Published in final edited form as:

Curr Opin Rheumatol. 2013 September ; 25(5): 584–590. doi:10.1097/BOR.0b013e32836437ba.

Update on pathogenesis and treatment of CLE

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Abstract

Purpose of review—Cutaneous Lupus Erythematous (CLE) is an autoimmune disease in which patients may present with isolated skin findings or have CLE associated with underlying systemic disease. The most significant recent studies on its pathogenesis and therapeutic management are reviewed here.

Recent findings—Patients with subacute and Discoid Lupus Erythematous had elevated IFN score, about a third of all cases of SCLE could be attributed to previous drug exposure, and smoking may be more closely associated with CLE than Systemic Lupus Erythematous (SLE). An underlying genetic defect in some subsets of CLE patients may also be shared with SLE. Efficacy of antimalarial therapy is enhanced by increasing treatment duration or maintaining higher blood drug concentrations. Combination antimalarials that include quinacrine, thalidomide analogs, and Mycophenalate Mofetil may also be effective in refractory CLE.

Summary—The pathogenesis of CLE remains unclear, and is likely multifactorial. Identified associations with subsets of CLE suggest future research questions in CLE pathogenesis. Subsets of CLE associated with interface dermatitis may share an underlying genetic defect in interferon signaling with SLE. The Cutaneous Lupus Disease Area and Severity Index is a valuable and widely used tool allowing for standardized assessment and reporting of cutaneous disease activity and damage. More evidence is available to guide treatment of refractory CLE, but larger studies are needed.

Keywords

Cutaneous Lupus Disease Area and Severity Index; Cutaneous Lupus Erythematous; hydroxychloroquine; interferon

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Conflicts of interest: This material is based upon work supported by a Merit Review Grant from the Department of Veterans Affairs (Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development) and by the National Institutes of Health (NIH K24-AR 02207) to V.P.W.

Video abstract available: See the Video Supplementary Digital Content 1 (SDC1, http://links.lww.com/COR/A4).

Introduction

Cutaneous Lupus Erythematous (CLE) is an autoimmune disease in which patients may present with isolated skin findings or have CLE associated with underlying systemic disease. The majority of patients with Systemic Lupus Erythematous (SLE) display skin involvement or experience worsening of their disease with sunlight exposure. Skin lesions specific to Lupus Erythematous are categorized into three categories, chronic (CCLE), subacute (SCLE), or acute (ACLE). Discoid Lupus Erythematous (DLE) and Lupus Tumidus (TLE) are two of several subsets of CCLE.

The mechanism of CLE is not fully understood, and is likely due to a combination of genetic and environmental factors. Increasing evidence suggests that ultraviolet irradiation, autoantibody generation, dysregulation of T cells, dendritic cells, and other immune cells, with a contribution from innate mechanisms for activation of immune cells, may be involved in the pathogenesis of CLE [1].

CLE is a heterogeneous condition associated with a significant negative impact on quality of life. Treatment is aimed at reducing inflammation, preventing permanent skin damage, and improving quality of life. Protection from UV radiation with broad-spectrum sunscreens is fundamental, and mild disease is initially treated with topicals, including topical steroids and calcineurin inhibitors. For more severe disease, systemic treatment with antimalarials is the standard of care. Other immunomodulatory or immunosuppressive drugs can be added for those who fail to adequately respond.

The Cutaneous Lupus Disease Area and Severity Index (CLASI), has become a valuable and widely used tool allowing for standardized assessment and reporting of cutaneous disease activity and damage. Recent work has demonstrated that a four-point or 20% decrease in CLASI activity score is the most specific criterion for classifying patients as responders or nonresponders, and represents the minimal clinically important change [2]. The CLASI has also recently been independently validated using rheumatologist-assessed disease activity and damage assessments, and CLASI activity and damage scores were found to correlate with physician-assessed cutaneous activity and damage [3▪].

Cutaneous Lupus Erythematous Risk Factors

Many recent studies have explored risk factors that define various forms of CLE and further characterize the relationship between the pathogenesis of CLE and that of SLE, highlighting future research questions that will further clarify the pathogenesis of CLE.

Braunstein *et al.* [4▪▪] examined interferon signature after stratifying CLE patients by disease subtype. High IFN scores were seen in the peripheral blood of both SCLE and DLE patients, regardless of SLE status, but not in tumid LE or controls, a novel finding. Furthermore, the level of IFN gene expression correlated with cutaneous disease activity as measured by the CLASI, indicating a possible biomarker for CLE activity.

