Cutaneous Lupus Erythematosus

Diagnosis, Relationship to SLE and Management

Jeffrey P. Callen, MD

Professor of Medicine (Dermatology)

Chief, Division of Dermatology

Jeffrey P. Callen, MD

Disclosure (previous 12 months)

- Consultant –Eli Lilly, Celgene, Castle Biosciences, XOMA, Pfizer, Biogen/IDEC, Elekta, Leo Pharma, Janssen Biotech, Abbvie
- Editorial Boards – UpToDate (editor-in-chief, Dermatology), JAMA Dermatology (Associate Editor), Journal Watch Dermatology (Deputy Editor), Journal of Rheumatology, Cutis, emedicine.com, Journal of Drugs in Dermatology, Journal of the European Academy of Dermatology and Venereology, Medicine, Psoriasis Forum, Australasian Journal of Dermatology
- I will discuss "off-label" uses of some of the currently available agents and will identify which are labeled v. off-labeled uses.

May 2016

Educational Objectives

- Following this talk the attendee will be able to:
  - Understand recent advances and their impact on diagnosis and management of patients with cutaneous LE
  - Design a systematic plan for evaluation of patients with cutaneous LE
  - Design a program for management for skin manifestations of cutaneous LE

My First Publication on LE

Chronic Cutaneous Lupus Erythematosus

Clinical, Laboratory, Therapeutic, and Prognostic Examination of 62 Patients

Jeffrey P. Callen, MD

• Chronic discoid lupus erythematosus (DLE) is a common condition. Sixty-two patients with biopsy-proved, active DLE were observed and their conditions were analyzed for clinical, laboratory, and therapeutic data. Fifty-six patients had disease limited to the skin—26 localized and 30 widespread (above and below the neck). At the time of follow-up examination, active disease was present in 32 patients, 28 of whom had widespread DLE. Six patients had DLE as a manifestation of systemic LE (SLE). In four patients, the DLE preceded the development of SLE. Laboratory abnormalities were substantially more common in patients with widespread DLE than in patients with localized DLE. An analysis of therapeutic results in this series confirmed the beneficial effects of intralesional corticosteroids and antimalarial agents and demonstrated relatively poor responsiveness to topical or oral corticosteroids.

(*Arch Dermatol* 1982;118:412-416)

Prystowsky et al[1] and others[2-9] have studied groups of patients with DLE. The results, including clinical data, prognosis, laboratory findings, and response to therapy, have been variable, which may reflect differences in disease definition. This study was undertaken to review the laboratory abnormalities and the therapeutic and prognostic features in a large group of patients from a practitioner's office. Another aim of this study was to identify how frequently DLE occurred as a manifestation of systemic LE (SLE) and how many patients with DLE had one or more symptoms referable to other systems.

PATIENTS AND METHODS

Patient Selection

Sixty-two patients were included in this study on the basis of their typical clinical features of chronic DLE. The patients all had DLE skin lesions characterized by erythema, telangiectasias,

Pierre Cazenave is attributed as the first to describe Cutaneous LE in 1856

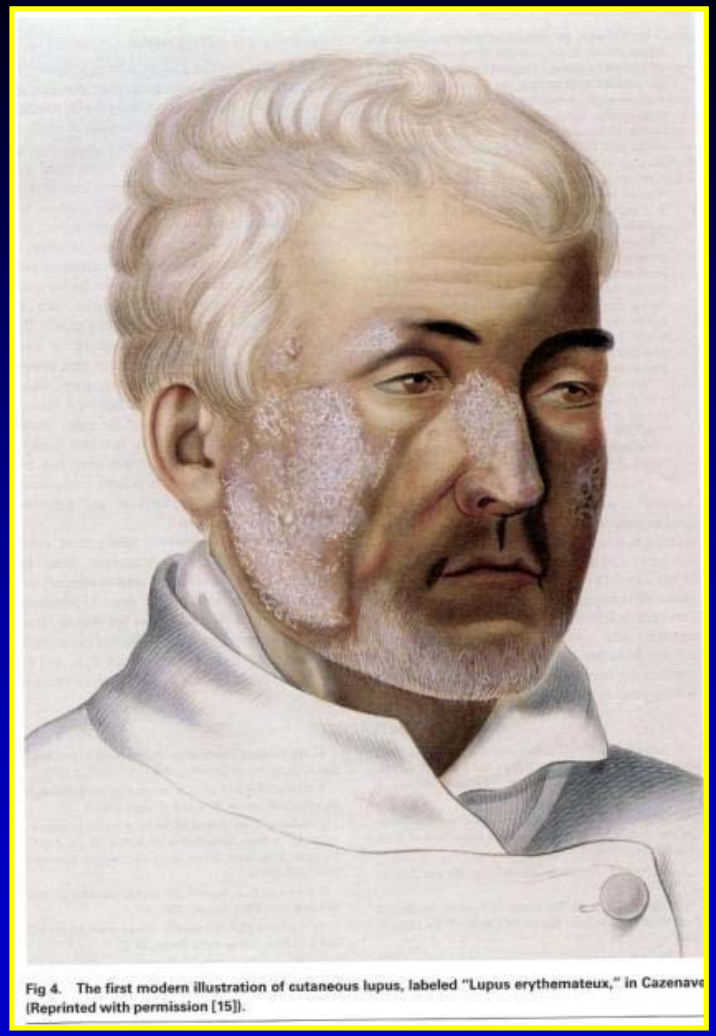


Fig 4. The first modern illustration of cutaneous lupus, labeled "Lupus erythemateux," in Cazenave
(Reprinted with permission [15]).

Cazenave PLA: Lescons sur les maladies de la peau. Paris: Labe 1856

What did we know about CLE in 1977?

- We did not recognize SCLE as a distinct subset – rather we thought of DLE, disseminated LE, and SLE
- We did not know how babies developed NLE
- We did not know how many patients with DLE might develop systemic disease
- We did not know that drugs might trigger or exacerbate cutaneous LE

What did we know about CLE in 1977?

- We thought that UVB was the responsible wavelength of light that exacerbated the disease
- We did not know how frequent and how severe is SLE might be in patients with various cutaneous subsets of LE
- We did not have the panoply of treatment options that we have today
- We did not know if treatments might prevent the progression of disease
- We had no idea regarding the effect of smoking on LE or its treatment

Cutaneous LE Subsets

- Histopathologically specific (interface dermatitis)
  - Chronic cutaneous LE (DLE)
  - Subacute cutaneous LE (SCLE)
  - Acute cutaneous LE (ACLE)
- Histopathologically non-specific
  - LE-related disease
  - Associated phenomena

Chronic cutaneous LE

- Discoid LE – localized or widespread
- Hypertrophic or verrucous LE
- Palmar and/or plantar lesions
- Oral lesions
- LE panniculitis
- ? Tumid LE

Discoid lupus erythematosus

- Localized – head and neck only
- Widespread – other areas than the head and neck
- Distinction is clinically relevant as patients with widespread DLE
  - Have a chronic course, less chance of remission
  - More frequent serologic abnormalities and risk of cytopenia
  - More difficult to control

Verrucous or hypertrophic LE

- Wart-like lesions most often on the arms and/or hands
- Typical DLE lesions elsewhere
- Differential diagnosis – warts, KA, SCC
- Rare serologic findings, no HLA association
- Difficult to treat – intralesional corticosteroids, retinoids

Palmar/Plantar LE

- Unusual
- Typical DLE elsewhere or SLE
- Lack of appendegeal structures makes it difficult to distinguish from lichen planus
- Difficult to treat

