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Cutaneous lupus erythematosus landscape: Pathophysiology, unmet needs, and related challenges in clinical practice. What is on the horizon?

Edited by
Nathalie Marie Franchimont, Filippa Nyberg, Joseph Merola and Victoria Patricia Werth

Coordinated by
Amanda Clark

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Topic editors
Nathalie Marie Franchimont – Biogen Idec, United States
Filippa Nyberg – Karolinska University Hospital, Sweden
Joseph Merola – Brigham and Women's Hospital, Harvard Medical School, United States
Victoria Patricia Werth – University of Pennsylvania, United States

Topic coordinator
Amanda Clark – Biogen Idec, United States

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EDITED AND REVIEWED BY
Robert Gniadecki,
University of Alberta, Canada

*CORRESPONDENCE
Victoria P. Werth
victoria.werth@pennmedicine.upenn.edu

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Editorial: Cutaneous lupus erythematosus landscape: pathophysiology, unmet needs, and related challenges in clinical practice. What is on the horizon?

Joseph F. Merola[1], Filippa Nyberg[2], Nathalie Franchimont[3], Catherine Barbey[4] and Victoria P. Werth[5]*

[1]Department of Dermatology and Department of Medicine, UT Southwestern Medical Center, Dallas, TX, United States, [2]Department of Dermatology, Karolinska University Hospital, Stockholm, Sweden, [3]Biogen, Cambridge, MA, United States, [4]Biogen, Baar, Switzerland, [5]Department of Dermatology, University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA, United States

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Editorial on the Research Topic
Cutaneous lupus erythematosus landscape: pathophysiology, unmet needs, and related challenges in clinical practice. What is on the horizon?

Cutaneous lupus erythematosus (CLE) is an autoimmune disease with heterogeneous skin manifestations that can occur with or without systemic manifestations with no approved drug(s) specifically for the treatment of CLE. Authors of this Research Topic provide an overview of the current landscape and the emerging understanding of CLE as a distinct autoimmune entity. They highlight future directions and obstacles that should be addressed to advance targeted therapies in CLE.

Investigation of the incidence and prevalence of CLE in the absence of systemic lupus erythematosus (SLE) has been limited to date (Walker et al.). Current epidemiological studies suggest that race and ethnicity do affect CLE diagnosis frequency: discoid lupus erythematosus (DLE) occurs more frequently in Black or Hispanic patients and subacute cutaneous lupus erythematosus (SCLE) occurs more frequently in White populations. Both the severity and disease course can differ by race for CLE. For instance, Black patients have been shown to have higher baseline disease damage [as measured by the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) instrument] than non-Black patients, and strong correlation was found between CLASI-damage and activity score in Black while there were no correlation in White patients. Disease activity has been shown to impact Quality of Life (QoL) (1). Additionally, socio-demographic factors contribute to overall outcomes in CLE patients with income, educational background, and access to health insurance among the contributing factors. Additional epidemiological data and analyses of CLE disease burden across race and ethnicity are needed and diversity inclusiveness is warranted in CLE studies (Walker et al.).

The pathophysiology of CLE resembles and overlaps with that of SLE. Many factors have been proposed to trigger immune responses in CLE including genetic predisposition, environmental factors such as ultraviolet irradiation, and certain pharmaceutical agents (Chen et al., Klein and Kunz, Fetter et al.). Multiple genes responsible for mediating innate immune response, cell growth, apoptosis, and interferon response as well as increased frequency of HLA-B8 and C2 complement deficiency have been identified as genetic aberrations or transcript anomalies linked to CLE (Chen et al.). Numerous mechanisms driven by ultraviolet light have been identified to contribute to the pathogenesis of CLE (Klein and Kunz). These mechanisms result in the chronic activation of immune pathways, which is considered a hallmark mechanism of CLE pathophysiology and is characterized by the production of type I interferon (IFN-I) (Fetter et al.).

CLE has three major subtypes: SCLE, acute (ACLE), and chronic (CCLE), and patients may exhibit more than one subtype at a time (Elmgren and Nyberg). Elmgren and Nyberg reviewed the association of CLE with SLE noting that while many shared features point to CLE and SLE as being part of a disease spectrum, current evidence suggests that they are closely related but distinct diseases with different courses. Histopathologically, CLE is characterized by the presence of lymphocytic infiltrates and necroptotic keratinocytes at the dermo-epidermal junction. However, CLE subtypes are heterogeneous in their clinical appearance, and histopathological features. Fetter et al. summarize the histopathological features characteristic of the different CLE subtypes in their review, acknowledging that the overlap in histology often does not allow a clinical subset diagnosis from histology and highlights the importance of knowing the specific subtype molecular signature to develop a precision medicine approach to CLE treatment.

There are no drugs approved specifically for the treatment of CLE to date. Current treatment guidelines for CLE recommend a combination of preventive measures and topical and systemic medications (Verdelli et al.). First-line treatment may include topical corticosteroids and systemic antimalarials. Second- and third-line systemic treatments include immunosuppressants and immunomodulatory drugs. Targeted biologics approved for the treatment of SLE may be available to the subset of patients with CLE. Despite recommended treatment guidelines, approximately 10% of CLE patients have been shown to be refractory to therapy (2). As such, there is a clear need to develop targeted therapies specifically for CLE.

Development of novel CLE specific therapies is currently a growing area, but is complicated by the lack of standardized outcome measures to be used in clinical trials. Gaffney et al. summarize a working core domain set and core outcome set for CLE recommended for use in clinical trials as an interim guide until standardized outcomes are fully available (3). The authors discussed currently available and new clinical outcomes, such as the CLASI scale and/or a CLE-specific investigator global assessment of disease activity (CLA-IGA). They also reviewed patient reported outcomes, and QoL measures such as the Skindex-29+3 and the CLE-QoL. Not all of these outcome measures have been validated in CLE highlighting future requirements for additional work in this area (Gaffney et al.).

Although no therapies have been approved specifically for the treatment of CLE, several emerging therapies are under investigation (Sprow et al.). Although anifrolumab and belimumab were previously not studied in CLE specific trials, analyses of skin focused outcome measures of SLE patients with skin manifestations showed improvement in the treatment groups over placebo suggesting promise of these agents for CLE. CLE specific studies are currently underway with agents targeting various pathways such as the IFN-alpha receptor (anifrolumab), plasmacytoid dendritic cell [litifilimab and daxdilimab], TYK-2 (deucravacitinib), toll-like receptor [enpatoran, and interleukin-1 receptor-associated kinase 4 (IRAK4) (edecesertib)]. Litifilimab and daxdilimab have previously demonstrated clinical benefit in some forms of CLE but need to be investigated in larger and longer trials (4, 5).

Patients living with CLE experience poor QoL, particularly in the psychological and social health domains (Drenkard et al.). Many factors have been reported to negatively impact health-related QoL (HRQoL) for CLE patients including female sex, low education, and higher skin disease activity among others. Pain, fatigue, disease activity, body image, and medication side effects are specific areas that CLE patients have reported impacting their QoL. With regards to the psychological domain, CLE patients have an increased prevalence of major depressive disorder, generalized anxiety disorder, panic disorder, suicide risk, and agoraphobia. Altogether, these observations highlight the need to provide new therapeutic solutions for CLE patients that would improve their QoL.

The current landscape of CLE presents many areas of opportunity for the scientific and healthcare community to pursue including improving diagnoses, identifying and understanding the molecular mechanisms driving disease, developing novel therapies to target these mechanisms. These endeavors should be considered in a patient-centric approach to ultimately improve patient outcomes and QoL for those living with CLE.

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Current Concepts on Pathogenic Mechanisms and Histopathology in Cutaneous Lupus Erythematosus

*Tanja Fetter, Christine Braegelmann, Luka de Vos and Joerg Wenzel**

Department of Dermatology and Allergy, University Hospital Bonn, Bonn, Germany

Cutaneous lupus erythematosus (CLE) is an interferon (IFN)-driven autoimmune disease that may be limited to the skin or can be associated with systemic lupus erythematosus (SLE). CLE occurs in several morphologic subtypes ranging from isolated, disc-shaped plaques to disseminated skin lesions. The typical histopathologic pattern of skin lesions is named interface dermatitis and characterized by a lymphocytic infiltrate and necroptotic keratinocytes at the dermo-epidermal junction. Other histopathologic patterns primarily involve the dermis or subcutis, depending on the subtype. One critical mechanism in CLE is the chronic reactivation of innate and adaptive immune pathways. An important step in this process is the recognition of endogenous nucleic acids released from dying cells by various pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and other cytosolic receptors. Crucial cells in CLE pathogenesis comprise plasmacytoid dendritic cells (pDCs) as major producers of type I IFN, T cells exerting cytotoxic effects, and B cells, previously believed to contribute *via* secretion of autoantibodies. However, B cells are increasingly considered to have additional functions, supported by studies finding them to occur in highest numbers in chronic discoid lupus erythematosus (CDLE), a subtype in which autoantibodies are often absent. More precise knowledge of how CLE subtypes differ pathophysiologically may allow a tailored pharmacotherapy in the future, taking into account the specific molecular signature in relation to the morphologic subtype.

