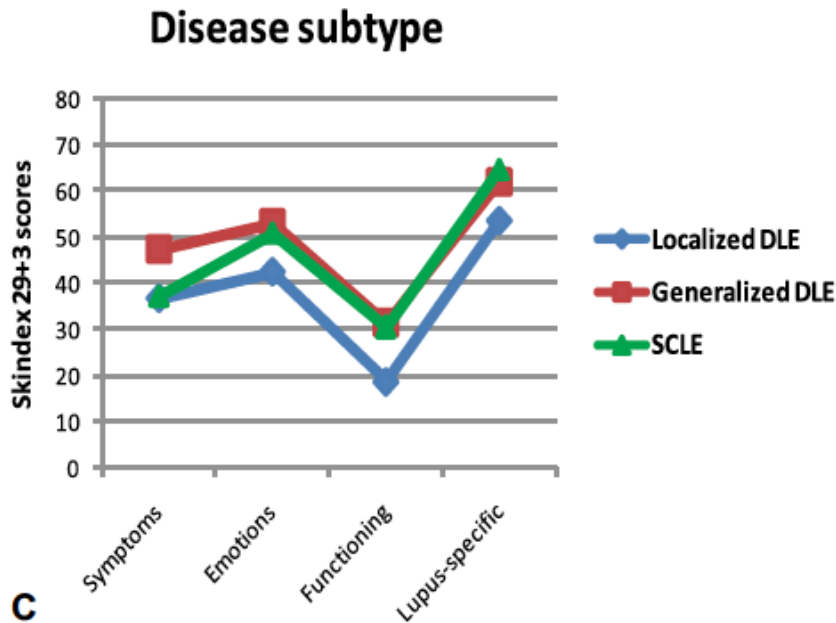
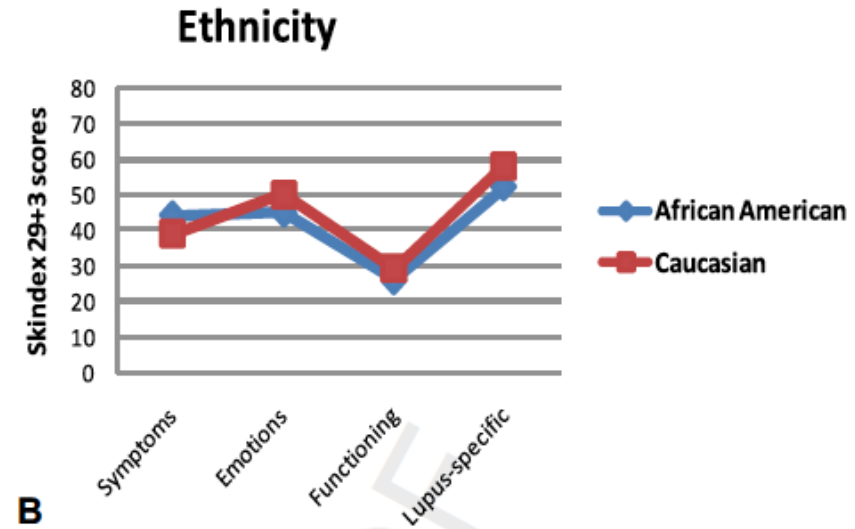
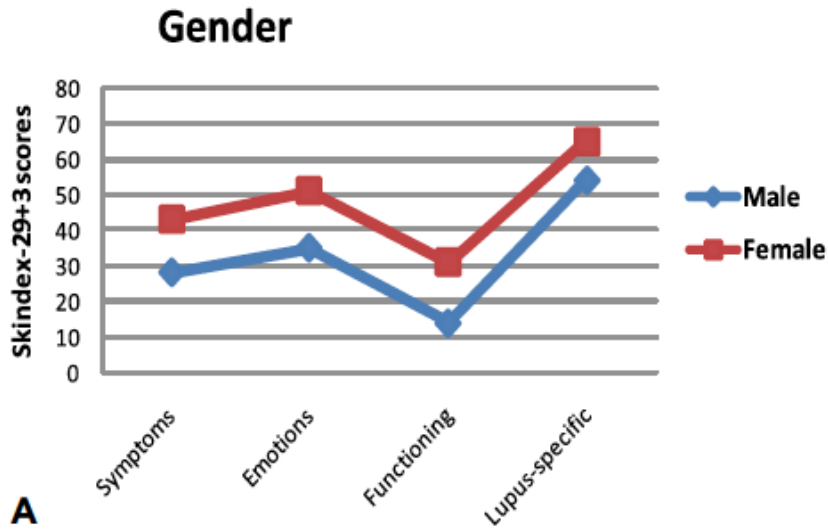
## **Disease severity measure (CLASI)**

- **Many validation studies over past 6 years to make sure it measures reliably and responds to change with treatment**
- **Can study effects of new medications on skin**