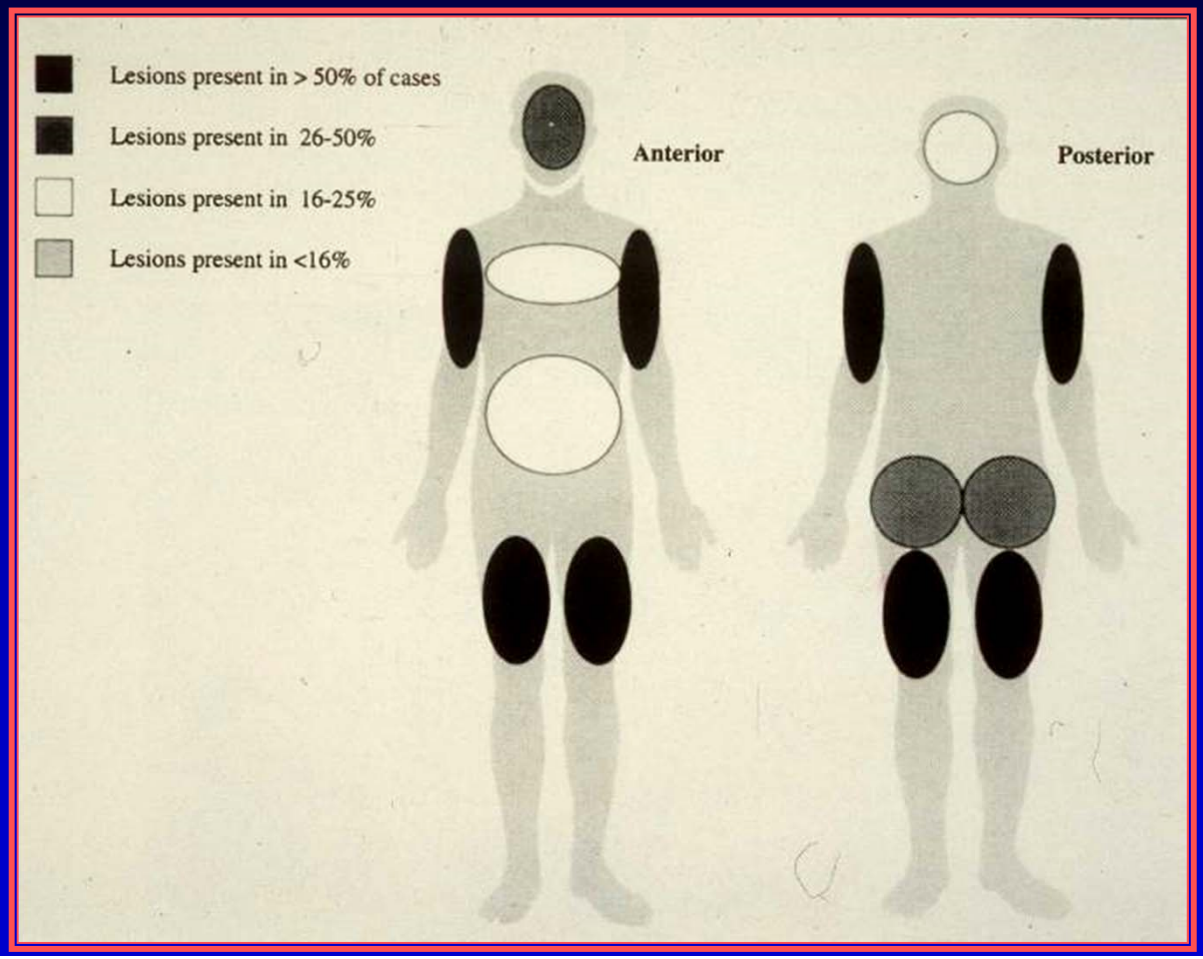
Oral LE

- Oral lesions of DLE occurs in 5-25% of LE patients
- Isolated oral LE
- Lesions are most common on the palate, buccal mucosa or vermillion border of the lips
- Mucosal lesions are clinically similar to those on the skin

Lupus Panniculitis
Clinical perspectives from a case series

- 40 patients from Mayo Clinic records (4:1 – M:W)
- Only 4 fulfilled 4 or more criteria for SLE
- ANA negative – 14, 1:80 or less – 15, 1:80 to 1:320 – 8, >1:320 – 3
- Anti-nDNA – 5/34, anti-U1RNP – 3/21
- Ro, La, Sm, antocardiolipin – 0
- Nephritis 2, neurologic disease - 0

Lupus panniculitis –Distribution of lesions



Lupus panniculitis (continued)

- Chronicity (>1 year) – 38 (95%)
- Clinical features
  - Nodules or plaques – 39 (98%)
  - Scarring – 30 (75%)
  - Pain – 29 (73%)
  - Ulceration – 11 (28%)
- Treatment
  - Antimalarials – 23/33 “improved”
  - Surgery did not worsen lesions in 7 patients
    - J Rheumatology 1999; 26: 68-72

Lupus erythematous tumidus

- First described in 1930
- Onset in summer
- Photosensitivity > 70%
- Histopathology – periadnexal, perivascular lymphocytic infiltrate with increased mucin
- ANA < 10%
- Systemic disease – 0
- Complete resolution with therapy usually w/o residual changes
- The Controversy – this ‘subset’ is not characterized by an interface dermatitis, there are rarely serologic or systemic manifestations & the is resolution without residual change

Subacute cutaneous lupus erythematosus

- Lesions often begin as papules that coalesce to form either
  - Annular lesions
  - Papulosquamous lesions
- Associated phenomena
  - Deficiency of the 2nd component of complement
  - Drug-induced SCLE
  - Neonatal LE
  - Sjogren's syndrome

Ultraviolet light induction/exacerbation of LE

- 1963 – Auerbach & Weinstein report two patients with Occupationally-induced LE from UV light exposure
- 1965 – Epstein, Tuffanelli & Dubois demonstrated that cutaneous LE is could be reproduced with UV light in those patients who reported photosensitivity
- 2001 – Kuhn et al report further studies on more than 400 patients noting that LE may be experimentally reproduced in all forms of LE and that UVB and/or UVA may cause this phenomenon

Drug-induced SCLE

- Reed et al described 5 patients with SCLE, all anti-Ro +, clearing in 2-4 weeks
- Serology resolved in 1/3
- Positive rechallenge in 1 patient

Ann Intern Med 1985; 103: 49-51

Drug-induced Ro+ Cutaneous LE

- Study of 70 patients
- 15 patients had a history of new drug exposure within 6-months of disease onset
- Drugs – HCTZ (5), ACE inhibitors (3), Ca channel blockers (2), interferons (2) and statins (2).
- Clinical improvement or resolution occurred within 2-8 months after d/c of drug. Also, Ro titers decreased.

– Srivastava et al: Arch Dermatol. 2003;139: 45-9.

Demographics of DI-SCLE

	Drug induced SCLE	Idiopathic SCLE
Age	58 years	43 years
Gender (female)	72 %	75%
Ro/SS-A	81 %	80-90%
La/SS-B	48 %	12-42%
ANA	82 %	40-70%
Histone	33 %	?

Lowe et al: Br J Dermatol 2011; 164:465-72.

Drug induced SCLE

	% of total cases
Antihypertensives	34
Antifungals	26
Chemotherapeutic agents	9
Antihistamines	8
Immunomodulators	7
Others	16

Lowe et al: Br J Dermatol 2011; 164:465-72.

Clinical Course DI-SCLE

- Incubation time
  - Median 6 weeks (range 3 days to 11 years)
    - Longer for calcium channel blockers
    - Shorter for terbinafine
- Not distinguished from idiopathic SCLE
  - Annular and/or papulosquamous plaques in photodistributed locations
  - Histopathologically with an interface dermatitis/licheniod tissue reaction. Eosinophils were a not prominent feature.
- Resolution upon discontinuation
  - Mean 7.3 weeks
  - Median 4 weeks
  - 67% remained Ro/SS-A positive after resolution

DI-SCLE in Sweden

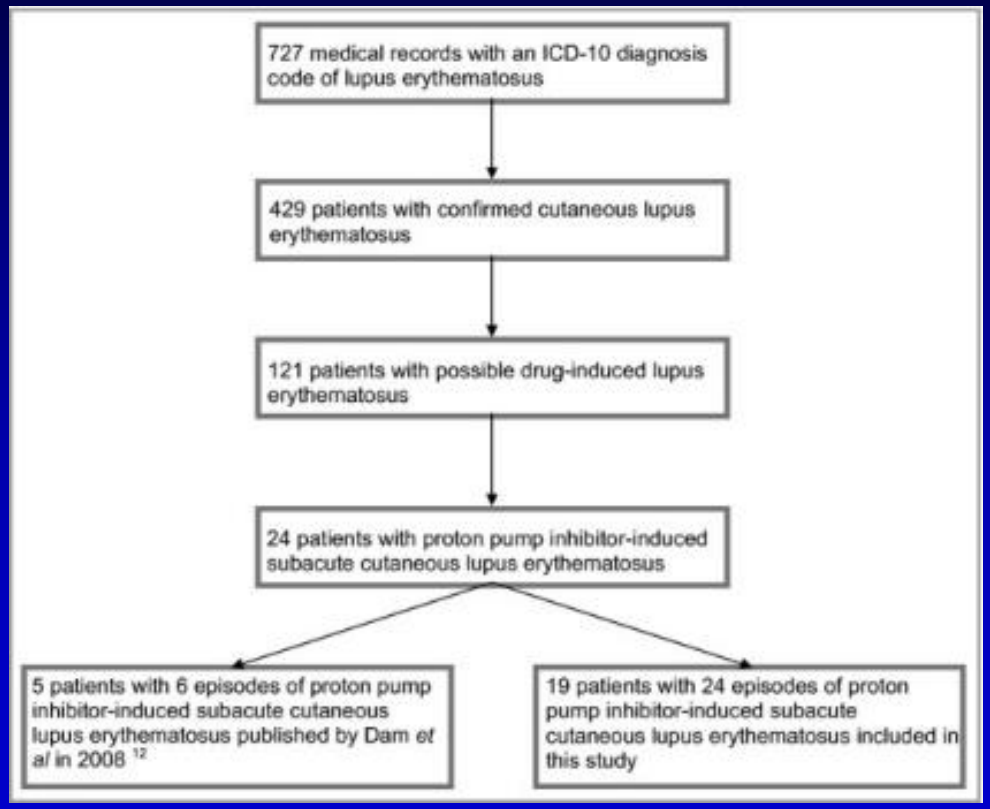
- Population-based, matched, case-control study using ICD-10 diagnosed patients with SCLE (234 patients) compared 1:10
- Use of Prescribed Drug Registry
- Roughly 33% of their SCLE patients had a potential drug associated with the onset of the diagnosis of SCLE