Further evidence has emerged to support clinical evidence that the presence of concomitant DLE may represent a negative risk factor for disease severity in patients with SLE [5] with

the finding that distinctive patterns of IgG and IgM autoantibodies may distinguish subsets of DLE and SLE patients. Lower IgG autoantibodies against nuclear antigens, which have previously been shown to correlate with SLE severity [6], have been found in DLE+SLE+ versus DLE-SLE+ patients, and are lower still in DLE+SLE-patients and healthy individuals [7]. Additionally, the same study suggests that higher IgM autoantibodies against selected antigens in healthy and DLE+SLE- patients may be nonpathogenic.

Building upon prior data demonstrating TNFα expression in the skin of and sera of CLE patients, Nabatian *et al.* [8▪] have also shown that PBMCs cultured from patients with DLE also release TNFα in significantly greater amounts as compared to controls. The major producers of TNFα were found to be monocytes and mDCs, and pDCs produced minimal amounts of TNFα in comparison. This increase in TNFα production likely explains the higher number of inflammatory cells seen in DLE lesions as compared to other forms of CLE. As a result of this new data, the authors postulate that monocytes and mDCs may play a larger role in the pathogenesis of DLE than was originally believed.

Piette *et al.* [9▪▪] using the CLASI score to assess for differences in disease severity, and Skindex-29 to measure quality of life, demonstrated that for patients with CLE smoking is associated with higher disease severity and lower quality of life. Additionally, this study found that CLE patients that smoke and require an immunomodulator in addition to antimalarial treatment are more refractory to this combination of treatment. In contrast to prior work [10–12], the study found that current smokers, when they did respond to antimalarials, had a better response to monotherapy with antimalarials than never and past smokers, indicating the need to further investigate the dose-dependence between cigarette smoking and CLE disease severity and response to antimalarials. Additionally, building upon prior studies suggesting that smoking is associated with CLE in general [13], here, individuals in the CLE-only group had a higher percentage of current smokers than did the SLE with skin involvement group, suggesting that smoking may be more closely associated with CLE than SLE.

In the first study to systematically examine the relationship between a prescription of previously reported drugs and the development of SCLE in a large group of patients with incident SCLE, Grönhagen *et al.* [14▪▪] found that about a third of all cases of SCLE could be attributed to previous drug exposure. The most increased odds ratios (OR) were found for terbinafine (OR 52.9), tumor necrosis factor-α inhibitors (OR 8.0), antiepileptics (OR 3.4), and proton pump inhibitors (OR 2.9) (Table 1).

Immunologically, histopathologically, and clinically, drug-induced SCLE (DI-SCLE) is indistinguishable from idiopathic SCLE. Greater than 80% of patients with SCLE display Ro/SSA autoantibodies and about 85% are photosensitive [15,16]. The study establishes a causal relationship between implicated drugs and SCLE but it remains unknown whether DI-SCLE represents de-novo development of pathogenic autoantibodies after drug exposure or onset of disease in a predisposed person. In conjunction with prior work demonstrating that Ro/SSA auto-antibodies have been present long before clinical symptoms of LE [17], this study further suggests that certain drugs may trigger subclinical disease to become evident in prone individuals. This work is important in conveying that DI-SCLE is likely an

underdiagnosed entity, which is significant because symptoms are completely reversible upon drug cessation.

Braunstein *et al.* [18▪] have also, for the first time, characterized the circulating leukocyte phenotype in a patient with severe treatment-refractory CLE, noting fewer CLA + leukocytes than previously described, baseline findings of granulocytopenia, and higher levels of B cells and memory and activated T cells, although further study is required to assess whether or not these findings have any prognostic value.

Finally, using standardized photoprovocation, one study observed that TLE was the most photosensitive subset studied, at 74.8% [19]. Significantly, a patients' history of photosensitivity was not a predictor for photoprovocation outcome, highlighting that results are not always reproducible, and more investigation into the significance of photoprovocation is needed.

Genetics of Cutaneous Lupus Erythematous

Recent studies provide further evidence to suggest that CLE shares genetic abnormalities with SLE. Recent studies have focused heavily on the genetics of interferon signaling in CLE pathogenesis and continue to support the theory that the disease may be characterized by inflammatory cascade derangements.