# Overview

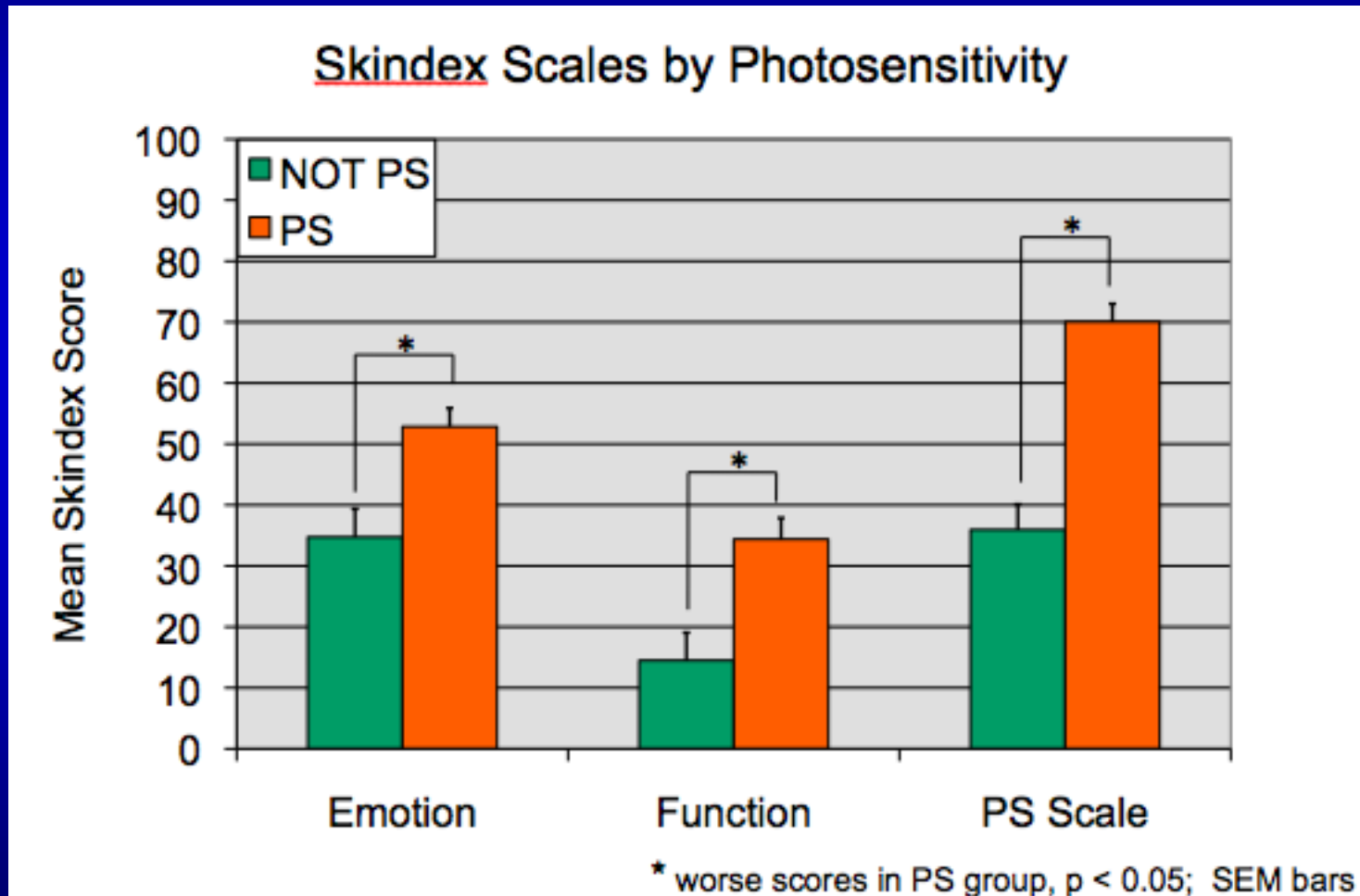
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# Correlation of Disease Severity (CLASI) with Quality of Life (Skindex)



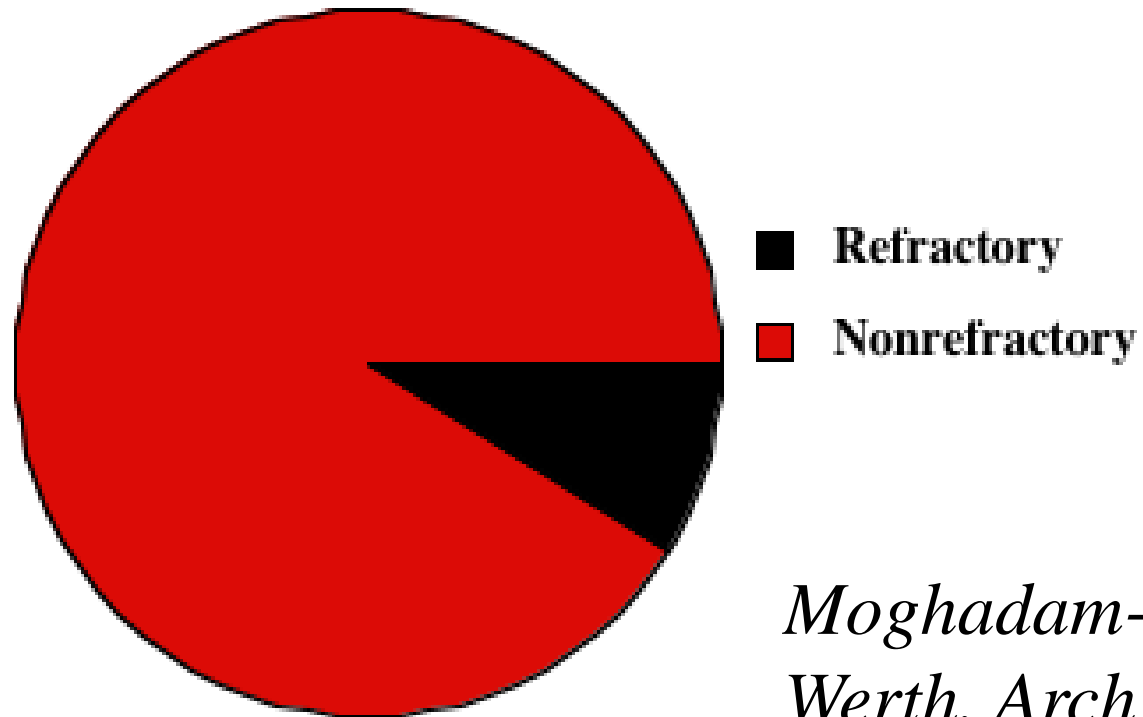
*Klein et al, J Am Acad Dermatol 2011;64:849-58*