DI-SCLE in Sweden

- Terbinafine (OR=38.5), TNF-α inhibitors (OR=8.0), antiepileptics (OR=3.4) and proton pump inhibitors (OR=2.9).
- They did not find increased risk associated with diuretics or antihypertensive agents
- SCLE diagnosis was not validated and patients with exacerbations of existing disease were not included

Gronhagen C, et al: Br J Dermatol 2012; 167:296-305

Proton pump inhibitor-induced subacute cutaneous lupus erythematosus



Br J Dermatol. 2014;170(2):342-51

Results

- 19 patients with 21 episodes of SCLE attributed to PPI use.
  - 3 “definite” cases, 14 “probable” cases, 2 “possible” cases
  - 89% female with an average age of 61 years
  - Those with SLE and PPI-induced SCLE tended to be younger with an average age of 41 years.
  - 12 cases attributed to lansoprazole, 6 cases to omeprazole, 4 cases to esomeprazole and 2 cases to pantoprazole
  - 3 patients had flares after switching to a different PPI

Results (cont.)

- Average amount of time between prescription of PPI and development of SCLE was 8 months.
  - Range of 1 week to 3.5 years
- After discontinuing the medication, eruption cleared on average in 3 months.
  - Range of 4 weeks to 8 months
- Serology similar to *de novo* SCLE with 61% having a positive ANA, 73% with anti-Ro antibodies, 33% with anti-La antibodies, 8% with anti-dsDNA antibodies and 8% with anti-histone antibodies.

Comparison of Drug-induced SLE and SCLE

	SLE	SCLE
Skin lesions	Rare	SCLE or gyrate erythema
Serositis	Common	Occasional
Serology	Anti-histone	Anti-Ro
Drugs	Procainamide, hydralazine, INH, minocycline, anti-TNF agents, etc.	Over 100 agents: HCTZ, Calcium channel blockers, terbinafine, ACE inhibitors, statins, PPIs, anti-TNF agents, docetaxel

Histopathology of DI-SCLE

- We compared DI-SCLE to naturally occurring SCLE, specifically assessing the presence of tissue eosinophilia
- No differences were noted

Hillsheim P, et al: Arch Dermatol 2012; 148(2):190-3

Management of DI-SCLE

- Withdrawal of offending drug – remember to inform the prescribing physician and obtain permission as well as discuss substitute medication(s)
- Topical corticosteroids
- Antimalarial agents
- Short course of systemic steroids

DI-SCLE - Conclusions

- Drugs may induce or exacerbate subacute cutaneous lupus erythematosus
- Somewhere between 20% and 30% of patients with newly diagnosed SCLE have a drug as a trigger, perhaps the incidence is higher in older patients (>50)
- The most common agents are antihypertensives, terbinafine, and PPIs
- None of the drugs that induce/exacerbate cutaneous LE are associated with a high prevalence rate of this reaction

DI-SCLE - Conclusions - II

- Drug-induced cutaneous LE differs from drug-induced SLE clinically, serologically and etiologically
- Perhaps the patient with known LE or photosensitivity should avoid some of these agents, or at least be forewarned about the potential for such a reaction
- Management involves drug withdrawal, short courses of corticosteroids and/or antimalarial agents
- Some patient's disease is 'awakened' and does not resolve

Systemic disease in SCLE: A controlled comparison with SLE

- Study of 30 matched patients with SCLE v. SLE in a University setting
- Identical frequency of severity and associated disease – i.e. nephritis, neurologic disease, etc.

  - J Rheumatol 1994; 21: 1665-9

Frequency & Severity of Systemic Disease in SCLE – a case-control study of 76 SCLE patients

Abnormality	*SCLE*	*SLE*	*P value*
Cytopenia	7.9%	54.2%	p<0.001
Serositis	1.3%	12.5%	p=0.041
Renal	15.8%	25%	p=0.363
ANA +	68.4%	95.8%	p=0.006
Anti-Ro (SS-A) +	48.7%	41.7%	p=0.642
Other + serology	7.9%	62.5%	p<0.001
Photosensitivity	85.5%	45.8%	p<0.001

Black DR, Hornung CA, Schneider PD, Callen JP. Arch Dermatol. 2002 Sep;138(9):1175-8.

Discussion

- There is a dissimilar frequency of internal organ involvement in patients with SCLE and those with SLE.
- The renal abnormality that occurs is roughly equal in its frequency and in its severity.
- The limitation of this study is that the patients were selected from a relatively healthy populations followed in rheumatology and dermatology practices.

Black DR, Hornung CA, Schneider PD, Callen JP. Arch Dermatol. 2002 Sep;138(9):1175-8.

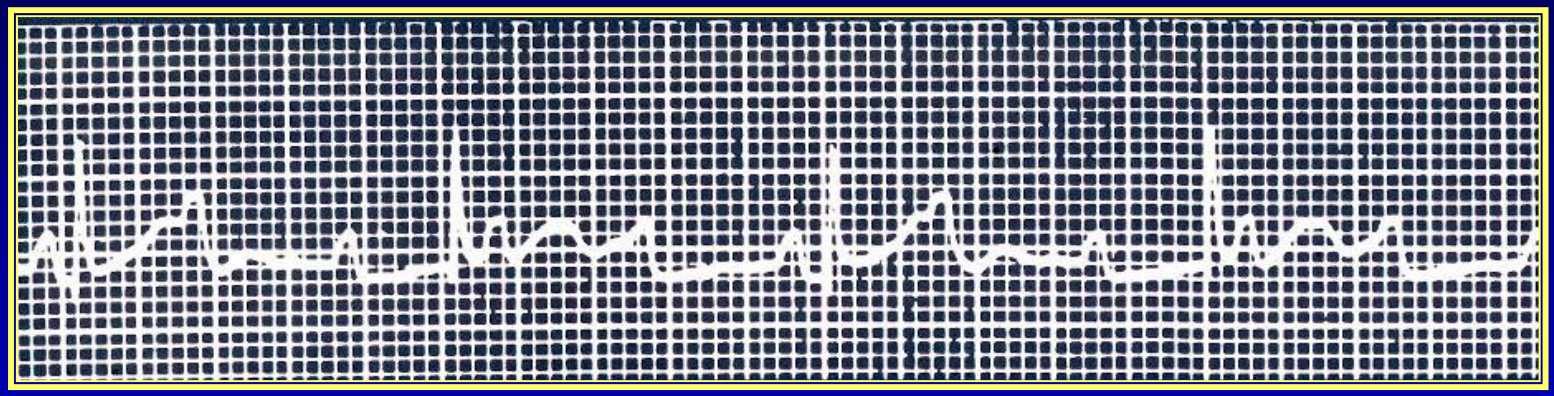
Neonatal Lupus Erythematosus

- Incidence – 1/20,000 live births
- No ethnic predilection
- F > M – 2:1 for heart block, 3:1 for skin disease
- Risk for a Ro+ woman to deliver a neonate with NLE or CHB is < 1%
- Risk for a second affected child is ~ 25%

Cutaneous Disease in NLE

- Annular plaques with fine scale
  - "Owl" eyes
  - Crusted papules with petechiae
- DLE lesions
- Facial involvement is most common
- Photosensitivity
- Angiomatous papules or telangiectatic mats

Heart block in NLE



- Complete Heart block – 90%
- May result in congestive heart failure in early childhood and the need for pacemaker placement
- Associated congenital heart defects – 30%

Maternal outcome in NLE

- Majority of mothers have some symptoms at the time of delivery, but only ½ have a defined CTD
- 80% develop symptoms within 5 years
  - Arthritis/arthralgia
  - Xerostomia
  - Xerophthalmia
  - LE – SLE or SCLE
  - MCTD

Other features of NLE - 1

- Hepatosplenomegaly, abnormal Liver derived enzymes
- Cytopenia – thrombocytopenia, leukopenia, hemolytic anemia
- These processes are usually transient, but some patients with severe disease have had fatal outcomes

Other features of NLE - 2

Hydrocephalus and macrocephaly

- **Study of 75 Ro+ mothers with 87 live births (42 with NLE – 20 cutaneous, 18 hepatic, 18 hematologic, 13 CHB and 33 otherwise normal neonates)**
- **Hydrocephalus occurred in 5 patients with other manifestations of NLE and 2 otherwise healthy neonates (background frequency 1.6/1000 live births)**
- **Head circumference was greater in infants of Ro+ mothers, but with time most infants normalized**

(Arthritis Care Res 2007; 261-266)

Histopathologically-non-specific skin disease in patients with LE

- Bullous LE
- Skin lesions associated with APS
  - LR, blue toes, cutaneous necrosis
- Vasculitis
- Mucinous infiltration
- Porphyria cutanea tarda
- Psoriasis
- Other “autoimmune” disorders

Blisters/erosions in patients with LE

- Three clinical/pathologic patterns are recognized:
  - TEN-like acute eruption with an interface dermatitis
  - Lesions occurring on LE skin lesions (primarily SCLE) with an interface dermatitis
  - Vesicles and bullae with a neutrophilic infiltrate (usually responsive to dapsone)

Medicine (Baltimore). 2015 Nov;94(46):e2102

Do Patients with Cutaneous LE "Progress" to Develop SLE?