Keywords: lupus erythematosus, skin inflammation, histology, interface dermatitis, interferon, plasmacytoid dendritic cells, B cells, T cells

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Edited by:
Filippa Nyberg, Karolinska University Hospital, Sweden

Reviewed by:
Marwah Adly Saleh, Cairo University, Egypt

****Correspondence:***
Joerg Wenzel
joerg.wenzel@ukbonn.de

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INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a heterogeneous autoimmune skin disease that can occur isolated to the skin or with additional systemic manifestation in several organs [systemic lupus erythematosus (SLE)] (1). CLE can be classified based on clinical and histopathologic findings: typical morphological subsets are acute cutaneous (ACLE), subacute cutaneous (SCLE), intermittent cutaneous [ICLE, also termed lupus erythematosus tumidus (LET)], and chronic cutaneous (CCLE) lupus erythematosus (2, 3). CCLE can be further subdivided into chronic discoid lupus erythematosus (CDLE), lupus erythematosus profundus (LEP) and chilblain lupus erythematosus (ChLE), of which CDLE represents the most frequent CCLE subtype (4). ACLE is most commonly associated with SLE—in approximately 80% of cases—whereas localized CDLE only presents with SLE in about 5% of cases (5, 6). CLE subtypes are heterogeneous in their clinical appearance. ACLE and SCLE occur with disseminated maculopapular to gyrated skin lesions, predominantly

in sun-exposed skin. In CDLE, scattered disc-like scarring plaques can be found (3). Lupus erythematosus (LE) skin lesions typically feature a histopathologic pattern termed interface dermatitis, defined by the presence of necroptotic keratinocytes and an epitheliotropic cytotoxic lymphocytic infiltrate at the dermo-epidermal junction (7, 8).

The classification of CLE subtypes, however, should not be understood too rigidly as overlaps in clinical and histological appearance are not uncommon. This also supports the assumption of Ackerman, who considers the different CLE subtypes as manifestations of the same pathological process (9). Nevertheless, there is evidence that the individual subtypes differ pathophysiologically, for example, with respect to their cellular composition as recently shown for B cells (10). Not only the molecular differences leading to the different clinical presentations need to be better understood, but also the pathogenic mechanisms of CLE in general: the precise role of involved cell types, the impact of different cytokines described in the disease, and their interaction and regulation in a complex network need further exploration. In the long term, this could help to select a targeted therapy taking the individual molecular profile of a patient into account. A deeper knowledge could also serve to predict the course of the disease, for instance which group of patients with previously isolated CLE lesions will develop SLE.

In this review, we provide an overview of histopathologic patterns observed in different CLE subtypes. We also discuss the current concept of the pathophysiology of CLE. Here, we highlight the cell types and cytokines involved as well as the central mechanisms of chronic reactivation of innate and adaptive immune responses.

SELF-AMPLIFYING INNATE AND ADAPTIVE IMMUNE RESPONSES AS A HALLMARK OF LE SKIN LESIONS

In principle, active CLE is characterized by a hyper-activated type I interferon (IFN) pathway, which triggers an inflammatory response against lesional skin (11). This response entails cell destruction, release of proinflammatory mediators and activates immune pathways. The most important step in this proinflammatory vicious cycle is the (re)activation of innate immune pathways by effector mechanisms of the adaptive immune system, leading to a sustained parallel activation of both arms in lesional skin (12, 13).

This vicious cycle can be triggered by provoking factors such as UV light, cigarette smoke and various drugs (14–16). These factors can lead to cellular damage with DNA alterations, such as upregulation of proinflammatory 8-hydroxyguanine (8-OHG) and formation of reactive oxygen species (ROS) (17). Cellular damage can result in apoptosis with release of cellular blebs, which in CLE is initially seen throughout the entire epidermal layer (18). Under physiological conditions, apoptotic cells are engulfed by phagocytes and destroyed within the lysosomes. Moreover, nuclear components are rapidly degraded. However, in CLE, these mechanisms may be defective or of limited efficacy (19). Several factors are assumed to contribute to this deficiency, for example (i) reduced phagocytic activity, (ii) polymorphisms in genes associated with IFN such as IFN-regulatory factor 5 (IRF5) leading to hyper-activation of IFN in response to nucleic acids, (iii) mutations in genes encoding for DNAses such as DNAse I and DNAse III, of which the latter is also known as three prime repair exonuclease 1 (TREX1) (3, 19–24). Interestingly, there is one rare monogenetic variant of ChLE, in which loss of function mutations in TREX1 or activating mutations in the cGAS-STING pathway have been described (25, 26).

These mechanisms lead to secondary necroptosis and thus unwanted release of nuclear components, including nucleic acids and other danger associated molecular patterns (DAMPs) such as high mobility group box 1 protein (HMGB1), reflecting potential autoantigens (27–29). Accumulating nucleic acids can subsequently be recognized by antigen-presenting cells (APCs) and keratinocytes *via* pattern recognition receptors (PRRs) (12). In plasmacytoid dendritic cells (pDCs), Toll-like receptors (TLRs) are considered predominant PRR, which sense nucleic acid motifs as immune complexes bound to autoantibodies (30). In keratinocytes, PRR-recognition is primarily thought to be TLR-independent, although they express TLRs (31–38). Several cytosolic PRR play a role in nucleic acid sensing: (i) the RIG-I-like receptors MDA5 and RIG-I, both enhancing type I IFN expression and (ii) cGAS-STING, also promoting type I IFN expression as well as cell death (39, 40). Moreover, AIM2 (Absent in Melanoma 2) inflammasome activation has been reported (12, 41, 42).

APCs are known to induce the development and clonal expansion of autoantigen-specific B- and T-lymphocytes. Upon repeated autoantigen contact, activated B cells can differentiate into plasma cells to produce specific autoantibodies against nuclear components, and T cells can migrate into lesional tissue to assist in B cell activation and exert cytotoxic effects against keratinocytes, which in turn again leads to the release of endogenous nucleic acids, fueling the self-reinforcing vicious cycle of lesional inflammation (43).

Neighboring cells can engulf released nucleic acids into the cytosol *via* lipofection—a process known to be mediated by the antimicrobial peptide cathelicidin (44). This enables their subsequent recognition by PRR. Following PRR activation, pDCs and keratinocytes express large amounts of the proinflammatory mediators type I and type III IFNs (especially IFN-κ and IFN-λ) among other cytokines such as several interleukins, Tumor necrosis factor (TNF) and B cell activating factor BAFF, also known as B lymphocyte stimulator BLyS (45–48). IFNs then bind to IFN receptors on keratinocytes in an autocrine loop and induce the expression of IFN-regulated cytokines, most importantly CXCL chemokines (in particular CXCL9, CXCL10, and CXCL11) *via* JAK-STAT signaling (12, 45). CXCL chemokines are known to recruit effector cells expressing the corresponding chemokine receptor CXCR3 (which are CD8+ and CD4+ T cells, pDCs and macrophages) into lesional skin (18). CD8+ T cells can then exert their cytotoxic effect particularly against keratinocytes in the basal epidermal layer, leading to the typical histopathologic pattern of interface dermatitis (**Figure 1**) (49).