# QoL in Photosensitivity



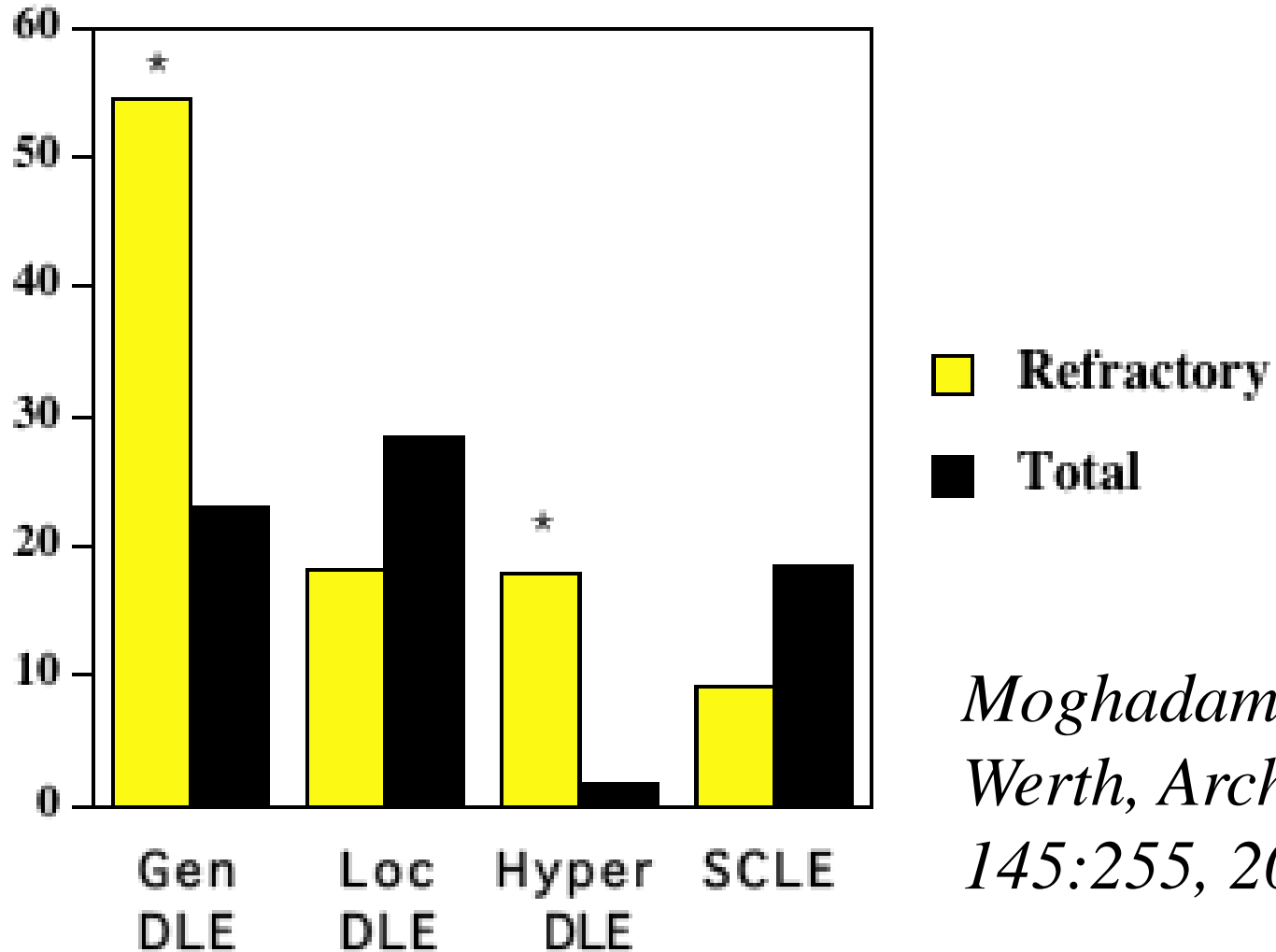
*Foering et al, JAAD, in press*

# Incidence of Refractory Disease



*Moghadam-Kia and  
Werth, Arch Derm  
145:255, 2009*

# Subsets of CLE with Refractory Disease



*Moghadam-Kia and  
Werth, Arch Derm,  
145:255, 2009*

# Conclusions

- **Patients with generalized DLE are more refractory to current therapies than those with localized DLE or SCLE**
- **Smokers more refractory to all treatments**

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# Treatment of DLE, SCLE, Tumid LE, LE, Panniculitis

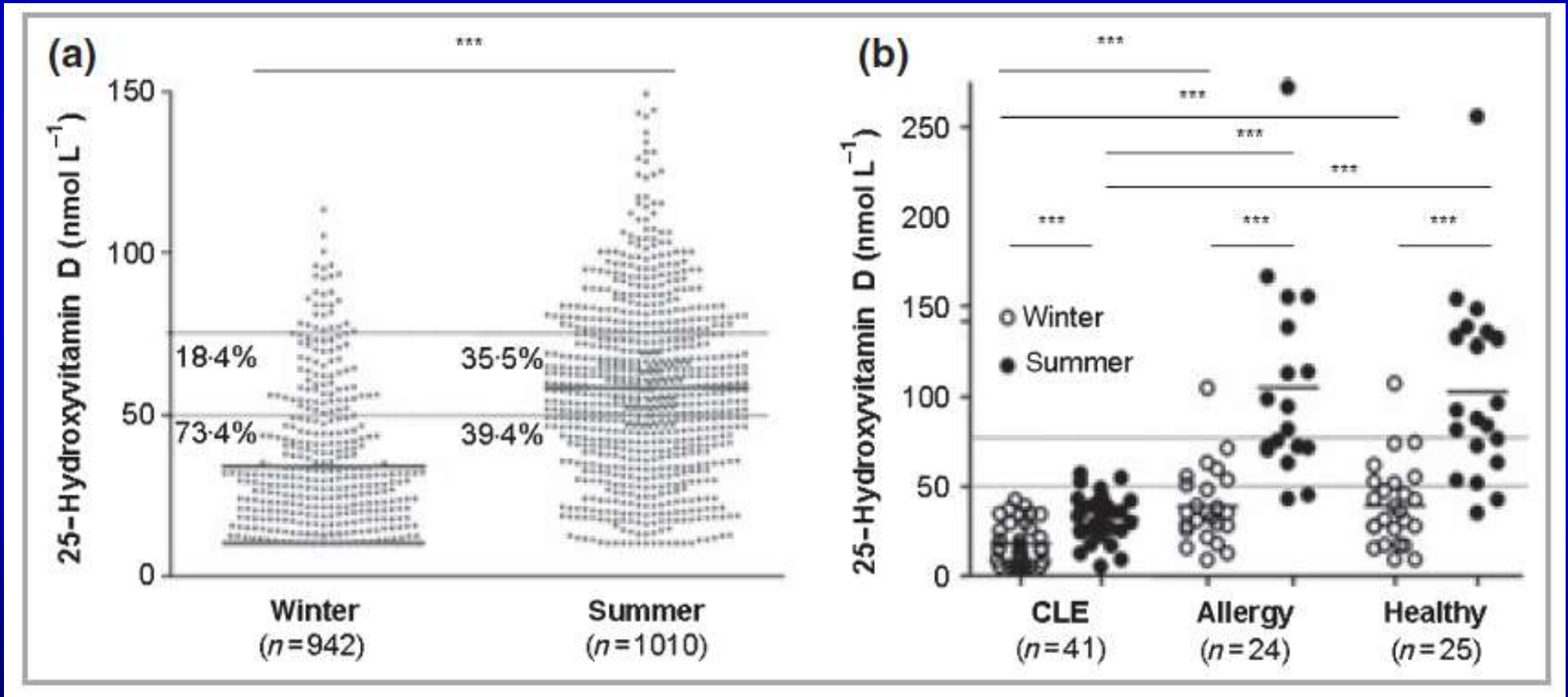
- Heat avoidance
- Drug Avoidance
- Sunscreens
  - UVB #30 or greater
  - Mexoryl
  - Helioplex
  - Physical Blockers (Titanium, Zn Oxide)