Braunstein *et al.* [4▪▪] reported an elevated Type 1 IFN score in DLE and SCLE, which is also characteristic of SLE. These results may suggest a mutation in interferon signaling representing a shared pathogenesis between SLE and some subtypes of CLE. Also of note, TLE, a form of CLE not usually associated with SLE [20], was not found to have an elevated IFN signature, providing an interesting correlate to this clinical finding. This study builds upon prior work that identified a polymorphism in IFN-regulatory factor 5 (IRF5) that was found in patients with SCLE and DLE [21]. It is important to note that some studies in SLE failed to show an association between type I IFN gene expression and longitudinal changes in disease activity, highlighting the need for further study of IFN-regulated genes as biomarkers of CLE disease activity [22,23].

Furthermore, mutations in TREX1, a $3' \rightarrow 5'$ exonuclease that degrades single-stranded and double-stranded DNA, are associated with SLE, Aicardi–Goutières Syndrome (AGS) and familial chilblain lupus, suggesting a common mutation in these autoimmune diseases characterized by type I IFN signaling. It has been demonstrated that the failure to degrade genomic dsDNA is a principal pathway of immune activation in TREX1-mediated autoimmune disease [24].

Recently, Tüngler *et al.* [25], have reported two novel cases of heterozygous TREX1 mutations associated with CLE, an inherited mutation (D18N) of autosomal dominant familial chilblain lupus and a de-novomutation (D18H) with chilblain lupus in the context of AGS. Previously, three patients with a heterozygous *de novo TREX1* mutation had been described.

Additionally, a published abstract suggests that TREX1 contributes to the regulation of PARP1, a nuclear DNA repair enzyme involved in the DNA damage response, and furthermore, that mutation-induced alterations in the function of TREX1 may be a factor in the development or progression of these autoimmune diseases by affecting PARP1 activity [26].

Finally, the crystal structures of TREX1 exonuclease mutations have also recently been determined, with all of the mutant structures revealing a reduced mobility in the catalytic residue, providing further explanation for the loss of catalytic activity [27].

Zahn *et al.* [28] provide the first evidence that the IFN-inducible TRAIL ligand, an apoptosis-inducing protein implicated in SLE pathogenesis, is also involved in the formation of LE skin lesions. Investigators demonstrated that TRAIL is strongly expressed in the skin and the blood of patients with CLE and may trigger the apoptotic death of keratinocytes in CLE via the TRAIL receptor R1, causing skin lesions. The group also demonstrated that TRAIL expression in keratinocytes and PBMCs is induced by IFN-α.

Augmenting Response to Systemic Therapy with Antimalarials

Significant recent work has highlighted new strategies to improve response to systemic antimalarial therapy by adjusting certain treatment variables. Antimalarials are the standard of care in systemic therapy, and the antimalarials used to treat CLE at present include hydroxycholoroquine, chloroquine, and quinacrine.

For patients who are refractory to treatment with antimalarials, new research from Chang *et al.* [29] suggests that an increase in response may be seen with increased duration of treatment with hydroxychloroquine beyond 2 months, even if no initial response to therapy is seen. This study also found that treatment may also be augmented with the addition of quinacrine, or treatment longer than 2 months with the combination of hydroxychloroquine and quinacrine. According to Gammon *et al.* [30], the addition of mycophenalate mofetil to hydroxychloroquine also improves response.

Hydroxychloroquine monotherapy may also be more efficacious at higher blood concentrations. One study found that patients who experienced complete remission had higher median blood concentrations of the drug (910 ng/ml), versus those with partial remission (692 ng/ml) and those considered to have failed treatment (569 ng/ml) [31▪▪]. The study authors suggest that monitoring of blood drug concentration may be used to guide future management.

New Insight into Immunomodulatory and Immunosuppressive Therapy

For those patients who are refractory to standard systemic therapy with antimalarials, several potential therapeutic agents exist including dapsone, azathioprine, thalidomide, methotrexate, sulfasalazine, cyclosporine, cyclophosphamide, intravenous immunoglobulin, and rituximab [32]. Recent work has expanded understanding of the safety and efficacy of additional systemic agents.

Thalidomide Analogs

Thalidomide has been used successfully in a variety of inflammatory dermatologic conditions with an underlying autoimmune pathogenesis, including CLE. In a prospective study, Cortes-Hernandez *et al.* [33▪] demonstrated, for the first time, efficacy of low-dose thalidomide according to the CLASI score, and identified prognostic factors of clinical response. Identified prognostic factors were that patients with a diagnosis of SCLE were more frequently long-term responders to the drug and that relapse was more frequently associated with DLE.