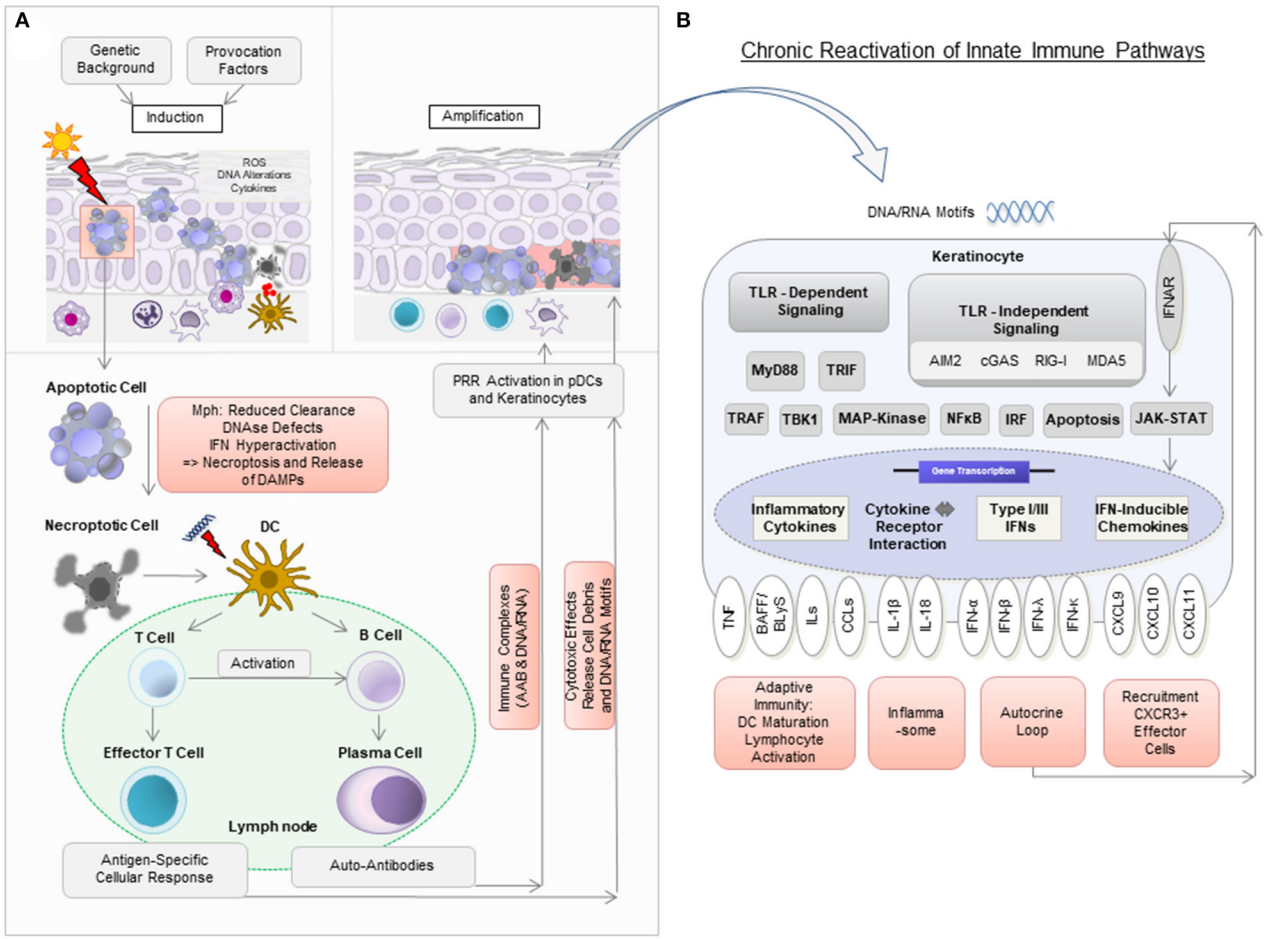

FIGURE 1 | Model of pathogenic mechanisms in cutaneous lupus erythematosus (CLE). **(A)** In a person with a genetic background predisposing to CLE, the exposure to provocation factors such as UV light can induce cellular stress [reactive oxygen species (ROS), DNA alterations, cytokine secretion], apoptosis, and the release of DNA components in so-called "apoptotic blebs" in keratinocytes. Normally, these "blebs" are rapidly degraded and apoptotic cells are removed by macrophages (Mph). In CLE, delayed degradation and clearance leads to secondary, more pro-inflammatory, forms of cell death such as necroptosis, which results in the release of cell debris. Dendritic cells (DC) recognize this debris as potential autoantigens and migrate to nearby lymph nodes to present it to T and B cells. Upon activation, naïve B cells develop into plasma cells to produce autoantibodies (AAB). AAB form immune complexes with nucleic acids and can induce type I IFN production in plasmacytoid dendritic cells (pDCs). T cells mature into CD4+ and CD8+ T cells, with the latter exerting cytotoxic effects against keratinocytes. **(B)** Nucleic acids (DNA and RNA motifs) released from dying cells can be recognized by pattern recognition receptors (PRR) as so-called damage-associated molecular patterns (DAMPs), leading to activation of both Toll-like receptor (TLR)-dependent and TLR-independent inflammatory signaling cascades. In CLE, this leads to increased expression of several cytokines, particularly type I IFN. Type I IFN is known to bind to IFN-α/β receptors on keratinocytes in an autocrine loop and mediates increased expression of proinflammatory chemokines such as CXCL10 via the JAK-STAT pathway. This leads to the recruitment of CXCR3+ cells, which induce keratinocyte cell death, release of cytokines and a chronic reactivation of innate immune pathways.

CHARACTERIZATION OF HISTOPATHOLOGIC FINDINGS AND THE CELLULAR SPECTRUM IN LE SKIN LESIONS

The inflammatory cell infiltrate in LE skin lesions varies in composition and distribution depending on the subtype (10, 11, 50). Lipsker has developed a classification of specific histologic findings in CLE based on the primarily affected anatomic structure of the skin (9, 51). He subdivides into (i) dermo-epidermal, (ii) dermal (iii) and hypodermal LE, to which the classic morphological variants can be assigned. The classification of Lipsker is described in more detail with representative micrographs in **Figure 2**. In the following, we will discuss the main cell types of the innate and adaptive immune system in LE skin lesions.

Adaptive Immune Cells

The original concept of CLE pathogenesis primarily ascribed a dominant role to the adaptive immune system. This concept emerged primarily from observations in SLE that

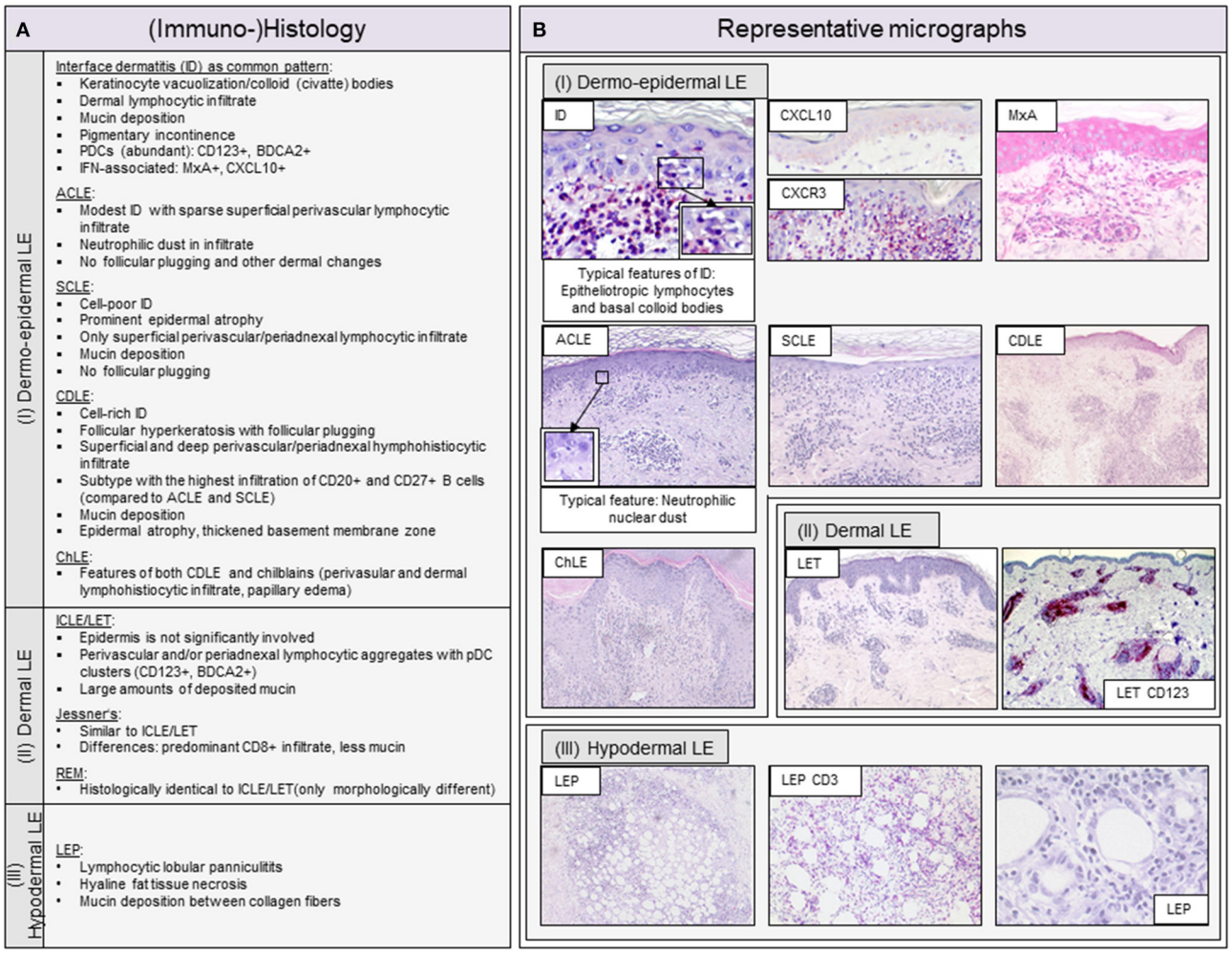

FIGURE 2 | Overview of typical histopathologic patterns observed in different cutaneous lupus erythematosus (CLE) subtypes. **(A)** Typical (immuno-)histologic findings of (I) dermo-epidermal lupus erythematosus (LE), (II) dermal LE and (III) hypodermal LE. Dermo-epidermal LE, presenting as interface dermatitis (ID) includes the morphologic variants acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE) and chronic discoid LE (CDLE) among others. Dermal LE consists of intermittent cutaneous LE (ICLE), also named LE tumidus (LET), Jessner-Kanof lymphocyte infiltrate (Jessner's), and reticular erythematous mucinosis (REM), however, some authors consider Jessner's and REM as separate (only lupus-like) entities. Hypodermal LE includes LE profundus (LEP). ID, interface dermatitis; PDCs, plasmacytoid dendritic cells; IFN, interferon. **(B)** Representative micrographs of different CLE subtypes and selective immunohistochemical features. The typical histopathologic pattern of skin lesions is termed interface dermatitis (ID) and is characterized by epitheliotropic lymphocytes and necroptotic keratinocytes, of which the latter are also called colloid or civatte bodies, at the dermo-epidermal junction. CXCR3+ effector cells are recruited into lesional skin by CXCL10+ expressing keratinocytes. Among these effector cells are CD3+ T lymphocytes, which form the largest immune cell population in LE. The interferon (IFN)-regulated protein MxA reveals a strong expression of IFN in keratinocytes and infiltrating immune cells. ACLE typically features a moderate ID with neutrophilic nuclear dust in the infiltrate. SCLE shows a mild ID with a prominent epidermal atrophy. CDLE features a cell rich ID with a dense perifollicular and perivascular infiltrate and follicular hyperkeratosis and plugging. ICLE/LET presents with a patchy dermal infiltrate and large amounts of deposited mucin. In LEP, a lymphocytic lobular panniculitis can be observed.