- Population-based study in Rochester, MN
- Incidence of CLE and SLE were equal
- Nineteen of the 156 patients (12.2%) had disease progression to SLE; the mean (SD) time from CLE diagnosis to SLE progression was 8.2 (6.3) years.
- 9 had the localized discoid subtype of CLE, 4 had the generalized discoid subtype of CLE, 2 had the lupus panniculitis subtype of CLE, and 4 had the psoriasiform subtype of CLE.

Arch Dermatol. 2009;145(3):249-253.

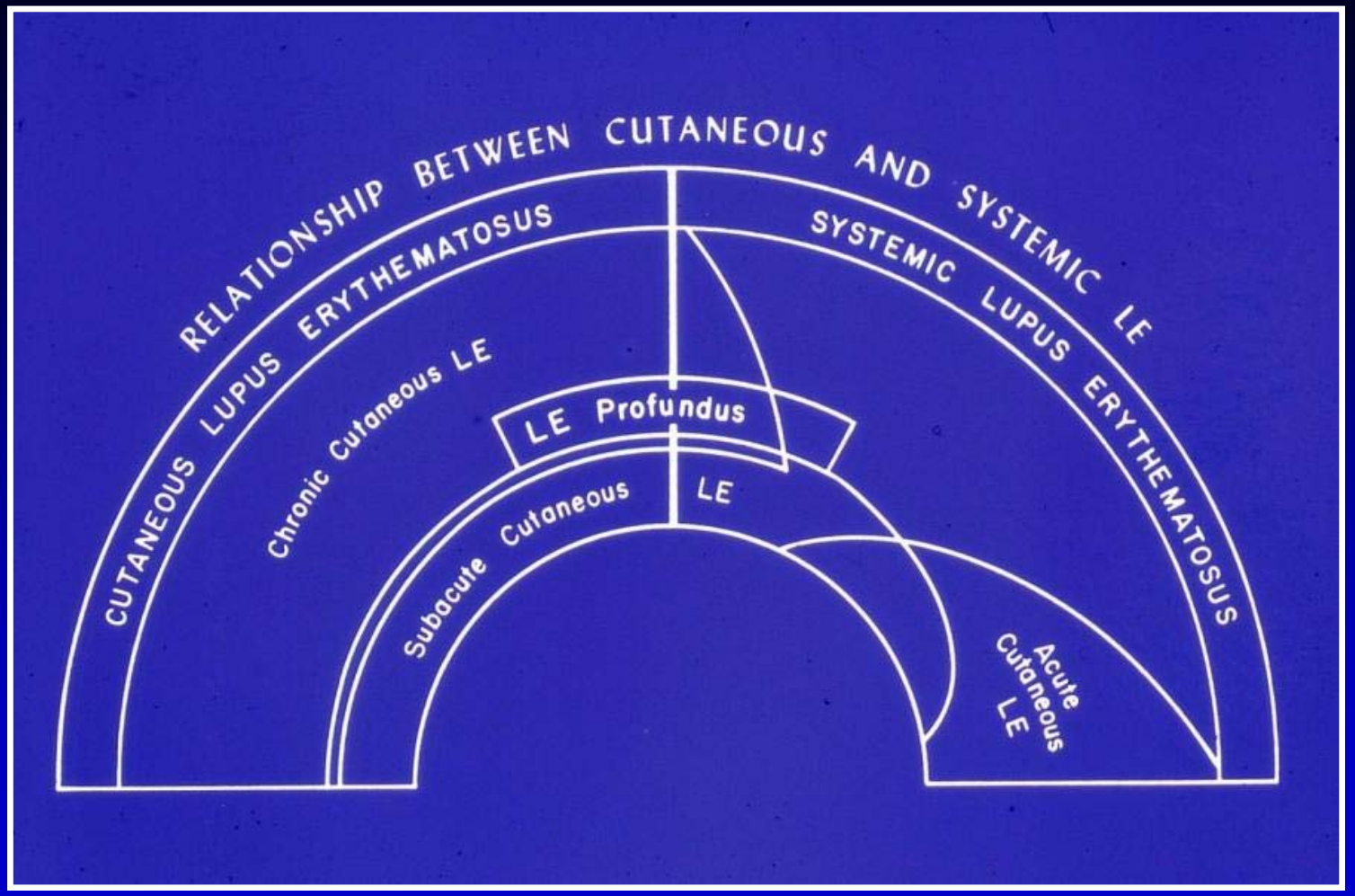
Do Patients with Cutaneous LE "Progress" to Develop SLE?

- Study of 77 patients followed prospectively at U Penn over a 4 year period (2007-11)
- 13 patients with CLE went on to meet ACR criteria for SLE (1 mucocutaneous criteria only, 3 mucocutaneous criteria + serology)
- Only 5/13 patients with CLE/SLE developed moderate to severe SLE-related disease over a period of 2.81 years

Do Patients with Cutaneous LE "Progress" to Develop SLE?

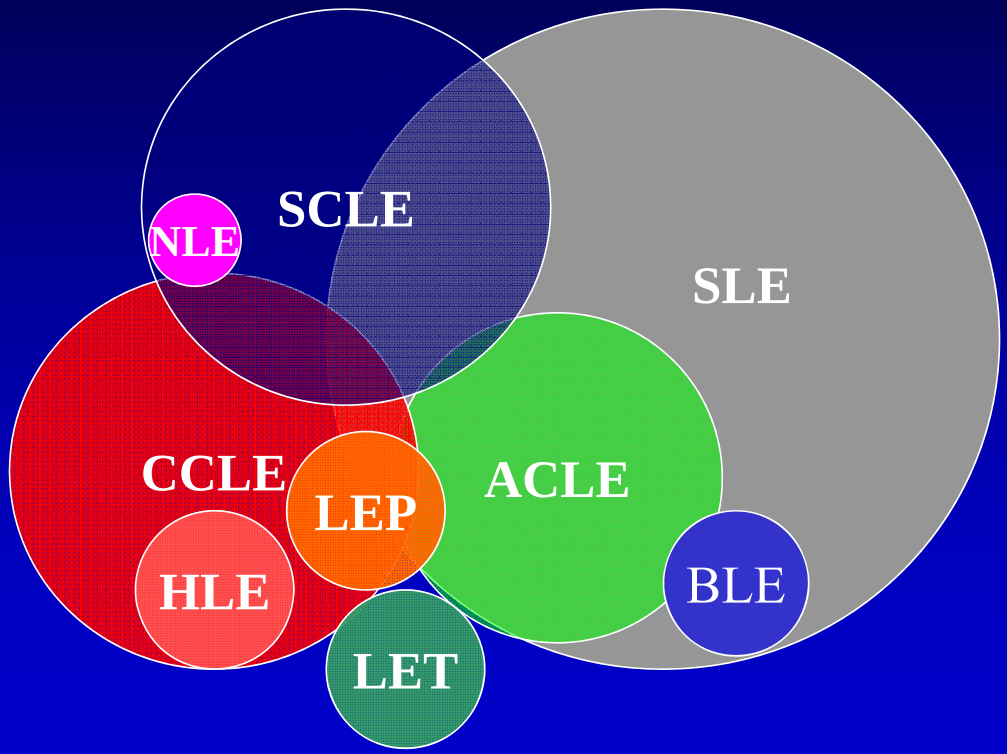
- Characteristics at baseline that might predict development of SLE (none statistically significant)
  - Positive ANA
  - Widespread disease
  - Female sex
- Conclusions: Although patients might progress, the criteria for SLE are primarily mucocutaneous (malar rash, discoid lesions, photosensitivity & oral ulcers. The SLE seems milder than unselected SLE patients.

JAMA Dermatol. 2014 Mar;150(3):291-6.



From Gilliam 1978

Relationship of cutaneous subsets to SLE



Pathogenesis of Cutaneous LE

- Cutaneous LE is thought to be due to antibody dependent cell cytotoxicity
- The first signal may be the expression on the cell surface of antigens including Ro/SS-A that might be photo-induced
- This is followed by a complex, as yet poorly studied inflammatory cascade that is mediated by cytokines including TNF
- Detection of type 1 cytokines in discoid lupus erythematosus. (Arch Dermatol 2000; 136(12):1497-501)
  - DLE is associated with type 1 cytokines characterized by the expression of IL-2 and IFN-gamma. Type 1 cytokines may be critical for induction, development, and maintenance of DLE.