Lenalidomide is a thalidomide analogue that may serve as an adjunctive therapy for treatment-refractory CLE. Similarly to thalidomide, frequent relapses occur after withdrawal. Braunstein *et al.* [18▪] found that Lenalidomide led to clinical improvement in the majority of study patients, measured by decrease in CLASI score, but also was associated with the development of SLE in one patient. The authors suggest that further research defining risk factors for the development of SLE in patients with CLE may help assess which patients would benefit from Lenalidomide treatment.

Following Braunstein *et al.*, in an open-label pilot study, Cortes-Hernandez *et al.* [34▪▪] also found the drug to be well tolerated and effective as measured by CLASI score. Of interest, cutaneous relapse occurred in 75% of patients within 2–8 weeks after tapering dosage or withdrawing medication. Although the study was not designed to measure response between the different histological subtypes of CLE, researchers noted that patients with refractory SCLE tended to remain in remission after withdrawing medication, whereas those with DLE or TLE relapsed more frequently. In contrast to the previous study on Lenalidomide, this research found no systemic side-effects.

Finally, Aprimelast, a thalidomide analog and PDE4 inhibitor currently in development for inflammatory conditions such as psoriasis and ankylosing spondylitis, demonstrated a significant decrease in CLASI score in an open-label study of a small group of patients with DLE, with only mild adverse effects noted [35].

Additional Second-Line Systemic Therapies

In a retrospective analysis, Mycophenolate Mofetil (MMF), an immunomodulatory drug used in the treatment of SLE, was highly effective in the treatment of antimalarial-resistant CLE when added to antimalarial therapy [30]. With the addition of MMF to the existing regimen, a majority of the study patients achieved complete control of disease signs and symptoms, although treatment response was often delayed. Significantly, response, if obtained, was durable for the treatment duration. The group did not measure response after cessation of therapy. This agent may be promising due to its more favorable side-effect profile as compared to other immunomodulatory agents.

Chang *et al.* [36], using the CLASI, also provided insight into efficacy across several different treatment modalities, including antimalarial and immunomodulatory therapy, with findings that suggested that methotrexate and Mycophenolate Mofetil were more effective than Azothioprine. They also found that treatment efficacy correlates with improved quality

of life, as measured by the Skindex-29. However, due to the small number of patients included, this study was limited in the ability to draw a conclusion about the role of immunosuppressives in CLE.

Monoclonal Antibodies

Belimumab, a human monoclonal antibody that inhibits B-cell activating factor and is newly approved for SLE in the United States, Canada, and Europe, may also have implications for CLE. Cutaneous symptoms are among the treatment areas in which Belimumab, in addition to standard therapy in these patients, is most efficacious [37▪]. The drug is specifically noted to improve rash, mucosal ulcers, and alopecia. Belimumab has also been demonstrated to be well tolerated in long-term follow-up [38]. However, it is important to consider the retrospective design of the study and to acknowledge that the SLEDAI was used as an outcome measure, as opposed to a CLE specific tool.

Topical Therapy

Corticosteroids are the first-line topical treatment of active CLE lesions, with one large population study demonstrating that corticosteroids are the most frequently used, and the most effective topical in lowering CLASI activity score [39]. Patients utilize topical Calcineurin inhibitors less commonly, and their use is associated with a smaller reduction in CLASI score as compared to corticosteroids. However, recent studies continue to validate their efficacy. Avgerinou *et al.* [40] demonstrated that Tacrolimus and Pimecrolimus improved cutaneous symptoms as monotherapy and in combination with HCQ in all types of CLE, suggesting that these topicals enhance systemic therapy. Some studies of topicals specifically addressed discoid lesions. In a comparison between twice-daily tacrolimus and once daily clobetasol for DLE, both significantly decreased CLASI activity score, although clobetasol had better efficacy [41]. Investigators also found 1% Pimecrolimus cream to be efficacious for localized DLE [42].

Finally, Pulse dye laser has demonstrated effectiveness in treating acute flares of Lupus Tumidus, with a better response achieved if purpura were present prior to treatment, as opposed to atrophic changes [43].

