CUTANEOUS LUPUS ERYTHEMATOSUS: BETTER TREATMENTS, BETTER OUTCOMES

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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
Classification of Cutaneous Lupus Erythematosus

• Acute
• Subacute
• Chronic

Subacute Cutaneous Lupus Erythematosus

• Case series of 27 patients
• Associated with anti-Ro antibody

1Sontheimer RD et al, Arch Dermatol 1979; 115:1409-15
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
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
UNIVERSITY OF TEXAS SOUTHWESTERN
CUTANEOUS LUPUS REGISTRY

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

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Non-Hispanic</td>
<td>182</td>
<td>50.8%</td>
</tr>
<tr>
<td>White Non-Hispanic</td>
<td>118</td>
<td>33.0%</td>
</tr>
<tr>
<td>White Hispanic</td>
<td>38</td>
<td>10.6%</td>
</tr>
<tr>
<td>Asian</td>
<td>17</td>
<td>4.7%</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
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% ointment**
  - 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. betamethasone**
  - 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

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

### Cutaneous Lupus Erythematosus Disease and Severity Index (CLASI)

#### Activity

<table>
<thead>
<tr>
<th>Anatomical Location</th>
<th>Erythema</th>
<th>Scale/Hypertrrophy</th>
<th>Dyspigmentation</th>
<th>Scarring/Alopecia</th>
<th>Anatomical Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp</td>
<td></td>
<td></td>
<td>0-absent, 1-dyspigmentation</td>
<td>0 ... absent</td>
<td>Scalp</td>
</tr>
<tr>
<td>Ears</td>
<td></td>
<td></td>
<td></td>
<td>1 ...scarring</td>
<td>Ears</td>
</tr>
<tr>
<td>Nose (incl. malar area)</td>
<td></td>
<td></td>
<td></td>
<td>2 ... severe atrophic scarring or panniculitis</td>
<td>Nose (incl. malar area)</td>
</tr>
<tr>
<td>Rest of the face</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rest of the face</td>
</tr>
<tr>
<td>V-area neck (frontal)</td>
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<td></td>
<td></td>
<td></td>
<td>V-area neck (frontal)</td>
</tr>
<tr>
<td>Post. Neck &amp;/or shoulders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post. Neck &amp;/or shoulders</td>
</tr>
<tr>
<td>Chest</td>
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<td></td>
<td></td>
<td>Chest</td>
</tr>
<tr>
<td>Abdomen</td>
<td></td>
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<td></td>
<td></td>
<td>Abdomen</td>
</tr>
<tr>
<td>Back, buttocks</td>
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<td></td>
<td></td>
<td></td>
<td>Back, buttocks</td>
</tr>
<tr>
<td>Arms</td>
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<td>Arms</td>
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<td>Hands</td>
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<td>Hands</td>
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<td>Legs</td>
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<td>Foot</td>
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<td>Foot</td>
</tr>
</tbody>
</table>

- **Erythema**: 0-absent; 1-localized
- **Scale/Hypertrrophy**: 0-absent; 1-scale
- **Dyspigmentation**: 0-absent, 1-dyspigmentation
- **Scarring/Alopecia**: 0 ... absent, 1 ... scarring, 2 ... severe atrophic scarring or panniculitis
- **Anatomical Location**

#### Damage

- **Total Activity Score**: For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrrophy, 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/Alopecia, Panniculitis and Scarring of the Scalp.