# Treatment of Cutaneous LE

- **Topical Steroids**
- **Topical nonsteroidal T cell inhibitors**  
*(Heffernan M et al, Arch Dermatol 141:1170, 2005)*
  - Tacrolimus (Protopic)
  - Pimecrolimus (Elidel)
- **Intralesional Steroids**

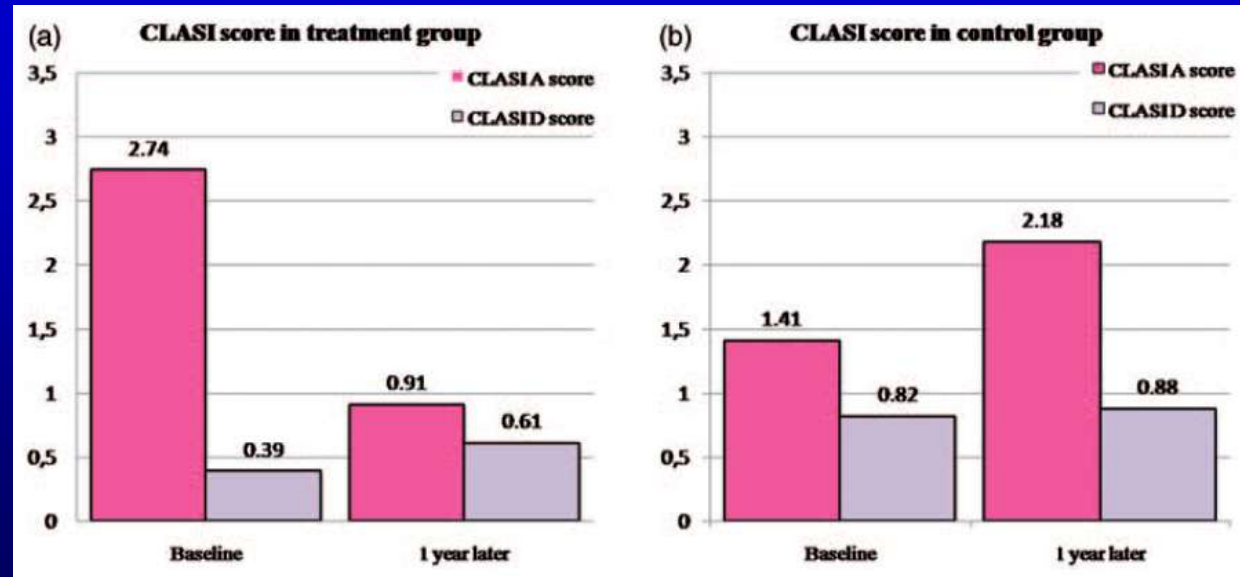
# Treatment of Cutaneous LE

- Check 25-hydroxy Vitamin D level



# Evidence for Systemic Therapy in CLE

- Frequently low Vitamin D in CLE
- OR 3.47 for Vitamin D deficiency
- Disease activity improved in treatment group (p=0.003)