began about 70 years ago, in which autoantibodies directed against host structures (such as nuclear components) are considered particularly important (52, 53). However, there are CLE patients without a typical autoantibody profile, especially in CDLE (54). Here, the "classical" pathogenic concept is not sufficient to explain the development of the disease. Detailed analyses of skin lesion expression patterns revealed the complex interplay of innate and adaptive immune responses (12).

T Cells

CLE is considered a Th1-dominated disease. The pathogenic importance of T cells results from their cytotoxic function, which they exert against structures of the skin, particularly basal keratinocytes (7, 8, 55). Th1 cells promote cellular immune responses as they support cytotoxic T cells and macrophages and produce IFN-γ (49, 56). These cell types represent a central mechanism in the development of the typical histopathologic pattern in all CLE subtypes and contribute to the reactivation

of innate immune responses by induction of keratinocyte cell death (49).

B Cells

According to the classical concept, B cells are crucial in LE pathogenesis because of their ability to produce autoantibodies against nuclear components. However, this concept could not explain the occurrence of the disease in autoantibody-negative patients (57). Interestingly, some studies reveal a B-cell-rich lesional infiltrate and a strong B cell associated gene signature (e.g., genes encoding B cell activator proteins such as BAFF as well as BAFF receptors) particularly in CLE subtypes lacking autoantibodies such as CDLE (10, 46). Keratinocytes can produce large amounts of BAFF and thus can possibly interact with lesional lymphocytes expressing BAFF receptor (46, 58). In addition, T and B cells appear to gather together in nest-like structures and thus may form a proinflammatory microenvironment (59, 60).

These findings suggest that B cells have other functions besides autoantibody production such as antigen presentation, co-stimulation and cytokine secretion, remaining to be explored in further studies. For instance, an ongoing study investigates the therapeutic effect of the BAFF inhibitor and human monoclonal antibody Belimumab on lesional B lymphocytes in CLE and aims to further characterize these cells (EudraCT 2017-003051-35).

Innate Immune Cells

Plasmacytoid Dendritic Cells

In CLE, Plasmacytoid Dendritic Cells (pDCs) cluster in the dermis to locally produce massive amounts of type I IFN and thus drive the lesional inflammatory process (61, 62). Their direct pathogenic role is underlined by the finding that erasing pDCs in patients with CLE did not only lead to reduction of type I IFN levels, as to be expected, but also reduced disease activity (63). Interestingly, type I IFNs are thought to drive maturation of pDCs (besides many other effects as discussed later) (64), implying a self-amplifying inflammatory process. Immune complexes consisting of nucleic acids and autoantibodies serve as ligands for the activation of pDCs (65). These ligands can be taken up *via* endocytosis with the help of CD32 receptor (66). They are considered to be recognized by PRR through several pathways in parallel: (i) an endosomal way, in which endosomal TLR7 and TLR9 are activated by those ligands and (ii) a cytosolic way, in which the cGAS-STING pathway is activated, both resulting in upregulated type I IFN (and type III IFN) expression (67, 68). Moreover, these pathways most probably interact with each other as the cGAS-STING pathway was shown to dampen the TLR-mediated IFN production in pDCs (67).

Neutrophil Granulocytes

In LE skin lesions, neutrophils accumulate primarily during the initial phase of CLE lesion development (69). Neutrophil-released extracellular traps (NETs) are thought to play a pathogenic role in SLE as they can be activated by immune complexes and their degradation is impaired, thus providing a source of potential autoantigens (70). NETs are present in skin lesions of various CLE subtypes and are particularly high in ACLE, CDLE and LEP, suggesting that NETs may be of greater importance in CLE featuring tissue damage and scarring (71).

PROINFLAMMATORY PATHWAYS IN CLE

Analysis of gene expression from skin lesions of CLE patients has greatly improved our understanding of immunopathological mechanisms and revealed interesting molecular structures for targeted therapies. A hallmark of all CLE subtypes represents a strongly upregulated IFN pathway as discussed below. Other important signaling pathways include TLR-dependent and TLR-independent (cGAS-STING, RIG-I, MDA5) pathways and their downstream signaling pathways (TRAF, TBK1, NFκB, MAP kinase, IRF), which are known to facilitate the chronic reactivation of innate immune pathways by nucleic acids and other DAMPs. Another well-described pathway in CLE is the JAK-STAT pathway, which is critical in pathogenesis as it is responsible for transmitting IFN signals (12, 72, 73).

INTERFERONS AS CRUCIAL CYTOKINES IN CLE PATHOGENESIS

The major pathway in CLE pathogenesis is the type I IFN pathway, which has been shown to be upregulated independently of the specific subtype and lead to the suggestion of CLE as an acquired interferonopathy (11, 74). Type I IFNs are of particular importance, with lesional pDCs as major producers (62). Keratinocytes also produce IFNs in response to PRR activation by endogenous nucleic acids (12). Type I IFN-κ has been found to be upregulated in lesional skin and even in clinically healthy skin of LE patients (45). It is probably the major type I IFN produced by keratinocytes (75). To date, the function of IFN-κ is not fully understood. It is assumed to play a role in the development of CLE lesions in clinically healthy skin and to enhance responsiveness to IFN-α and sensitivity to UV light in keratinocytes. Since depletion of IFN-κ was found to abrogate enhanced apoptosis of keratinocytes in response to UV irradiation, IFN-κ may be important in driving apoptotic responses (45).

Type III IFNs have also been detected to be increased in CLE patients with active skin lesions (47). The main representative of this most recently discovered IFN family is IFN-λ (76). Keratinocytes as well as pDCs produce IFN-λ and also express the IFN-λ receptor (47, 77). In cultured keratinocytes, expression of IFN-λ is induced after stimulation with endogenous nucleic acids, following increased expression of IFN-stimulated genes such as CXCL9, CCL3, IL-8 and IL-6 (47). Consistent with previous findings, treatment of lupus-prone mice with IFN-λ led to enhanced levels of proinflammatory cytokines (IL-6, CXCL9, CXCL10, CXCL11) (78). Notably, CXCL10 is of particular importance as it is considered the

chemokine that determines the histologic pattern of interface dermatitis (11).

MOLECULAR FINDINGS FROM MOUSE MODELS

Lupus prone mouse models enabled insights into molecular mechanisms in CLE. CLE-like skin inflammation can be observed in mice with TREX1$^{-/-}$ knockout and when treated with TLR7 agonists, underscoring the role of innate DAMP signaling in CLE (12, 30, 79). Interestingly, in several studies, TLR9-deficient mice presented with an exacerbation of lupus-like skin lesions, suggesting contradictory effects of TLR7 and TLR9 (80, 81). TLR9 was also shown to suppress the expression of TLR7-dependent autoantibodies, which led to the assumption of cross-regulatory functions (82). Furthermore, mice with an activating JAK1 mutation exhibit CLE-like skin lesions (83), highlighting the importance of the JAK-STAT pathway in this disease.

INSIGHTS INTO CLE PATHOPHYSIOLOGY FROM THERAPEUTICS

The effectiveness of some therapeutics *in vivo* proves the importance of the respective corresponding targets and signaling pathways in the pathogenesis of CLE. One example is the JAK-STAT pathway: JAK inhibitors have proven to be beneficial in several preclinical studies and case reports in CLE, highlighting the role of the JAK-STAT pathway in the disease (72, 84–87).

However, even when a pathway proves to be particularly relevant, for instance the IFN pathway, it may not be sufficient to block individual components of this pathway, as demonstrated by the limited efficacy of selective anti-IFN-α and anti-IFN-γ antibodies in clinical trials (88–90). It may be necessary to prevent the common downstream effects, e.g., by blocking receptors that transduce signals by several IFNs. Accordingly, a type I IFN receptor antibody proved beneficial on lupus skin lesions (91).