Genetic Variants Associated with Significant Risk for Systemic Lupus Erythematosus

Gene	Genomic Location	Proposed Function
HLA	6p21.33 and 6p21.32	Presentation of antigen
ITGAM	16p11.2	Adhesion of monocytes and polymorphonuclear cells to endothelial cells
IFR5	7q32.1	Production of interferon-α
KIAA1542	11p15.5	Linkage disequilibrium with IRF7; production of type I interferon
PXK	3p14.3	Unknown protein kinase effect
PTPN22	1p13	Inhibition of leukocyte activity
FCGR2A	1q23	Clearance of immune complexes
STAT4	2q32	Modulation of the production of cytokines in T-cells and natural killer cells; activation of response of macrophages to interferon-α
BLK	8p23.1	Activation of B cells

HLA = *Histocompatibility antigen;* ITGAM = *Integrin-α_m (also known as CD11b, Mac-1 and complement receptor 3);* IFR5 = *interferon regulatory factor 5;* KIAA1542, PXK *were not defined further in any source;* FCGR2A = *Fc receptor for IgG;* PTPN22 = *protein tyrosine phosphatase receptor type 22;* STAT4 = *signal transducer and activator of transcription 4; and* BLK = *B-cell specific tyrosine kinase.*

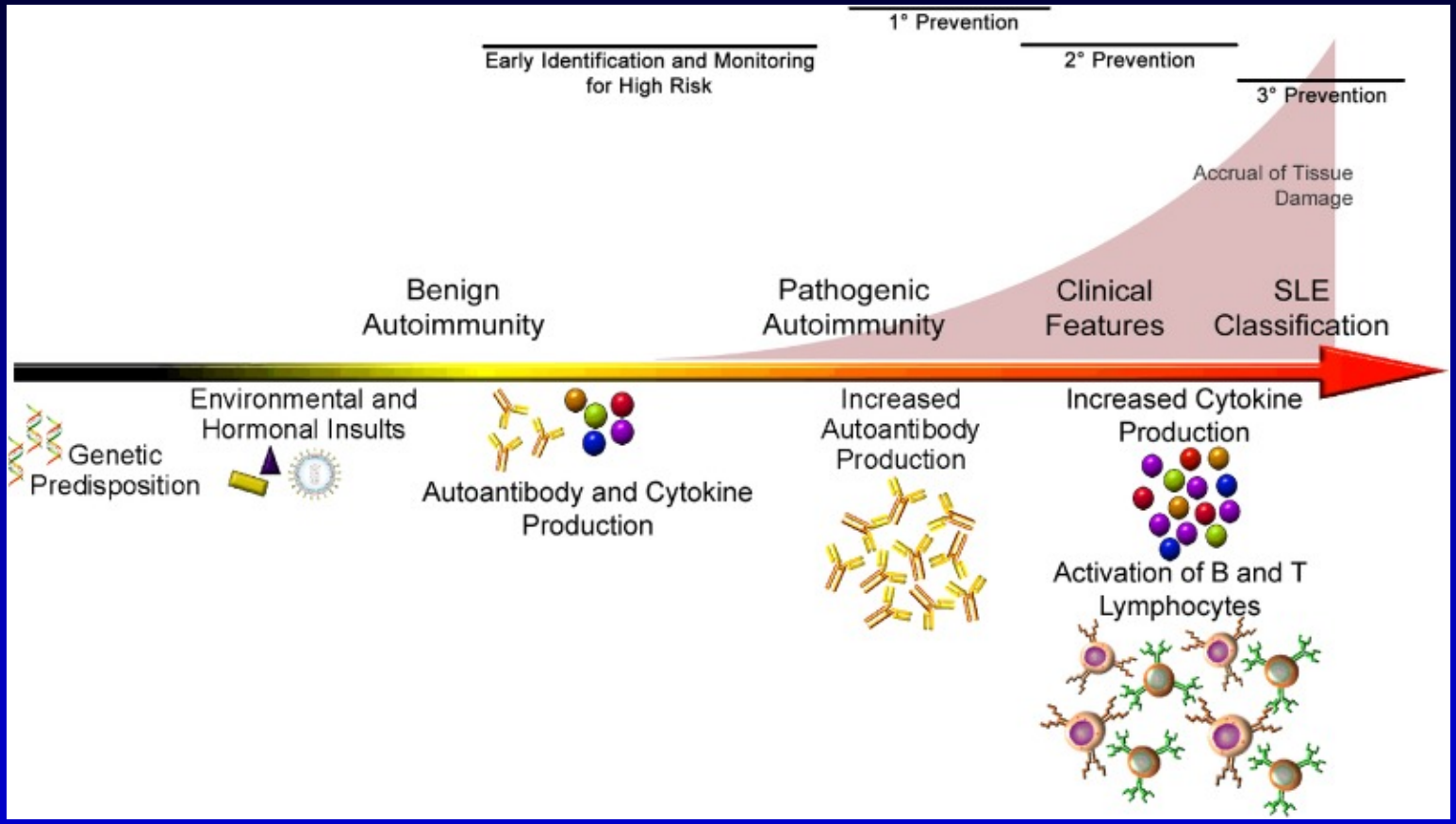
Table adapted from Crow MK, New England Journal of Medicine.

Development of Autoantibodies before the Clinical Onset of SLE

- Prospective evaluation of frozen serum samples in patients with SLE and matched controls
- SLE was diagnosed in 130 military personnel (36% male, 62% black, 10% Hispanic)
- Mean age at diagnosis – 30.4 +/- 6.4 years
- Available samples – 4.9 +/- 2.5, with earliest sample 4.4 +/- 2.5 years prior to Dx

Development of Autoantibodies before the Clinical Onset of SLE

- 90/130 SLE patients had +antibody in the 1st specimen available
- Intervals of antibody appearance (yrs) – ANA(3.01) , Ro (3.68), La (3.61), Antiphospholipid Ab (2.94), Anti-nDNA (2.24), Anti-Sm (1.47) and Anti-RNP (0.88)
- Insidious onset of disease – on average the first clinical symptom developed 1.5 years prior to diagnosis



Lupus Sci Med. 2015 Jun 30;2(1):e000087

Diagnosis of Cutaneous LE

- Clinical morphology
- Distribution of the lesions
- Histopathology
- Serologic testing in selected individuals
- Direct immunoflouresence microscopy in selected individuals

Differential diagnosis

- CCLE – other PS disorder, sarcoidosis
- SCLE – PMLE, BLI, rosacea, PS diseases, EAC, other figurate erythemas, DM
- Tumid LE – Sarcoid, BLI, PMLE, REM
- SLE – rosacea, drug-induced photosensitivity, DM

Evaluation of Patients with Cutaneous Lupus Erythematosus

- Purpose
  - Assess severity & internal involvement
  - Predict prognosis
- CBC for hematologic involvement. Patients frequently are leukopenic, but hemolytic anemia and thrombocytopenia may occur
- Tests of renal function – the urinalysis is the most important
- Serologic testing

Evaluation of the Patient with Cutaneous Lupus Erythematosus

- The risk of systemic disease in any given patient exists, but the chances of severe disease is low except in those patients with acute cutaneous lupus erythematosus.

Condition	*Frequency*
DLE	Up to 18%
LET	<1%
LEP	<5%
SCLE	50%
ACLE	100%

Serologic Testing in Patients with Lupus Erythematosus

- ANA – almost always positive, higher titers and certain patterns may reflect systemic involvement
- Anti-Ro (SS-A) – frequently positive in SCLE, SS, NLE. Not useful in diagnosis or prognosis, must correlate with clinical findings. Rarely positive in DM.

Serologic Testing in Patients with Lupus Erythematosus -II

- Anti-Sm – more specific for SLE.
- Anti-nDNA – most specific for SLE, titers or levels predict prognosis and may reflect the activity of the renal disease.
- Cutaneous immunofluorescence – useful only in cases where clinical/pathological features are not characteristic.

Repeat Evaluation

- Periodic CBC and urinalysis
- Evaluate any new symptom

Management of the patient with Cutaneous LE: Goals

- Reassure the patient
- Improve the patient's appearance
- Prevent the formation of scars, dyspigmentation and atrophy
- Stop the formation of new lesions
- *Unfortunately, there are few double-blind, placebo-controlled studies with any of the agents that we will discuss*

Topical Therapies

Sunscreens and photoprotection
Smoking cessation
Consider Vitamin D and Calcium

Corticosteroids
Calcineurin inhibitors

First-line Systemic Therapies

Antimalarial Drugs
- Hydroxychloroquine or Chloroquine

Rarely, short-term oral corticosteroids

Second-line Systemic Therapies

Azathioprine, methotrexate mycophenolate mofetil,

Thalidomide

General Measures

- What drugs is the patient taking?
  - Eliminate the possibility of drug-induced cutaneous LE for patients with SCLE.
- Is the patient a smoker?
  - Smokers respond less well to antimalarials or possibly have more severe disease.