Conclusion

CLE is a heterogeneous disease entity with a pathogenesis that remains unclear. Identified associations with subsets of CLE suggest future research questions in CLE pathogenesis and some subsets of CLE may share an underlying genetic defect in interferon signaling with SLE. Overall, although new data for alternative systemic treatments for refractory CLE appears promising, there is a need for larger studies evaluating these drugs using a validated outcome measure. Calcineurin inhibitors have also demonstrated some efficacy in treating DLE lesions, but measuring response to treatment is limited by an unmet need in defining the quantitative description of skin induration.

Acknowledgments

None.

References and Recommended Reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000 000).

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Key Points

- The mechanism of CLE is not fully understood, but involves ultraviolet irradiation, autoantibody generation, dysregulation of T cells, dendritic cells, and other immune cells, with a contribution from innate mechanisms for activation of immune cells.
- The CLASI is a valuable and widely used tool allowing for standardized assessment and reporting of cutaneous disease activity and damage.
- Subsets of CLE associated with interface dermatitis may share an underlying genetic defect in interferon signaling with SLE.
- Antimalarials remain the standard of care for systemic CLE treatment but research is ongoing to evaluate other therapeutics in those who are refractory to antimalarial therapy.

Table 1

Estimated odds ratios and 95% confidence intervals for the association between exposure to certain suspected drugs and a subsequent diagnosis of subacute

Drug class and generic name (ATC code)	Cases, n=234 (controls, n=2311) drug exposure 0 6 months before SCLE diagnosis	OR cases: controls (95%Cl), drug exposure 0 6 months before SCLE diagnosis
Anti hypertensives		
Thiazides (C03A)	12 (101)	1.2 (0.6–2.2)
Beta blockers (CO7)	50 (450)	1.1 (0.6–1.6)
Calcium channel blockers (C08)	35 (238)	1.6 (10–2.4)
ACE inhibitors (C09A)	32 (199)	1.7 (1.1–2.7)
ACE inhibitors+ diuretics (C09BA)	4 (22)	1.8 (0.4–5.3)
Angiotensin II antagonists (C09C + C09D)	27 (196)	1.4 (0.9–2.2)
Statins		
HMG-CoA reductase inhibitors (C10AA)	42 (321)	1.4 (0.9–2.0)
Other lipid-modifying agents (C10AX)	0 (8)[a]	0.9 (0.0–6.5)
Antithrombotics		
Thromobocyte inhibitors (B01AC)	66 (406)	2.2 (1–5.32)
Proton pump inhibitors		
Proton pump inhibitors (A02BC)	65 (286)	2.9 (2.0–4.0)
NSAIDs		
NSAIDs (M01A)	51 (344)	1.6 (1.1–2.2)
Antifungals		
Terbinafine (D01B)	4 (0)[a]	52.9 (6.6–1)
Antiepileptics		
Antiepileptics (N03)	20 (61)	3.4 (1.9–5.8)
Biologies		
TNF-a inhibitors (L04AB)	4 (5)	8.0 (1.6–37.2)
Immunomodulating agents		
Pyrimidine analogues (L01BC)	1 (1)	10.0 (0.1–785)
Interferon (L03AB)	0 (1)[a]	10.0 (0.0–390)
Hormone-altering drugs		
Antihormones (L02B)	1 (23)	0.4 (0.0–2.6)
Go nadotro pin-releasing hormone analogues (L02AE)	1 (11)	0.9 (0.0–6.6)
Antihistamines		
H2 receptor antagonists (A02BA)	3 (26)	1.2 (0.2–3.9)
Adrenergios (R01BA)	3 (39)	0.8 (0.2–2.4)
Antidepressants		
Antidepressants (N06AX)	6 (65)	1.2 (0.5–2.6)
Antigout drugs		

Drug class and generic name (ATC code)	Cases, n=234 (controls, n=2311) drug exposure 0 6 months before SCLE diagnosis	OR cases: controls (95%Cl), drug exposure 0 6 months before SCLE diagnosis
Allopurinol (M04AA)	4 (33)	1.2 (0.3–3.4)
Antibiotics		
Amoxicillin + clavulanicacid (J01CR02)	0 (6)[a]	1.2 (0.0–8.5)
Anticholinergic agents		
Tiotropium (inhalation) (R03BB)	6 (45)	1.3 (0.5–3.2)

ATC, Anatomical Therapeutic Chemical classification system; ACE, angiotensin-converting enzyme; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; TNF, tumour necrosis factor. Bold type, 95% Cl does not include 1 0. Adapted from Ref. [14▪▪].

[a]In cases where zero events were observed a median unbiased estimate is reported [24].