Other treatment options with conflicting results illustrate the complex interplay of immune mechanisms and encourage further analysis of effects that are not yet understood. For example, antimalarials such as hydroxychloroquine are most commonly used in CLE and well tolerated. However, in some cases of CLE and in other autoimmune skin disorders such as dermatomyositis and psoriasis, worsening of skin disease could be observed (92–94). Antimalarials are assumed to inhibit TLR7/TLR9 and cGAS-STING signaling by preventing the binding of nucleic acids to the corresponding receptors (95, 96). They can also inhibit lysosomal activity and autophagy. Autophagy is thought to be involved in antigen presentation leading to adaptive immune responses (97, 98). However, inhibition of endolysosomal activity may also reduce degradation of DAMPs, which could possibly lead to enhanced activation of other (cytosolic) PRRs. Since TLR9 is increasingly considered to actually have anti-inflammatory capacity, concomitant blocking of TLR7 and TLR9 might potentially entail an overall stronger proinflammatory response (99–101). However, this is only one example of paradox effects of therapeutics that require further investigation.

CONCLUSION

CLE can be a highly burdensome disease for patients. Fortunately, more insights into CLE pathogenesis have been gained in recent years. A key mechanism is the chronic reactivation of innate immune pathways. *Via* different PRRs, endogenous nucleic acids, released from dying host cells, can be recognized, triggering an IFN- driven inflammatory process that leads to adaptive, especially cytotoxic, immune responses. The findings have led to the development of several targeted therapies that are currently being investigated in clinical trials, partially with promising results. Nevertheless, there is still a need for further therapeutic options, for example for therapy-resistant cases. In order to provide optimal therapy for each individual patient, a deeper understanding of (i) the molecular mechanisms in CLE pathophysiology and (ii) the effects of blocking or modulating a pathway that is part of a complex network is essential. In addition, it is important to determine to what extent the morphological CLE subtypes differ at the molecular level and what leads to the manifestation of a particular subtype. If there are typical molecular features for each subtype, identification of biomarkers would be desirable to reveal the leading mechanisms even in challenging cases with overlapping clinical manifestations. Another task is to better understand the mode of action of therapeutic agents. For instance, it remains to be determined whether and how B-cell-focused strategies such as BAFF inhibitors differ in efficacy in patients frequently featuring autoantibodies (such as ACLE and SCLE) and in patients with particularly high B cell levels in skin lesions lacking autoantibodies (such as CDLE), as they both feature B cell associated processes. A deeper understanding of these mechanisms will hopefully allow stratified or even personalized therapy options for patients in the future.

AUTHOR CONTRIBUTIONS

TF and JW performed the literature review and wrote the manuscript. TF, LdV, and JW designed the figures. CB and LdV added intellectual content and critically revised the manuscript. All authors approved the final manuscript for publication.

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The Genetic Landscape of Cutaneous Lupus Erythematosus

*Henry W. Chen, Grant Barber and Benjamin F. Chong**

Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, United States

Cutaneous lupus erythematosus (CLE) is an autoimmune connective tissue disease that can exist as a disease entity or within the context of systemic lupus erythematosus (SLE). Over the years, efforts to elucidate the genetic underpinnings of CLE and SLE have yielded a wealth of information. This review examines prior studies investigating the genetics of CLE at the DNA and RNA level and identifies future research areas. In this literature review, we examined the English language literature captured within the MEDLINE and Embase databases using pre-defined search terms. First, we surveyed studies investigating various DNA studies of CLE. We identified three predominant areas of focus in HLA profiling, complement deficiencies, and genetic polymorphisms. An increased frequency of HLA-B8 has been strongly linked to CLE. In addition, multiple genes responsible for mediating innate immune response, cell growth, apoptosis, and interferon response confer a higher risk of developing CLE, specifically TREX1 and SAMHD1. There was a strong association between C2 complement deficiency and CLE. Second, we reviewed literature studying aberrations in the transcriptomes of patients with CLE. We reviewed genetic aberrations initiated by environmental insults, and we examined the interplay of dysregulated inflammatory, apoptotic, and fibrotic pathways in the context of the pathomechanism of CLE. These current learnings will serve as the foundation for further advances in integrating personalized medicine into the care of patients with CLE.

Keywords: cutaneous lupus erythematosus, DNA, RNA, genetic polymorphism, microarray, inflammation, apoptosis, fibrosis

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***Correspondence:**
Benjamin F. Chong
Ben.Chong@UTSouthwestern.edu

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INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a heterogeneous autoimmune disease that can be skin-limited or exist within the context of systemic lupus erythematosus (SLE). With the advancement of genetic sequencing technology at the DNA and RNA level, more dysregulated pathways and gene networks that contribute to the development of CLE have been identified. Specifically, differential expression of key genes involved in various pathways, such as inflammation, apoptosis, and immunity has revealed a complex, heterogeneous picture. These new gene expression profiles offer

Abbreviations: BAFF, B-cell activating factor; CCLE, chronic cutaneous lupus erythematosus; circRNAs, circular RNAs; CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LET, lupus erythematosus tumidus; lncRNAs, long non-coding RNAs; NLE, neonatal lupus erythematosus SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; SYK, spleen tyrosine kinase.

the opportunity to further delineate classification subsets of CLE and potentially predict prognosis, such as response to treatments and progression to systemic disease (1, 2).

Up until recently, the development of new therapies for CLE has been stymied by an incomplete understanding of the underlying pathophysiology of CLE. Given the importance of understanding the genetic landscape of CLE, we performed a literature review to summarize studies examining DNA and RNA genetic aberrations in CLE.

METHODS

This was a review of the English-language literature captured within the MEDLINE and Embase databases using pre-defined search terms (**Supplementary Table 1**) from inception through 7 February 2022. Two independent reviewers (H.W.C. and G.B.) reviewed all studies, and a third reviewer (B.F.C.) resolved any discrepancies. Inclusion criteria were original studies, case series, and case reports related to CLE in humans in the English language. Articles underwent title and abstract screening with a subsequent full-text review. Articles were included if their findings were pertinent to DNA or RNA in the context of CLE. Reviews, conference abstracts, editorials, and all non-peer-reviewed findings were excluded from this review. In total, 1,253 studies were identified for screening, and 105 studies were ultimately included for final review after applying inclusion and exclusion criteria (**Supplementary Figure 1**).

RESULTS

DNA

Studies examining DNA have long been performed to better our understanding of cutaneous lupus. Three major themes emerged from our review of these studies, such as HLA profiling, complement deficiencies, and genetic polymorphisms.

Human Leukocyte Antigen Genes Have Been Associated With CLE and Its Subtypes

Human leukocyte antigen (HLA) is quintessential in the differentiation of self and non-self and plays a strong role in autoimmunity. HLA profiling studies have been performed in small groups of patients with CLE and controls to better understand genetic variations. Fowler et al. (3) found an increased frequency of HLA-DRw6 among both White and Black patients with CLE. In further studies, HLA-B8 has repeatedly been found to be increased among patients with discoid lupus erythematosus (DLE) and subacute cutaneous lupus erythematosus (SCLE) (4–7). Bielsa et al. (4) found an increased frequency of HLA-B8 and HLA-DR3 along with a decreased frequency of HLA-DR5 in patients with annular SCLE when compared with controls. Another study of 11 Finnish patients with SCLE and 23 controls showed that HLA-DR3, HLA-B8, and HLA-DR2 were higher in patients with SCLE vs. controls (7). Fischer et al. (8) found the HLA-DQA1*OI02 allele was significantly increased among 26 patients with chronic CLE (CCLE) vs. healthy controls. The HLA-DQA1 alleles have also been studied in neonatal lupus erythematosus (NLE), with mothers of seven NLE children all carrying at least one DQA1 allele with glutamine at position 34 of the first domain compared with just 44% of controls (9). Another study of 28 patients with DLE showed a higher frequency of HLA-DRB1*04 (10). These studies highlight the inherent importance of HLA variations in CLE, though many are limited by small sample sizes. Larger studies, such as genome-wide association studies, in diverse populations, would help elucidate these variations.

Deficiencies in the Complement Cascade Contribute to Cutaneous Lupus Erythematosus Pathogenesis

The complement cascade is indispensable in mediating phagocytosis and inflammation. C1q is a subcomponent of C1 comprised of three heterotrimeric subunits (C1qA, C1qB, and C1qC). In a cohort of 19 White patients with SCLE, homozygous C1qA A > G transition mutation in exon 2, which results in a synonymous mutation, was found to occur more frequently in patients with SCLE relative with healthy controls (11). Despite no alterations in the protein sequence, decreased C1q protein was still observed. Another case study identified a homozygous G > C transversion mutation in C1qC exon 1, resulting in a Gly61Arg mutation (12). Multiple case studies have identified C2 deficiency in patients with SCLE and DLE (13–15). The gene encoding C2 lies within the major histocompatibility complex and is thus linked with HLA-A10, -A25, -B18, -DR2, and -Dw2. Agnello et al. (16) examined the pedigrees of four patients with DLE and found a partial genetic deficiency of C4 in patients carrying the null C4 allele B*QO. Given the important function of the complement cascade in mediating phagocytosis and inflammation, further studies on the complement system's role in the pathogenesis of CLE would be beneficial.