General Measures

- Cosmetic agents or devices.
  - Wigs, cover-up makeup, etc.
- Sun protective measures
  - Sunscreens – broad spectrum, daily use
  - Sun avoidance, behavioral alteration
  - Clothing – hats, tested clothing

Photoprotective effects of a broad-spectrum sunscreen in ultraviolet-induced cutaneous lupus erythematosus: A randomized, vehicle-controlled, double-blind study

Annegret Kuhn, MD,[a] Kristina Gensch, MD,[b] Merle Haust, MD,[b] Anna-Maria Meuth, MA,[a] France Boyer, MD,[c] Patrick Dupuy, MD,[c] Percy Lehmann, MD,[d] Dieter Metze, MD,[a] and Thomas Ruzicka, MD[e]
Muenster, Duesseldorf, Wuppertal, and Munich, Germany; and Toulouse, France

Methods: A total of 25 patients with a medical history of photosensitive CLE were included in this monocentric, randomized, vehicle-controlled, double-blind, intraindividual study. The test product and its vehicle were applied 15 minutes before UVA and UVB irradiation of uninvolved skin areas on the upper aspect of the back in a random order, and standardized phototesting was performed daily for 3 consecutive days.

Conclusion: These results indicate clearly that the use of a highly protective broad-spectrum sunscreen can prevent skin lesions in photosensitive patients with different subtypes of CLE. (J Am Acad Dermatol 2011;64:37-48.)

Standard Therapy

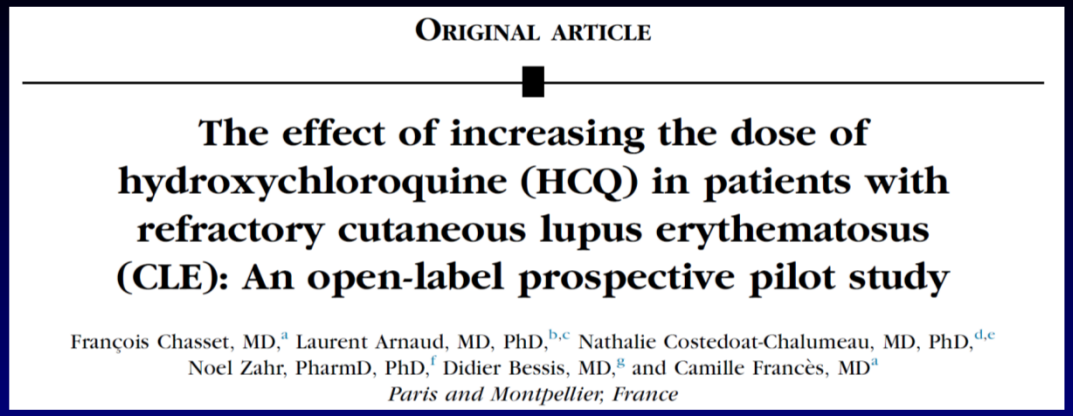
- Topical corticosteroids
  - Selected for the lesion and site that is being treated
- Intralesional injection of corticosteroids
  - Temporary improvement, avoid large doses
- Antimalarial agents
  - Hydroxychloroquine or chloroquine with or without quinacrine

Alternative Topical Agents

- Tretinoin
- Tazarotene
- Calcipotriene
- Imiquimod
- Tacrolimus
- Pimecrolimus
- Intralesional interferon α

Antimalarial therapy

- Hydroxychloroquine, chloroquine or quinacrine
- Quinacrine may be combined with either H or C
- Monitor for hematologic or ocular toxicity



ORIGINAL ARTICLE

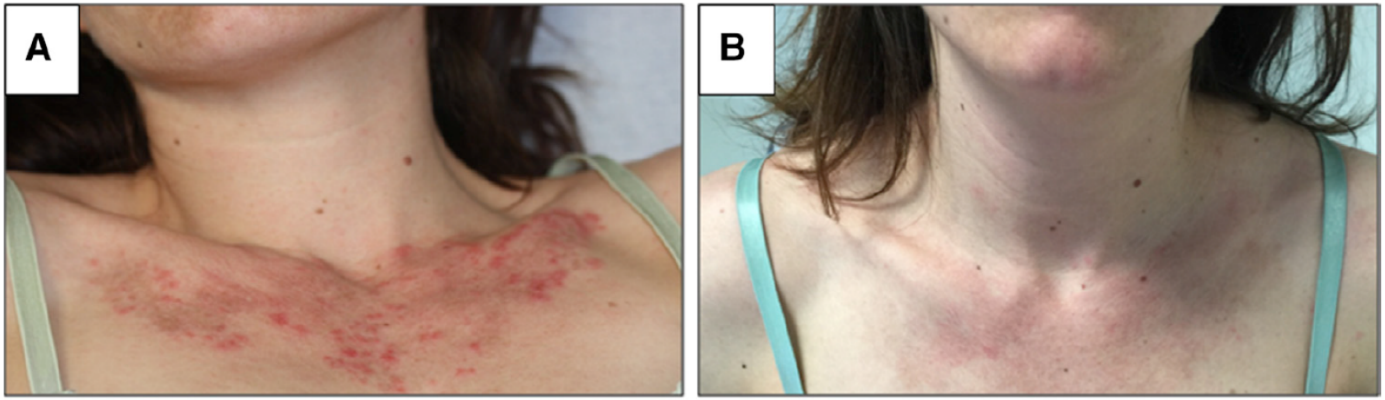
The effect of increasing the dose of hydroxychloroquine (HCQ) in patients with refractory cutaneous lupus erythematosus (CLE): An open-label prospective pilot study

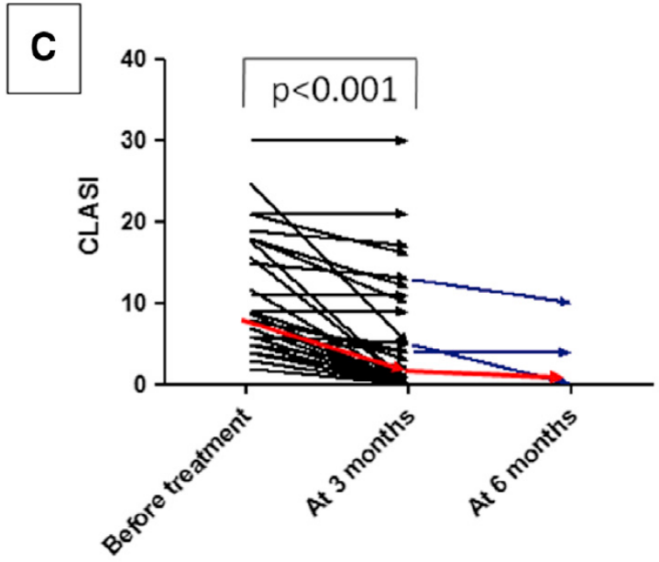
François Chasset, MD,[a] Laurent Arnaud, MD, PhD,[b,c] Nathalie Costedoat-Chalumeau, MD, PhD,[d,e] Noel Zahr, PharmD, PhD,[f] Didier Bessis, MD,[g] and Camille Francès, MD[a]
Paris and Montpellier, France