*Cutillas-Marco E et al, Lupus 23:615, 2014*

## **Antimalarials**

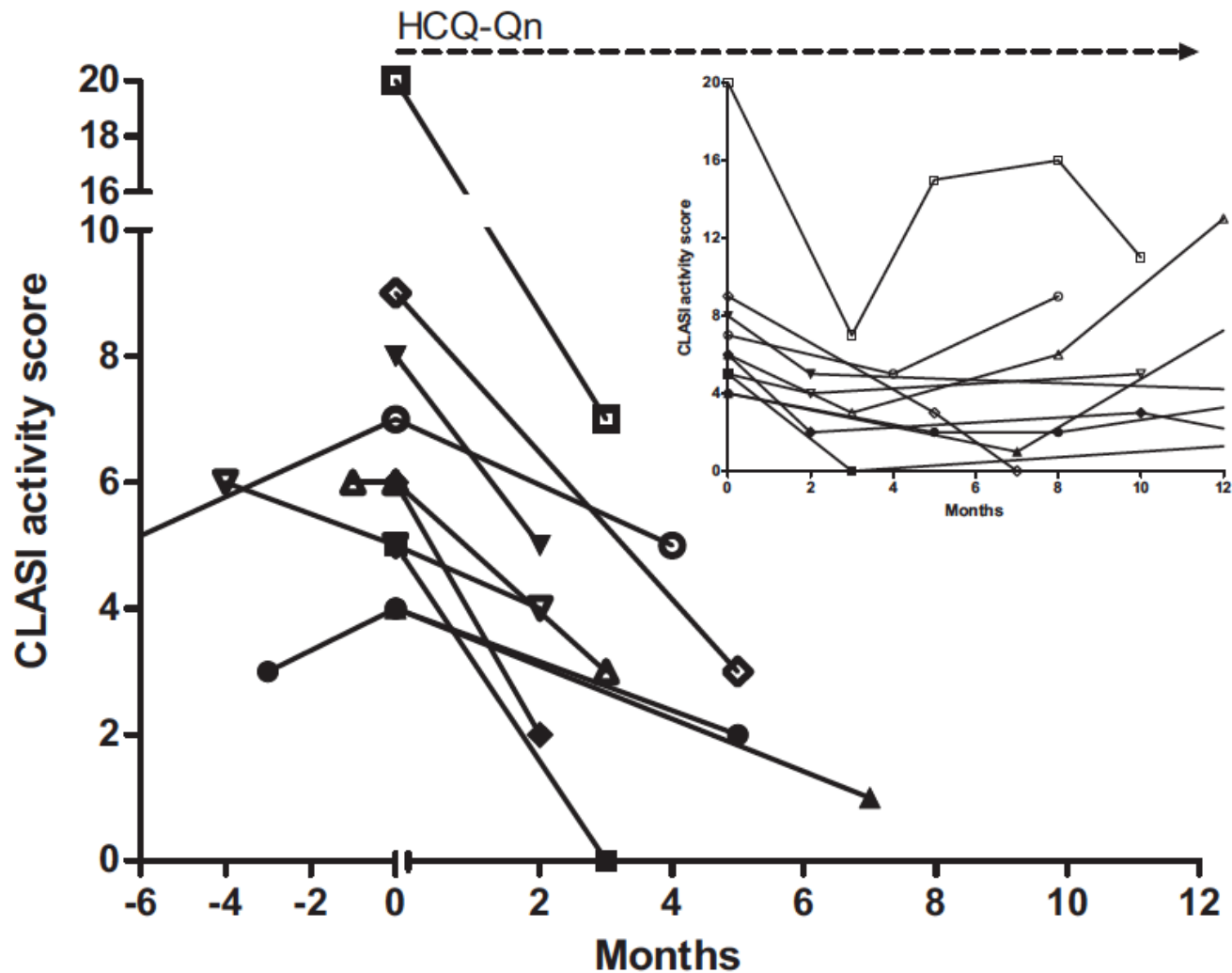
- **Hydroxychloroquine <6.5 mg/kg/day**
- **Chloroquine <3.5 mg/kg/day**
- **Quinacrine 100 mg/day**
  
- **Hydroxychloroquine for 6-8 weeks**
- **If no better, add quinacrine 100 mg/day for 6-8 weeks**
- **Switch from Hydroxychloroquine to Chloroquine if still not improved**

# Antimalarials

- Antimalarial concentration correlates with response (*Frances C et al, Arch Dermatol 148:479, 2012*)
- 10% had very low blood HCQ, considered noncompliant
- Combination antimalarials (HCQ or Chloroquine, + Quinacrine) work frequently when HCQ alone doesn't work (*Chang A et al, Arch Dermatol 147:1261, 2011*)

# Antimalarials in Cutaneous LE

A. HCQ-Qn initiation at month 0  
*Responders*



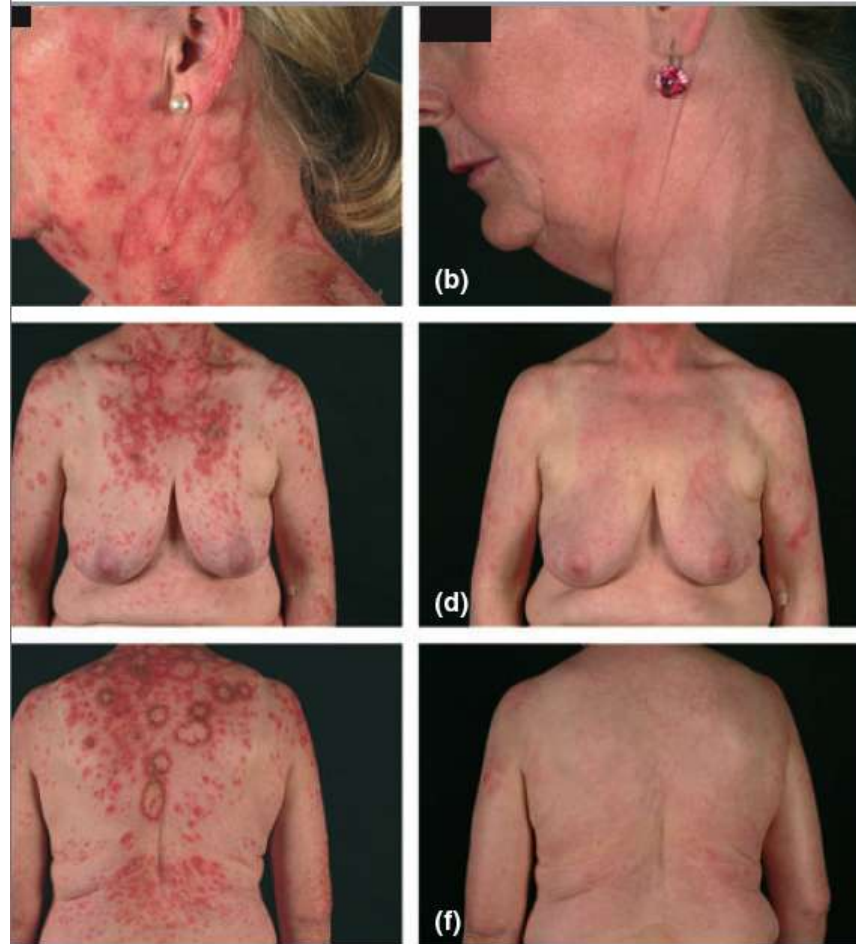
*Chang  
et al,  
JID  
Arch  
Dermat  
ol, in  
press.*