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

### Activity

<table>
<thead>
<tr>
<th>Anatomical Location</th>
<th>Erythema</th>
<th>Scale/Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp</td>
<td>0-absent; 1-pink; faint erythema</td>
<td>0-absent; 1-scale</td>
</tr>
<tr>
<td></td>
<td>2-red; 3-dark red; purple/violaceous/crusted/hemorrhagic</td>
<td>2-verrucous/hypertrophic</td>
</tr>
<tr>
<td>Nose (incl. malar area)</td>
<td></td>
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</tr>
<tr>
<td>Rest of the face</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Arms</td>
<td></td>
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<tr>
<td>Hands</td>
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<tr>
<td>Legs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feet</td>
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</tr>
</tbody>
</table>

### Damage

<table>
<thead>
<tr>
<th>Scarring/Atrophy/Panniculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-absent, 1-dyspigmentation</td>
</tr>
<tr>
<td>2-severely atrophic scarring or panniculitis</td>
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<tr>
<td>Legs</td>
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<tr>
<td>Feet</td>
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</tbody>
</table>

**Mucous membrane**

- Mucous membrane lesions (examine if patient confirms involvement)
  - 0-absent; 1-lesion or ulceration

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**Dyspigmentation**

- Report duration of dyspigmentation after active lesions have resolved (verbal report by patient... tick appropriate box)
  - \[\square\] Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)
  - \[\square\] Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)
# ALOPECIA IN CLASI

## Alopecia

<table>
<thead>
<tr>
<th>Recent Hair loss (within the last 30 days / as reported by patient)</th>
<th>1-Yes</th>
<th>0-No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dividing 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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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

• 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

<table>
<thead>
<tr>
<th>Improved Disease Activity</th>
<th>Improved Disease Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CLASI activity score ≥ 10</td>
<td>Baseline CLASI damage score ≥ 10</td>
</tr>
<tr>
<td>Baseline CLASI damage score ≥ 10</td>
<td></td>
</tr>
<tr>
<td>Minority race</td>
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</tr>
<tr>
<td>Disease duration ≤ 1 year</td>
<td></td>
</tr>
</tbody>
</table>
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)

**RCT of 103 patients with CLE**

- Hydroxychloroquine (HCQ) vs. placebo for 1\textsuperscript{st} 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

Yokogawa et al, Arth Rheum 2017; 69:791-9
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)

Okon L et al, J Am Acad Dermatol 2014; 70:583-4
5-point Likert scale that evaluates severity of signs of CLE disease activity

- Erythema
- Scale
- Elevation
- Follicular involvement
- Secondary changes

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

• Validation cross-sectional study of CLEQoL

• SKINDEX-29 + 7 CLE-specific questions (e.g. photosensitivity, alopecia, dyspigmentation)

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.

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

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Questionnaires</td>
<td>Examination</td>
<td>Photographs</td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL TRIALS IN CLE
THERAPEUTIC TARGETS IN CLE

UV radiation
Trauma
Genetics

Keratinocyte apoptosis

Type III IFNs
CXCL9, CXCL10

Type I IFNs

Macrophages

Anifrolumab, Sifalimumab

CXCR3+ T cells
(Th1, CD8+)

Plasmacytoid dendritic cells

BIIB059, VIB7734

Filgotinib, Baricitinib

Gadina M. J Investig Dermatol Symp Proc 2013; S70-S72
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

SIFALIMUMAB MAY BE EFFECTIVE FOR CLE

Anifrolumab – type I IFN receptor antagonist

Phase IIIB 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)

Furie R et al, Arthritis Rheum 2017; 69:376-386
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 CLE\(^1\)
  - 1 IV dose of 20 mg/kg
  - 6/8 patients showed clinical response in skin
- Phase II RCT trial of 132 patients with CLE\(^2\)
  - Dose-related improvement seen in CLASI-A scores

\(^2\)Werth 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 ≥ 50% improvement) vs 50 mg VIB7734 and placebo at day 141

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

- Filgotinib (JAK1 inhibitor) and lanraplenib (spleen kinase (Syk) inhibitor)
  - 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)
  - Phase 2 RCT study of 314 SLE patients
  - No significant improvement in CLASI-A score seen

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1 Werth VP et al, Rheumatology (Oxford) 2021 [epub]
2 Wallace DJ et al, Lancet 2018; 392:222-31
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

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
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!