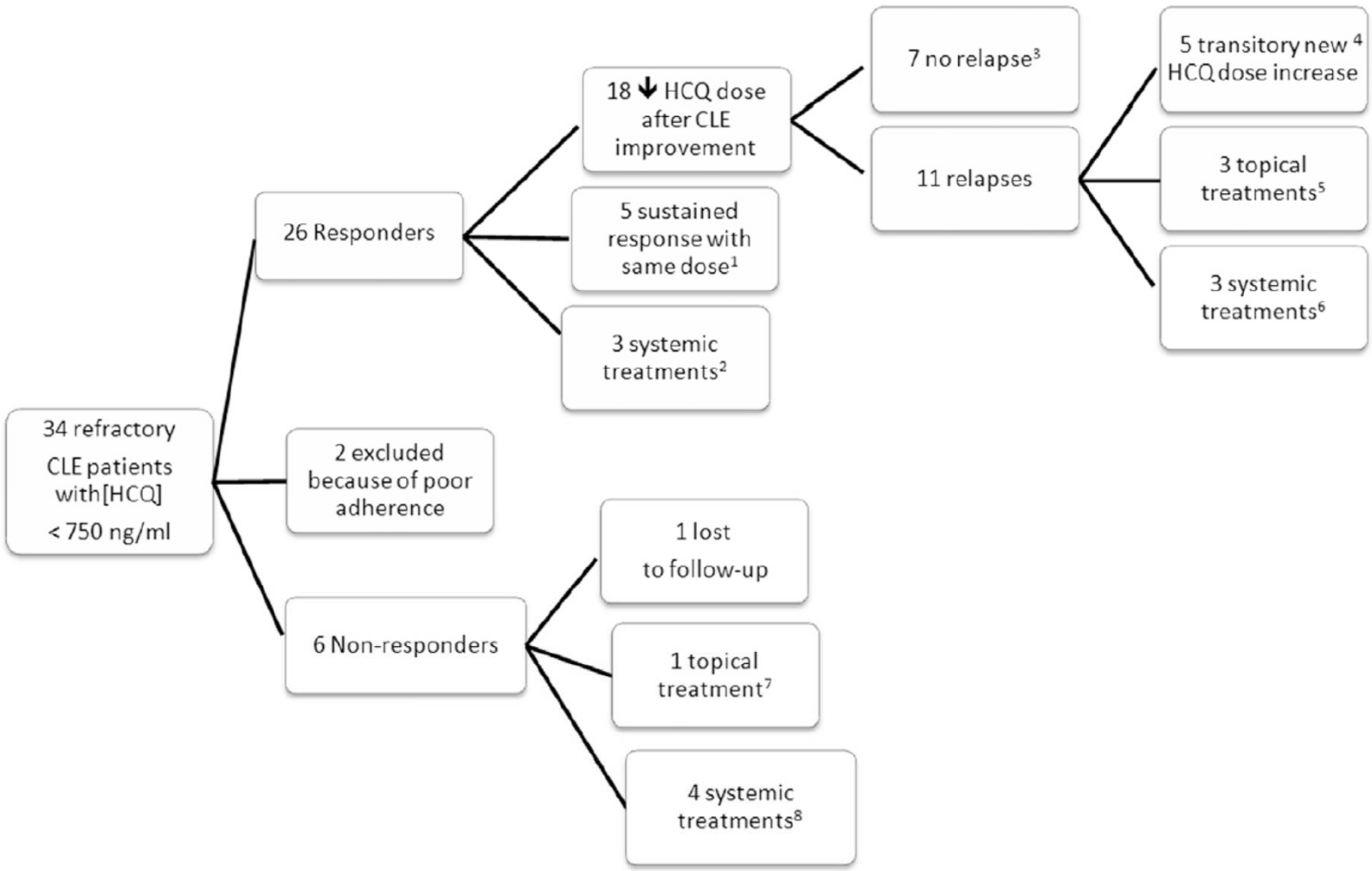
- Up to 1/3 of patients are not responsive to antimalarial therapy
- 36 of 74 patients had blood levels of less than 750 ng/mL
- 4 were not studied including 2 non-adherent patients
- 26/32 noted pre-defined clinical response with increased dose to achieve an adequate blood level
- 15/26 were able to reduce their dosing and maintain response

Antimalarial Dosing for Patients with Low Blood Levels

- Types of CLE – 17 DLE, 11 SCLE, 6 LET, 1 chilblain LE, 1 LE panniculitis (4 patients had more than one type)
- Smoking history – 15 current smokers, 3 past smokers
- Concomitant medications – prednisone 4 patients, MMF 2 patients, methotrexate 2 patients


A
B


C
p<0.001
CLASI
40
30
20
10
0
Before treatment
At 3 months
At 6 months


34 refractory CLE patients with [HCQ] < 750 ng/ml
26 Responders
2 excluded because of poor adherence
6 Non-responders
18 ↓ HCQ dose after CLE improvement
5 sustained response with same dose[1]
3 systemic treatments[2]
1 lost to follow-up
1 topical treatment[7]
4 systemic treatments[8]
7 no relapse[3]
11 relapses
5 transitory new [4] HCQ dose increase
3 topical treatments[5]
3 systemic treatments[6]

Comments

- Limitations
  - Small sample size
  - Open-label nature
  - Variability of cutaneous manifestations
  - Concomitant drug use
  - Short-term nature of the study, limiting the ability to assess potential retinal toxicity
  - Cost and availability of hydroxychloroquine blood level testing

J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.09.064

Antimalarial prophylaxis for LE

Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus

JA James[1,2*], XR Kim-Howard[1,3], BF Bruner[1,2], MK Jonsson[4], MT McClain[1], MR Arbuckle[1], C Walker[5], GJ Dennis[5,6], JT Merrill[7] and JB Harley[1,2,8]

Systemic lupus erythematosus (SLE) is a clinically diverse, complex autoimmune disease which may present with coincident onset of many criteria or slow, gradual symptom accrual. Early intervention has been postulated to delay or prevent the development of more serious sequelae. One option for treatment in this setting is hydroxychloroquine. Using 130 US military personnel who later met ACR SLE criteria, a retrospective study of onset, development and progression of SLE with and without pre-classification hydroxychloroquine ($n = 26$) use was performed. Patients treated with hydroxychloroquine prior to diagnosis had a longer (Wilcoxon signed rank test, $P = 0.018$) time between the onset of the first clinical symptom and SLE classification (median: 1.08 versus 0.29 years). Patients treated with prednisone before diagnosis also more slowly satisfied the classification criteria (Wilcoxon signed rank test, $P = 0.011$). The difference in median times between patients who received NSAIDs before diagnosis, as opposed to those who did not, was not different ($P = 0.19$). Patients treated with hydroxychloroquine also had a lower rate of autoantibody accumulation and a decreased number of autoantibody specificities at and after diagnosis. These findings are consistent with early hydroxychloroquine use being associated with delayed SLE onset. A prospective, blinded trial testing the capacity of hydroxychloroquine to delay or prevent SLE in high risk populations is warranted. *Lupus* (2007) **16**, 401–409.

Antimalarial Therapy

Concise report

Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine

Peter M Izmirly,[1] Mimi Y Kim,[2] Carolina Llanos,[1] Phuong U Le,[3] Marta M Guerra,[3] Anca D Askanase,[1] Jane E Salmon,[3] Jill P Buyon[1]

Ann Rheum Dis 2010; 69:1827-30

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DOI 10.1002/art.27289

The Protective Effect of Antimalarial Drugs on Thrombovascular Events in Systemic Lupus Erythematosus

Alternative Systemic Therapies

- Antibiotics
- Non-steroidal immunomodulators
- Cytotoxic/immunosuppressive agents

Antibiotics

- Dapsone – 25-200 mg/d
  - Particularly useful for bullous LE, may be useful for SCLE, rarely useful for CCLE
  - Klebbes M, et al: Dapsone as Second-Line Treatment for Cutaneous Lupus Erythematosus? A Retrospective Analysis of 34 Patients and a Review of the Literature. Dermatology. 2016;232(1):91-6.
- Clofazimine –
  - Recent RCT compared clofazimine to chloroquine and found them equally effective, however more patients on clofazimine developed a flare of their SLE (Arthritis Rheum 2005; 52: 3073-8)
- Others - Cefuroxime axetil (500 mg/d), sulfasalazine (1.5 - 2 gm/d)

Clofazimine v. Chloroquine for LE

- DB, RCT of clofazimine 100 mg/d in 16 patients v. chloroquine 250 mg/d in 17 patients
- Good response in 75% of the clofazimine group and 82.4% of the chloroquine group (ns)
- CR - 18.8% and 41.2%
- Twenty-seven patients completed the trial including 11 treated with clofazimine and 16 with chloroquine, drop out in clofazimine group was primarily due to flare of SLE

Clofazimine v. Chloroquine for LE

- Limitations
  - There were too few patients for the authors to note differential response between subsets of cutaneous LE.
  - The inclusion of patients with malar erythema as this is usually easily treated
- Bottom line – I will not likely change my practice based on this article

Arthritis Rheum 2005; 52: 3073-3078.