# Other Therapies for Cutaneous LE

- **Dapsone**
- **Retinoids**
- **Thalidomide**
- **Methotrexate, CellCept, Azathioprine**
- **Corticosteroids**

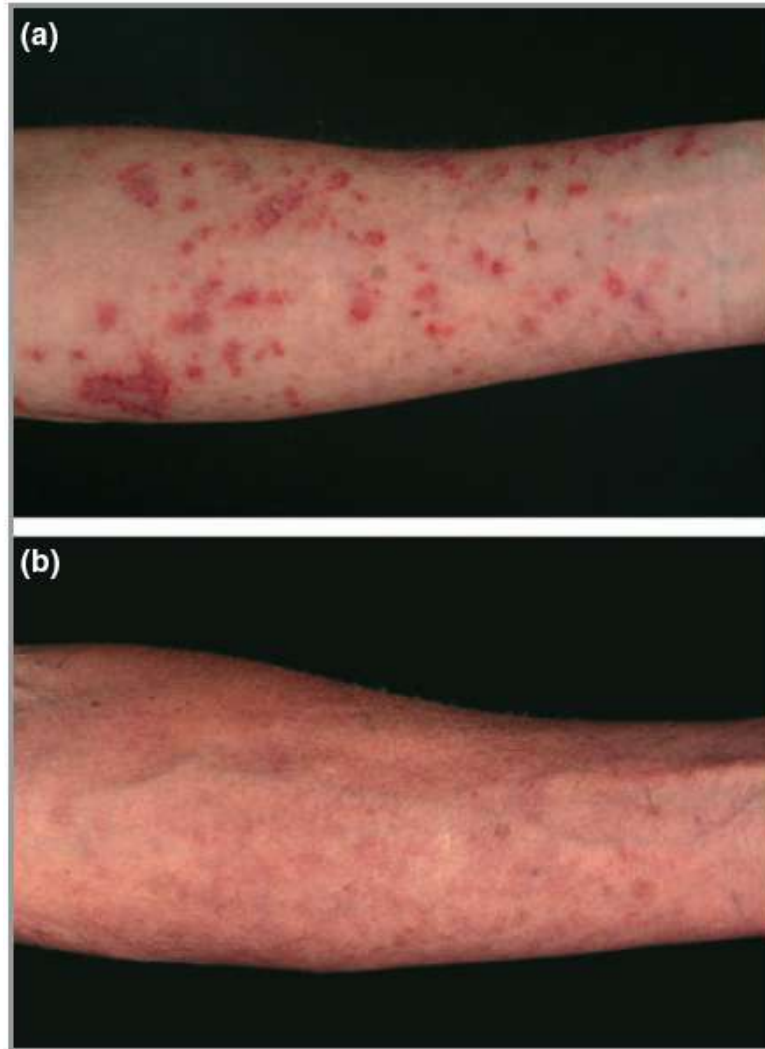


# Mycophenolate Mofetil Trial



*Kreuter et al. Br J Dermatol 156:1321, 2007*

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# Mycophenolate Mofetil Trial

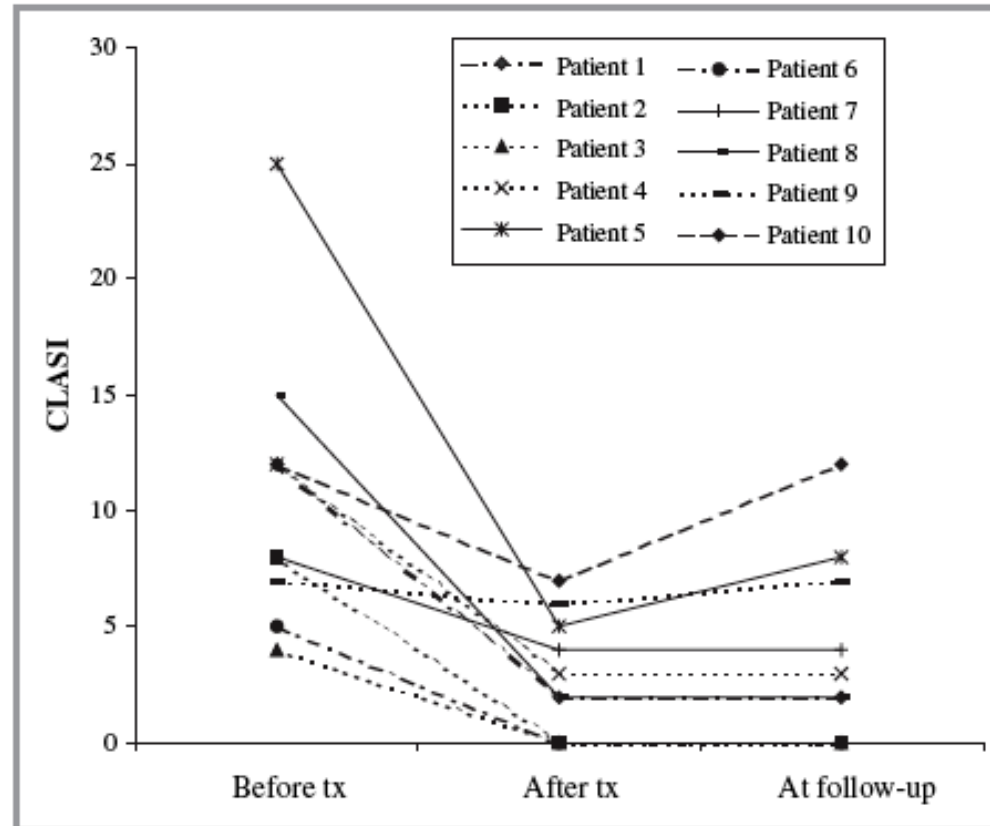


Fig 3. Course of Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in patients with subacute cutaneous lupus erythematosus treated with mycophenolate sodium. tx, treatment.