Genetic Polymorphisms Have Been Featured in Familial Chilblain Lupus and Other Cutaneous Lupus Erythematosus Subtypes

Genetic polymorphisms have also been a frequent focus of study for lupus. **Table 1** summarizes prominent ones that have been identified, such as *TREX1*, *SAMHD1,* and tumor necrosis factor *(TNF)*. *TREX1* has been identified as a significant factor in familial chilblain lupus. Günther et al. (17) identified a potential mutation hotspot for *TREX1* where 4 of 6 families affected by familial chilblain lupus all present the same mutation. Günther et al. (18) also linked *TREX1* with the upregulation of type I interferon (IFN) activity in familial chilblain lupus. Another case report of a family with familial chilblain lupus revealed that three affected individuals all carried the same heterozygous mutation (19). Heterozygous mutations in *SAMHD1* have also been identified in patients with familial chilblain lupus independently of *TREX1* mutations, as reported by Ravenscroft et al. (20). Further, Linggonegoro et al. (21) found a deletion of the *SAMHD1* gene's initiator region in a child with familial chilblain lupus, who did not show an increased IFN signature. *TNF* is another gene investigated extensively in lupus. Mutations involving this gene seem to be distinctly associated with SCLE rather than DLE (6, 22, 23). Millard et al. (6) reported a

TABLE 1 | Genetic polymorphisms investigated in cutaneous lupus studies and their functions.

Gene	Function	Relevance to CLE and its subtypes
C1QA	Encodes the C1q subcomponent of the C1complement system	SNP of gene has significant association with SCLE compared to normal (11)
CSNK2B	Subunit of a protein kinase for regulation of metabolic pathways and DNA replication and transcription and mRNA translation	Has SNP strongly associated with CLE (26)
CTLA4	Protein involved in signaling T cell inhibition	Higher disease risk for DLE from haplotype variation (29)
HLA-DRB3	Cell surface molecule for antigen presenting cells. Presents extracellular protein derivatives for immune response	Independent SNP with a high association with CLE (26)
HLA-DQA1	Cell surface molecule for antigen presenting cells. Presents extracellular protein derivatives for immune response.	Has SNP with strong association with CLE (26)
IL10	Cytokine produced by monocytes. Affects immunoregulation and inflammation and regulated JAK-STAT pathway.	SNP associated with DLE but not SLE (23)
IRF5	Transcription factor with roles in virus-mediated activation and regulation of cell growth, differentiation, apoptosis and immune activity	SNP associated with increased risk for DLE and SCLE (29)
ITGAM	Integrin important for adhering neutrophils and monocytes to endothelium	Polymorphisms in DLE three-fold greater than normal and five-fold greater than SLE (25). Significantly greater allele frequency in SLE compared to normal but no allele variation in DLE (24).
IZKF	Protein involved with remodeling chromatin. Potential susceptibility gene for SLE	Two SNPs with nearly significant association to CLE are approximately ∼36kB and 41kB upstream of the gene (26)
MICA	Stress induced cell surface protein recognized by delta T cells in the intestinal epithelium	Believed to be associated with SNP ∼27kB away that is strongly associated with CLE (26)
MICB	Stress induced cell surface protein which activates NK cells and CD8 T cells	SNP for this gene is strongly linked to another SNP associated with CLE (26)
MSH5	Protein involved in mismatch repair associated with crossing over during meiosis. Also associated with radiation-induced apoptosis.	Has SNP strongly associated with CLE (26)
RPP21	Protein subunit of ribonuclease P. Processes 5' head for tRNA	Cluster of 3 SNPs with strong association to CLE (26)
SAMHD1	Protein involved in innate immunity and response to infection. Plays a role in TNF-α signaling.	Mutation of the gene linked with familial chilblain lupus (20, 21)
STAT4	Transcription factor essential for mediating IL-12 response and helper T cell differentiation	SNP of this gene has an association with both DLE and SLE compared to normal (24)
STING	Transmembrane protein that is a major regulator of innate immune response to viral and bacterial infections	Heterozygous gene mutation found in five family members with familial chilblain lupus (30)
TLR7	Toll-like receptor protein for pathogen recognition and activation of innate immunity	Two SNPs with frequencies in SLE patients two times greater than normal. No significant difference in DLE (27)
TNF	Cytokine secreted by macrophages that regulates cell proliferation, differentiation and apoptosis	Greater allele variation in SCLE and SLE patients than DLE and normal patients (6, 22, 23)
TNXB	Glycoprotein associated with the extracellular matrix that functions in matrix maturation during wound healing	Significantly greater allele frequency in SLE compared to normal but no allele variation in DLE (24)
TRAF3IP2	Protein involved with regulation cytokine response and plays a central role in innate immune response to pathogens, inflammation, and stress	Novel SNP found in four siblings with DLE (28)
TREX1	Protein associated with DNA polymerase proofreading. Has exonuclease activity that plays a role in DNA repair	Mutation of the gene linked with familial chilblain lupus (17–19)
TRIM39	Protein of the tripartite motif family. Believed to have a role in apoptosis but not fully studied	Cluster of three SNPs with strong association to CLE (26)
TYK2	Protein is part of JAK family. Is a component of type I and type III interferon signaling pathways	SNP with increased risk of DLE but not SCLE (29)

significantly higher frequency of *TNF*-α (−308 G/A) single nucleotide polymorphism (SNP) among 36 patients with SCLE compared with 49 patients with DLE and 102 healthy relatives of patients with lupus. Similarly, *TNF*-α (−308 G/A) SNP was found to be a significant risk factor among 192 patients with SLE, but not among 56 patients with DLE (23). Studies on *ITGAM* polymorphisms compared in patients with DLE and SLE have shown conflicting results. One study of 21 patients with DLE and 35 patients with SLE showed polymorphisms of *ITGAM* among patients with SLE but not among patients with DLE (24). However, another study of 177 patients with DLE and 85 patients with SLE found *ITGAM* polymorphisms to be 3-fold greater in DLE compared to controls and five times greater than in SLE (25).

To date, only Kunz et al. (26) have performed a genome-wide association study specifically examining patients with CLE. A comparison of 183 German patients with CLE, including DLE, SCLE, and lupus erythematosus tumidus (LET) subtypes, against healthy controls with a validation set of Finnish patients with DLE (n = 177) and SCLE (n = 42), revealed 62 SNPs predominantly on chromosome 6 in the major histocompatibility complex region. The presence of SNPs associated with apoptosis and inflammation (i.e.,

TRIM39/RPP21) and previously described in SLE (i.e., *HLA-DQA1, MICA/B*, and *IZKF*) suggests unique and overlapping genetic underpinnings of CLE and SLE.

In summary, numerous genes were found to have SNPs that were associated with a greater risk of CLE and SLE, such as *TLR7, TRAF3IP2*, *TYK2*, *IRF5*, *IL10*, *C1QA*, and *STAT4* (11, 23, 24, 27–29). **Table 1** summarizes other additional genes whose polymorphisms are distinctly different in CLE and SLE groups (23, 24, 28–30).

RNA

Understanding the genetic aberrations at the DNA level serves as a foundation for examining the changes in the CLE transcriptome. The interplay of multiple pathways, namely, inflammation, apoptosis, and fibrosis, lays the framework for the pathomechanisms behind CLE (**Figure 1**). Herein, we describe the major contributors to CLE pathogenesis identified in gene expression analyses.

UV Irradiation Is a Major Initiator in the Pathogenesis of Cutaneous Lupus Erythematosus

UV irradiation has been thought to play a key role in the development of CLE, specifically due to the induction of autoantigens. After UV irradiation, nitric oxide is synthesized by nitric oxide synthases, such as inducible nitric oxide synthase (iNOS), and functions to protect cells, such as keratinocytes, from apoptosis (31, 32). Early work showed abnormal iNOS gene expression in the skin of patients with CLE patients who demonstrated delayed kinetics of iNOS induction by 72 h relative to controls (33). UVB irradiation induces chemokines, such as CXCR3 ligands CXCL9, CXCL10, and CXCL11, necessary to orchestrate the innate and adaptive response central to the immunopathogenesis of CLE (34). More recently, Katayama et al. (35) showed upregulation of the *IFIT* gene family, *HLA-DPA1,* and normal UV response genes (i.e., nucleic acid binding and erythematous reactions) in CLE skin relative to healthy skin. The *IFIT* gene family has subsequently been shown to be the top hub genes in bioinformatics analysis of DLE skin (36). This inflammatory response is mediated by IFNs with greater concordant elevations in IFN-α levels in SCLE relative to DLE.