Non-Steroidal Immunomodulators

- **Auranofin – 3 mg bid**
- **Phenytoin 100-300 mg/d**
- **Retinoids – isotretinoin (1mg/kg/d) or acitretin ½ to 1 mg/kg/d), Alitretinoin**
- **Thalidomide – 50-200 mg/hs**
- **Etanercept – 25 mg SQ biw (Arthritis & Rheum 2002; 46: 1408-9)**
- **Intravenous immune globulin – 1 gm/kg/d x 2d/mo.**

Efficacy of Low Dose Thalidomide

Author	# Rx	CR	PR	NR/toxicity
Stevens, 1997	16 CLE	7/16 (44%)	6/16 (37%)	3/16 (19%)
Sato, 1998	18 (CLE + SLE)	13/18 (72%)	5/18 (28%)	
Duong, 1999	7 CLE	6/7 (86%)		
Kyriakis KP, 2000	22 DLE	54%	23%	14%
Ordi-Ros, 2000	22 (DLE-9, SCLE-7)	12/19(63%)	4/19 (21%)	3/22 (14%) 3/22 (14%)
Versapuech, 2000	13 SCLE	11 (85%)		2 (15%)
Kuhn A , 2001	3 DLE	3 (100%)		
Housman, 2003	23 CLE	17 (74%)	3- > 75% 3 - < 75%	Neuropathy 5

Thalidomide in Cutaneous LE

- Rapid clinical response (100 mg/d): 2 weeks
- Full clinical response: 2-3 months
- Maintenance: 50 mg/d-25 mg every third day
  - ? Can antimalarials be used to maintain response
- Discontinuation: Relapse
- Re-administration: Similar clinical response
- Effect on concurrent SLE: Not marked
- Concerns: neuropathy, teratogenecity, thrombosis

Cytotoxic/Immunosuppressive Agents

- Azathioprine – 1-2 mg/kg/d
- Mycophenolate mofetil 1-1.5 gm bid
- Methotrexate 15-30 mg/wk
- Others – cyclosporin, cyclophosphamide, cytarabine

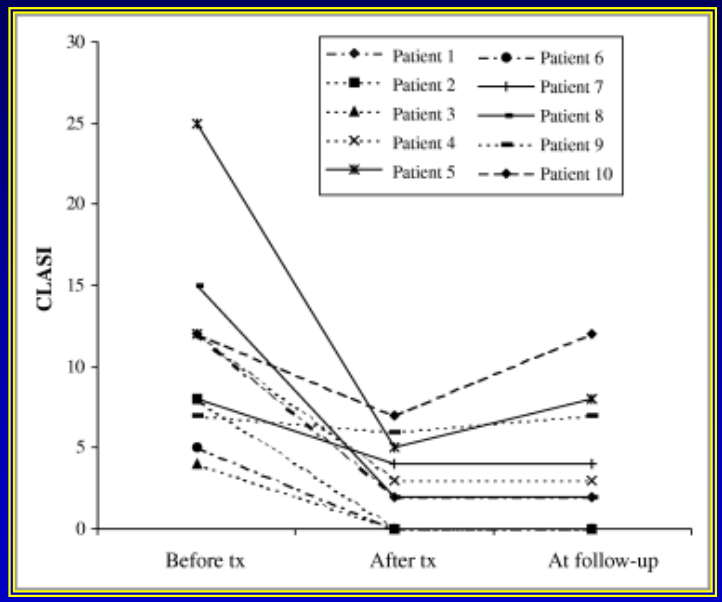
MMF for SCLE resistant to standard therapy

- Prospective, non-randomized pilot study of 10 patients with SCLE (4 PS, 6 A) using the CLASI
- Prior therapies – antimalarials (10), SS (7), azathioprine (3)
- 1440 mg/d of enteric-coated MMF for 3-months
- 7/10 were heavy smokers

Br J Dermatol 2007; 156: 1321-7

MMF for SCLE resistant to standard therapy

- All patients responded
- CLASI decreased from 10.8 +/- 6.0 to 2.9 +/- 2.6 ($p<0.05$)
- Responses held stable in 7 patients while 3 had relapses



Br J Dermatol 2007; 156: 1321-7

Methotrexate for Cutaneous LE

- 43 patients with cutaneous LE
  - SCLE 16, localized DLE 6, widespread DLE 4, tumid LE 3, chilblain LE 4, LEP 1
  - 7 had systemic LE with cutaneous manifestations
- Previous therapies – antimalarials 31, azathioprine 6, mycophenolate mofetil 4, and dapsone 2. No previous therapy – 6
- Concomitant therapies - antimalarial agents (14), antimalarial agents plus low-dose prednisone (5), and low-dose prednisone (13).

Methotrexate for Cutaneous LE

- Methotrexate dosage - 15-25 mg/w iv.
- Oral folic acid 5 mg was given on the morning following the methotrexate administration.
- 98% demonstrated marked improvement with minimal toxicity
- Lymphopenia was reversed by MTX.

Br J Dermatol 2005; 153: 157-62.

International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2012; **15**: 62–68

ORIGINAL ARTICLE

Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupus erythematosus

- Open label, prospective study comparing MTX and chloroquine
- 41 patients with SLE, 15 received MTX, 26 chloroquine

Table 3 Number of subjects with skin rash before and after treatment

Group	Total	At 0 week	At 24 weeks	*P*-value	Inter-group *P*
Methotrexate	13	06	0	< 0.001	NS
Chloroquine	24	19	03	< 0.001	

Do Belimumab or Rituximab have a role in the Management of Cutaneous LE?

- There are no studies that report validated information about the effects of belimumab on cutaneous lupus
  - My experience, albeit small and not controlled suggests that cutaneous disease continues during belimumab therapy
- One open-label study reported the effects of rituximab on cutaneous disease in patients undergoing therapy for SLE

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 6, June 2015, pp 1586–1591
DOI 10.1002/art.39085

BRIEF REPORT

Responses to Rituximab Suggest B Cell–Independent Inflammation in Cutaneous Systemic Lupus Erythematosus

Edward M. Vital,[1] Miriam Wittmann,[2] Sara Edward,[3] Md Yuzaiful Md Yusof,[1] Helen MacIver,[4] Colin T. Pease,[1] M. Goodfield,[1] and Paul Emery[1]

Goal of study:

Determine features associated with responses and flares after rituximab therapy in patients with various manifestations of SLE

- 82 patients receiving rituximab for SLE
- 26 with active mucocutaneous disease at baseline
  - 6 of these had flares or a new/different skin disease after treatment
- 6 with no mucocutaneous disease at baseline who developed flare or new/different skin disease

Results

- 12 patients with cutaneous flares
  - 6 with ACLE prior to treatment
  - 6 without skin disease prior to treatment
- Subtypes of skin disease flares:
  - SCLE = 4
  - CCLE = 5
  - Nonspecific lupus lesions (psoriasis, pemphigus) = 3
- No significant associations with serologic features, B cell depletion, or concomitant therapies

Comment

- **Relevance**
  - First evidence that clinical subgroups of SLE may require different targeted therapies
    - ACLE > CCLE with rituximab treatment
- B cell role in CLE may differ from their role in other manifestations of SLE
- **Limitations**
  - Selection bias
  - Lack of power (sample size) to compare all subtypes

On the Horizon

- Etanercept - NCT00797784 (open-label trial) (FL)
- Phosphodiesterase inhibitor (PDE-4) - NCT00708916 (open-label study of 10 patients [NYU])
- 595 nm Flashlamp Pulsed Dye Laser - NCT00523588 (single-blind study of 10 patinets [U Penn])
- Lenalidomide - NCT00633945 (Open-label study of 6 patients [U Penn])
- Safety and Efficacy of KRP203 in SCLE DB-RCT (Germany and Italy) sponsored by Novartis - NCT01294774

More on the Horizon

- A Multiple Dose Study Of PD-0360324 In Patients With Active CLE (Pfizer) - NCT01470313 (multi-national)
- Multicenter Study Assessing the Efficacy & Safety of Hydroxychloroquine Sulfate in Patients With SLE or CLE w/ Active LE Specific Skin Lesion (Sanofi-Aventis) - NCT01551069 (Japan)
- CC-11050 in Subjects With DLE and SCLE (Celgene) - NCT01300208 (US multicenter)
- Efficacy and Safety of Oral Alitretinoin (Toctino®) in the Treatment of Patients With CLE – (Basilea Pharmaceutica) NCT01407679 (Single center in Germany)

Therapeutic Ladder for Cutaneous Lupus Erythematosus

- Remove exacerbating factors
- Sunscreens
- Topical, intralesional corticosteroids
- Antimalarials – alone or combination
  - Assess drug levels and "push" dose in "poor responders"
- Thalidomide
- Other – retinoids, auranofin, dapsone, antibiotics
- Immunosuppressives – MTX, AZA, MMF
- Biologic agents – IVIg, other cytokines, T-cell modulating agents, possibly TNF inhibitors, ustekinumab
- Systemic corticosteroids

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- Biologic agents – IVIg, other cytokines, T-cell modulating agents, possibly TNF inhibitors, rituximab, belimumab, ustekinumab
- Systemic corticosteroids

Conclusions

- Diagnosis is based on clinical-pathological correlation
- Prognosis can be predicted by the type & severity of the cutaneous disease
- Successful management of cutaneous lupus erythematosus is possible
- Careful attention to exacerbating factors combined with topical and systemic therapies can lead to a control in the majority of patients

What do we know now about CLE?

- We recognize SCLE as a distinct subset – most, but not all patients are Ro antibody+
- We know that NLE is due to passive transfer of antibodies, there are other systemic manifestations and antimalarial therapy of the mother may lessen the risk of heart block
- We know that at least 10% of patients with DLE might develop systemic disease, but it is still less severe than unselected SLE patients
- We know that there are perhaps as many as 100 drugs that might trigger or exacerbate cutaneous LE

What do we now know about CLE?

- We know that the action spectrum is much broader than UVB
- We have many more therapies and others are in development
- We know that treatment with antimalarials might prevent disease and damage
- We believe that either CLE is worse or that antimalarial are less active in smokers