# Thalidomide in CLE

- 60 patients,  $\geq 18$  years old, Barcelona, Spain
- Effectiveness up to 80-90%
- Improvement starts in 2 weeks, with full effects in 4-8 weeks
- Highest response in SCLE and DLE (>90%), lowest in lupus profundus (50%)
- No difference in response in localized vs generalized DLE

# Thalidomide in CLE

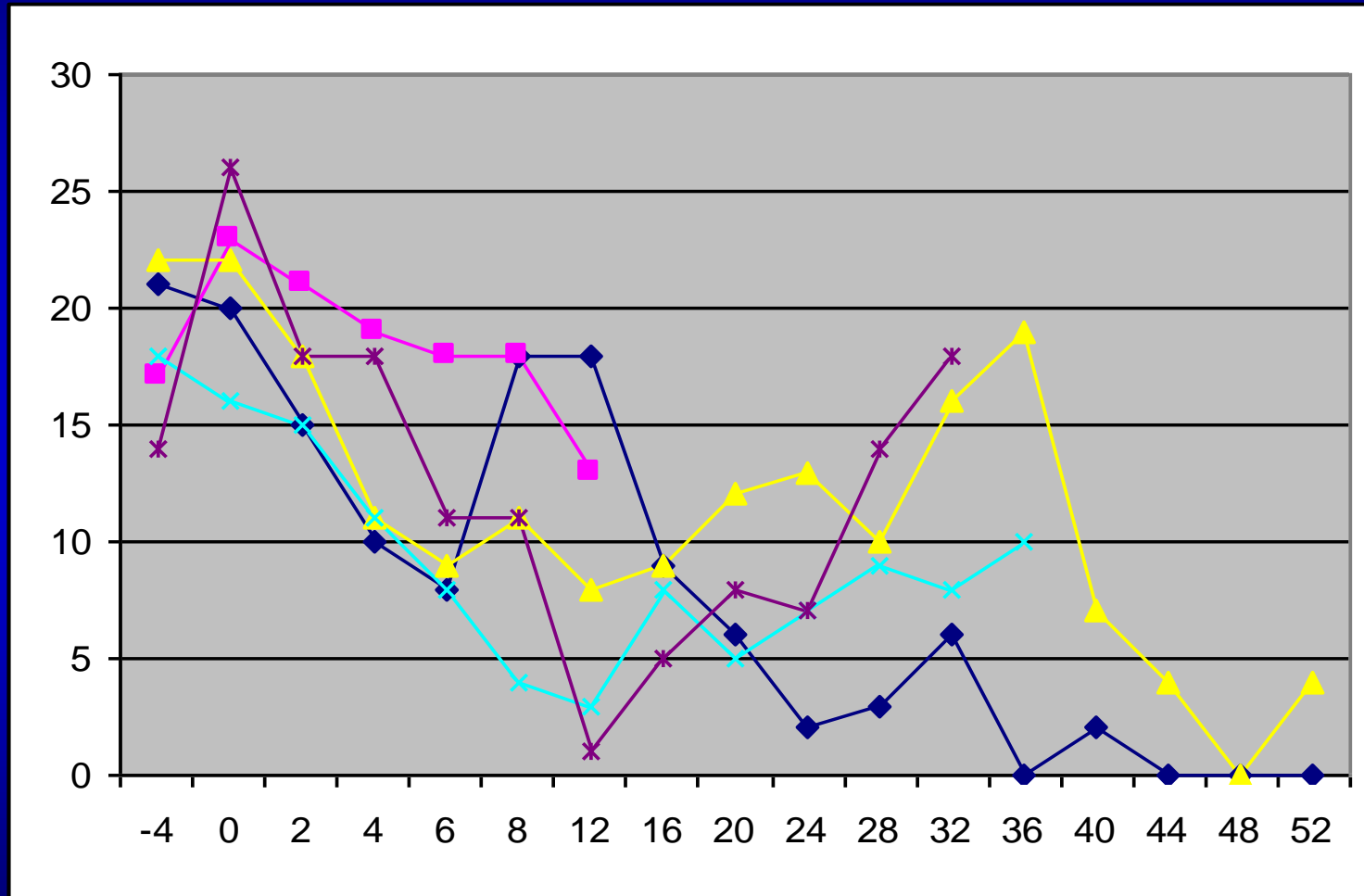
- High rate of relapse (70%), especially in DLE in 4-8 months after stopping treatment
  - SCLE relapse rate 24%
  - DLE relapse rate 84%
- Respond to retreatment
- 16% require maintenance
- Side effects: drowsiness, paresthesia (18%), reversible amenorrhea, stroke, teratogenicity

# Thalidomide Analogues

- Up to 50,000 times more active than thalidomide
- Potentially less neurotoxicity
- Have complex mechanisms of action that need to be evaluated in context of clinical trials for specific subsets of diseases