Innate and Adaptive Immune Responses Drive Inflammation in Cutaneous Lupus Erythematosus Pathogenesis

For many years, unfettered inflammation secondary to dysregulated Th1 axis has been understood to be at the heart of CLE pathogenesis. Early studies using reverse-transcriptase PCR identified the potential role of type 1 cytokines and inflammation pathways. Patients with DLE without SLE were found to have increased expression of IFN-γ and IL-2 (37). An examination of the T-cell cytokine profile in CLE showed an upregulation of IFN-γ but also IL-5, indicating a possible role for Th2 cells (38). In the context of the B7-CD28 pathway, the importance of T-cells in the pathogenesis of CLE is underscored by findings of B7-1 and B7-2 RNA expression primarily in the dermis of patients with DLE, SCLE, and SLE (39). Microarray experiments comparing DLE to psoriasis confirmed a predominant Th1 signature and no Th17 signature, which is a hallmark of psoriasis (40). Bioinformatics analysis of gene networks notes an overlap of Th1 skewing of DLE with sarcoidosis (41). When CLE subtypes are compared, DLE and SCLE gene expression predominantly had a type I IFN signature, but DLE had a relatively increased expression of Th1-related cytokines (42).

Innate immune response functions upregulated by the Th1 phenotype include JAK/STAT signaling, toll-like receptor signaling, pattern recognition receptors, and antigen processing and presentation. Microarray and RNA-sequencing experiments consistently demonstrate upregulation of these inflammatory pathways in CLE skin (43–46). Recently, JAK/STAT upregulation in CLE has been the focus of targeted therapies, with JAK1-specific inhibition being explored as a promising approach for the treatment of CLE (47, 48). Enhanced toll-like receptor-dependent and pattern recognition receptor pathways contribute to both innate and adaptive immune responses in CLE (45). While often overlooked, only one study has examined the glycome of CLE given the function of glycosaminoglycans in mediating inflammation by acting as pathogen-associated molecular patterns (49, 50). Upregulation of hyaluronan and chondroitin sulfate *via HAS2* and *CHSY1*/*C4ST1*, respectively, provides some evidence by which glycosaminoglycans participate in the characteristic inflammatory response of CLE. Finally, in a study by Zhu et al. (1), a unique machine learning approach leveraging modular analysis uncovered large heterogeneity in CLE, but central themes of Th1 dysregulation and interferon activation were largely preserved in identified clusters.

The adaptive immune response is also important in the pathogenesis of CLE *via* dysregulation in antigen presentation, activation of B-cells, and autoantibody production (36). Moreover, key players, such as IL-9 and B-cell activating factor (BAFF) may be important in CLE progression to SLE and the distinction of CLE from SLE. Elevated *IL9* expression has been linked to production of autoantibodies in lupus-prone mice (51) and in skin of CLE patients who progressed to SLE versus those who did not (52). Similarly, our group found that higher BAFF mRNA and protein levels in patients with DLE with SLE than in those without SLE (53). Taken together, these findings suggest intricate interactions between the innate and adaptive immune response in mediating CLE pathogenesis and facilitating progression to SLE.

Upstream Regulation Impacts the Degree of Inflammatory Signatures in Cutaneous Lupus Erythematosus

Upstream mediators of inflammation have also been investigated. Spleen tyrosine kinase (*SYK*) is known to be a mediator of multiple innate and adaptive immune responses (54). Gene expression analysis *via* microarray of DLE (n = 7) and SCLE (n = 5) skin revealed upregulation of *SYK* and multiple *SYK*-regulated innate immune-related genes relative to healthy skin (n = 5) (55). Vorwerk et al. (56) postulate NKG2D, an immune receptor on NK cells and a subset of CD8 + T cells, contributes to CLE, giving upregulation on whole transcriptome RNA sequencing. However, NKG2D plays a selective role in autoimmune disease, and further mechanistic studies are

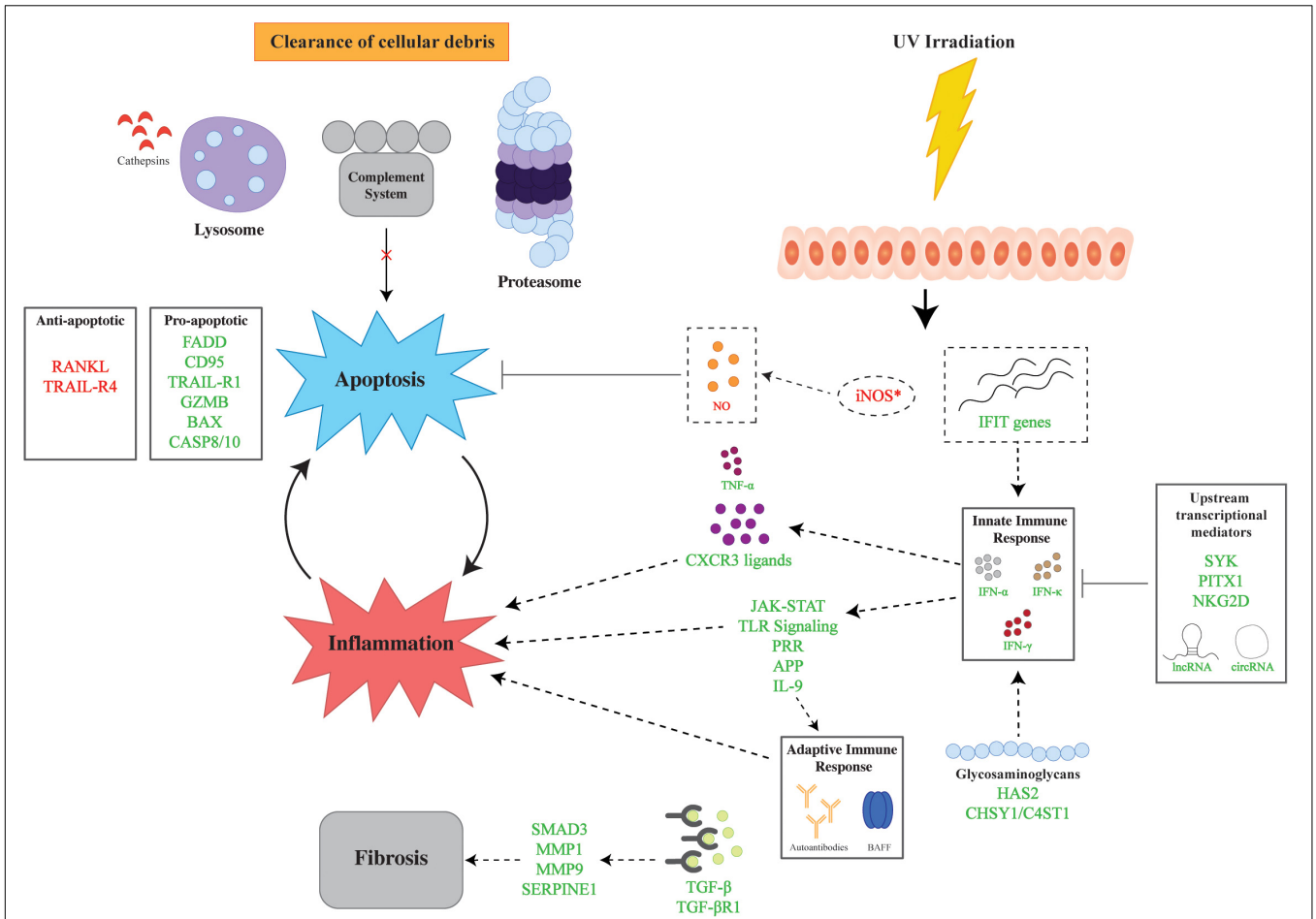

FIGURE 1 | Overview of major pathways in the genetic pathophysiology of cutaneous lupus erythematosus (CLE). The genetic pathophysiology of CLE encompasses three main pathways: inflammation, apoptosis, and fibrosis. UV irradiation is a major environmental insult that serves to initiate CLE pathogenesis by aberrant expression of iNOS and *IFIT* genes which lead to apoptosis and inflammation, respectively. The inflammatory response is mediated by the innate and adaptive immune response *via* IFNs and autoantibodies. Upstream transcriptional mediators regulate the innate immune response *via* transcriptional factors and non-coding RNAs. Glycosaminoglycans also modulate the inflammatory response *via* the upregulation of HAS2 and CHSY1/C4ST1. Apoptosis is facilitated by dysregulation of pro- and anti-apoptotic genes in tandem with impaired cellular clearance *via* aberrations in the lysosome, proteasome, and complement. Finally, fibrosis is mediated by TGF-β and downstream upregulation of effector molecules. Lines with bars indicate inhibition. Arrows depict subsequent effect of molecule or process. Green text signifies upregulation and red text signifies downregulation. APP, antigen processing and presentation; BAX, Bcl-2 Associated X-protein; GZMB, Granzyme B; C4ST1, carbohydrate sulfotransferase 11; CASP8/10, caspase 8/10; CD95, Fas; CHSY1, chondroitin sulfate synthase 1; circRNAs, circular RNAs; CXCR3, C-X-C motif chemokine receptor 3; FADD, Fas Associated via Death Domain; HAS2, hyaluronan synthase 2; IFIT, interferon induced proteins with tetratricopeptide repeats; IFN-α, interferon alpha, IFN-γ, interferon gamma; IFN-κ, interferon kappa; JAK-STAT, Janus kinase signal transducer and activator of transcription; lncRNAs, long non-coding RNAs; MMP1, matrix metallopeptidase 1; MMP9, matrix metallopeptidase 9, NKG2D, natural killer group 2D; PITX1, paired like homeodomain 1; RANKL, receptor activator of nuclear factor kappa-beta ligand, SERPINE1, Serpin Family E Member 1; SMAD3, SMAD Family Member 3, SYK, spleen tyrosine kinase; TGF-β, transforming growth factor beta; TGF-βR1, transforming growth factor beta receptor 1; TNF-α, tumor necrosis factor alpha; TLR, toll-like receptor; TRAIL-R1, TRAIL Receptor 1; TRAIL-R4, TRAIL Receptor 4; UV, ultraviolet.

required to understand its role in CLE (57). Recent RNA-sequencing data of SLE skin have identified another transcription factor, *PITX1*, which facilitates hypersensitive responses to type I IFNs in lupus keratinocytes (58). Finally, RNA-sequencing analysis of long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) was differentially expressed in patients with DLE and correlated with inflammatory immune response-related genes on coding and non-coding gene network analysis (59). Further functional studies of lncRNAs and circRNAs are required to fully understand their biological function.