# CLASI activity change over time

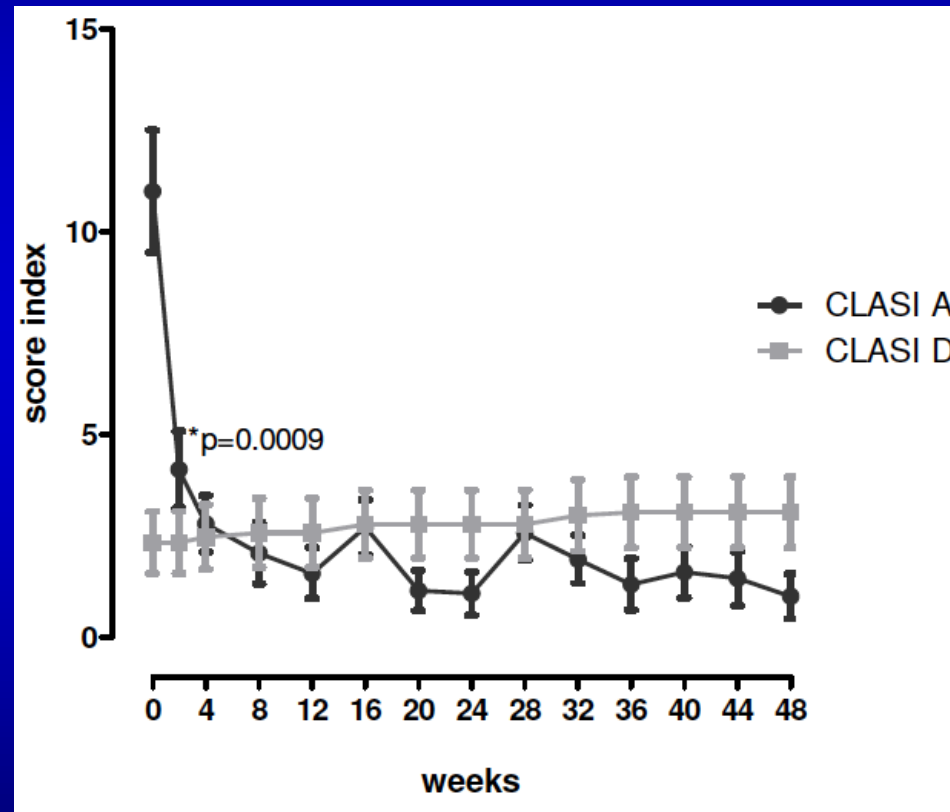
**CLASI  
Activity**



**Time (weeks)** *Braunstein and Werth, Arch  
Derm 66:571, 2012*

# CLASI lupus activity change over time

15 patients  
86% with  
CR



*Cortes-  
Hernandez  
J et al,  
Arthr Res &  
Ther  
14:R265,  
2012*



# **Biological Modifiers in Photosensitive LE: Potential Targets**

- **Anti-Cytokines (Anti-IFN $\alpha$ , –IFN $\gamma$ )**
- **T cell directed therapy (Anti-CTLA4, anti-CD4)**
- **B cell directed therapy (Anti-CD20, Rituxamab; Anti-Blys/April)**
- **Chemokine antagonists**
- **Anti-adhesion molecules**

# Other New Treatments

- Pulsed-dye laser (*Erceg A, et al JAAD 60:626, 2009*)
- Individual reports or case series: Rituximab (bullous LE), alitretinoin, polypodium leucotomas
- Sirukumab (anti-IL-6): negative result (*Szepietowski JC, Arthritis Rheumatism 65:2661, 2013*)

# Rituximab

- **82 SLE patients received rituximab**
  - **32 with significant skin disease before or after treatment**
- **10/29 (39%) with baseline skin disease had beneficial skin response at 6 months**
  - **6/14 (43%) with good response in ACLE**
  - **0/8 (0%) with CCLE**

*Vital EM et al, Arthr Rheumatol, in press.*

# Rituximab

- Flares of SCLE and CCLE occurred in 12 patients who had no skin disease or ACLE at baseline

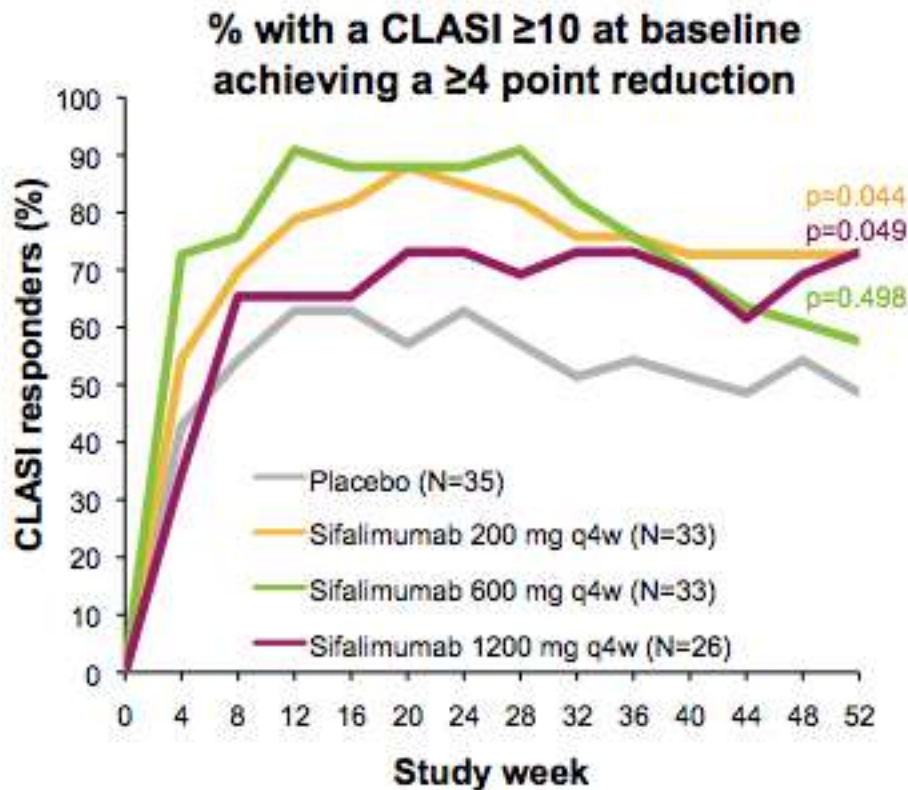
*Vital EM et al, Arthr Rheumatol, in press.*

# Other new treatments

- **Anti-IFN $\alpha$  monoclonal antibody (Sifalimumab)**
- Anti-IFN receptor monoclonal antibody
- Apremilast (PDE4 inhibitor)-study completed
- Many more approaches in the pipeline

# Skin Response with Sifalimumab Treatment: mITT Population

Secondary endpoint:  
CLASI response in patients with moderate-to-severe skin involvement



# Other new treatments

- Anti-IFN $\alpha$  monoclonal antibody (Sifalimumab)
- **Anti-IFN receptor monoclonal antibody**
- **Apremilast (PDE4 inhibitor)-study completed**
- **Many more approaches in the pipeline**

# **Biological Modifiers in Photosensitive LE: Potential Targets**

- **Increasing interest in looking at skin as outcome in studies**
- **If have refractory disease, important to participate in studies to determine potential new treatments**



# Summary

- **Better understanding about epidemiology and clinical subsets of cutaneous lupus**
- **Outcome measure (CLASI)**
- **More options for therapeutically resistant patients**
- **Potential new therapies in the pipeline**