Upregulated Cytokines and Chemokines Enhance Inflammatory Response in Cutaneous Lupus Erythematosus

One member of the type I IFN family, IFN-α, has had a well-established signature within SLE patients with skin involvement (60). In CLE, IFN-α is upregulated in both lesional and non-lesional skin (61). IFN-α recently has been shown to promote the adherence of *Staphylococcus aureus* with CLE and SLE keratinocytes (62). Thus, in concert with dysregulation of barrier proteins, such as filaggrin, IFN-α has been mechanistically

implicated in the colonization of CLE lesions. In addition to IFN-α, IFN-κ has also been important in the dysregulation of CLE keratinocytes (58, 63, 64). Responsiveness to hydroxychloroquine therapy has been associated with an increased type I IFN signature, while high TNF-α was associated with response to adjunct quinacrine (2).

Upregulated expression of chemokines CXCL9, CXCL10, and CXCL11 and its receptor CXCR3 is a hallmark of CLE (65). These chemokines exert their effect on CXCR3-expressing cells and orchestrate the Th1 immune response by promoting Th1 cell migration (34, 48, 66). These chemokines have been repeatedly shown to facilitate interface dermatitis (66). CXCL9 and CXCL10 expression were strongly correlated with IFN-γ expression in DLE (n = 15), SCLE (n = 11), and LET (n = 21) skin. (67). Novel bioinformatics approaches have shown that these chemokines as key genes are involved in CLE (68).

Apoptosis Perpetuates Inflammation

Apoptosis is broadly comprised of the extrinsic and intrinsic pathways. Current evidence suggests increased activity of the extrinsic apoptotic pathway *via* the upregulation of the TRAIL receptor system and CD95 (69, 70). Specifically, an increase of apoptotic keratinocytes has been observed in CLE with concomitant increased epidermal expression of TRAIL-R1, CD95, and FADD (64, 69). Apoptotic keratinocytes contribute to the pathogenesis of CLE *via* the release of cellular debris, which results in a positive feedback loop of inflammation. Recent work by Kingsmore et al. (71) noted increased apoptotic mitochondrial gene signatures in DLE and lupus nephritis, suggesting a role for the intrinsic apoptotic pathway, and positive correlation with inflammatory cell signatures supports the intrinsic link of apoptosis with inflammation. Gene set expression analysis with microarray and RNA-sequencing of CLE skin and blood identified other genes, such as *GZMB*, *BAX*, and various caspases (*CASP8*/*10*) among others (1, 64, 72–75). Differential expression analysis of CLE lesional skin and blood skewed toward lesional skin, though apoptosis signatures were noted in both environments. Apoptosis and necroptosis pathways *via RIP3* are activated in interface dermatitis characteristic in CLE (76).

Downregulation of anti-apoptotic genes has also been identified in CLE. RANKL, a regulator of apoptosis, is notably absent from CLE skin (77). While TRAIL-R1 has been shown to be pro-apoptotic, TRAIL-R4 serves as a decoy receptor, blocking TRAIL-induced apoptosis, and has been shown to be downregulated in CLE relative to psoriasis and lichen planus (69, 78).

Complements, Lysosomes, and Proteosome Contribute to Impaired Clearance of Cell Debris in Cutaneous Lupus Erythematosus

The complement cascade plays a pivotal role in the opsonization of cells undergoing apoptosis to facilitate phagocytosis, and the timely clearance of cellular debris is important to prevent the generation of autoantibodies. Similarly, lysosomal and proteasomal clearance of cellular debris *via* proteolysis plays an important role and has been shown to be dysregulated in CLE. Skin gene expression of complement has been shown to be more dysregulated relative to blood gene expression in CLE (74, 79, 80). This is contrasted with the upregulation of cathepsins associated with lysosomes and proteasome-related genes in CLE peripheral blood relative to lesional skin (35, 74). The complex dysregulation of the systems involved in the clearance of cellular debris at a localized and systemic level highlights the complexity of the pathogenesis of CLE.

Fibrosis Is Likely Driven by TGF-β in Cutaneous Lupus Erythematosus

Of the CLE subtypes, DLE has been most associated with scarring lesions with associated fibrosis. Comparison of patients with DLE and SCLE using Ingenuity Pathway Analysis revealed pathways associated with fibrotic processes, and longitudinal microarray analysis of patients with DLE and SCLE revealed sustained elevations of *TGF-B1, TGF-BR1, SMAD3, MMP1, MMP9,* and *SERPINE1* (42). Interestingly, while TGF-β, a M2 macrophage-related protein, was noted to be overexpressed in DLE skin relative to normal skin in an independent experiment, other M2 macrophage-related genes, such as *CD206*, *CD209*, *FOLR2*, *IL10,* and arginase-1, were not differentially expressed (65). Taken together, *TGF-β* likely plays a key role in fibrogenesis in scarring DLE lesions, though the exact downstream mechanisms have yet to be fully defined.

CONCLUSION

Our understanding of the underlying genetics governing the pathophysiology of CLE has greatly increased, thanks to advances in gene expression technology. Insights into the underlying genetic polymorphisms that predispose patients to CLE and knowledge of key dysregulated pathways in CLE afford the opportunity to develop targeted therapies for patients with CLE. Most recently, pathogenesis-directed therapy has focused on blockade of IFN receptors, such as anifrolumab (81). Other approaches, such as targeting the JAK/STAT pathway, are under investigation (82–84). The limitations of reviewed studies include small sample size, specific, non-generalizable cohorts, and technical limitations of gene expression profiling approaches, such as low resolution in microarray studies. Further studies using newer technologies, such as single-cell RNA sequencing, are warranted to define the genetic pathophysiology of CLE at greater resolution. Greater understanding of the underlying genetics of CLE can lead to further development of targeted therapies for CLE.

AUTHOR CONTRIBUTIONS

HC and BC conceived and designed the study. HC and GB acquired, analyzed, interpreted the data, and drafted the original manuscript. All authors contributed to critical revision of

the manuscript for important intellectual content, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.916011/full#supplementary-material

Supplementary Figure 1 | Flow diagram of workflow for the literature review.

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Conflict of Interest: BC was an investigator for Daavlin Corporation, Biogen Incorporated, and Pfizer Incorporated and consultant for Bristol Meyers Squibb, EMD Serono, Horizon Therapeutics, and Biogen Incorporated.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Emerging Therapies in Cutaneous Lupus Erythematosus

Grant Sprow[1,2], *Joshua Dan*[1,2], *Joseph F. Merola*[3] *and Victoria P. Werth*[1,2]*

[1] Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States, [2] Dermatology, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, United States, [3] Department of Dermatology, Department of Medicine, Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Cutaneous lupus erythematosus (CLE) is an autoimmune disease that can occur with or without underlying systemic lupus erythematosus (SLE) and often has a profoundly negative impact on patient quality of life. There is substantial need for new and more effective therapies to treat CLE. CLE has a multifactorial pathogenesis that involves several key immune cells and pathways, including abnormalities in innate (e.g., type 1 interferon pathways) and adaptive immune responses (e.g., B and T cell autoreactivity), presenting multiple opportunities for more targeted therapies that do not require immunosuppression. Here we review several emerging therapies and their efficacy in CLE. Anifrolumab and belimumab have both been approved for the treatment of SLE in recent years, and clinical trial evidence suggests some forms of CLE may improve with these agents. Therapies currently in development that are being evaluated with CLE-specific outcome measures include BIIB059 and VIB7734, which target plasmacytoid dendritic cells (pDCs), and iberdomide, a cereblon modulator. These novel therapies all have previously demonstrated clinical benefit in some forms of CLE. Other therapies which target molecules believed to play a role in CLE pathogenesis, such as Janus kinases (JAKs), spleen tyrosine kinase (SYK), interferon γ (IFNγ), IL-12, and IL-23, have been evaluated in lupus clinical trials with skin-specific outcomes but failed to meet their primary endpoints.

Keywords: cutaneous lupus erythematosus, autoimmune, skin, connective tissue disease, drug development

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***Correspondence:**
Victoria P. Werth
werth@pennmedicine.upenn.edu

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that can have various manifestations in the skin and internal organs. Most SLE patients develop cutaneous involvement at some point in the disease course which often has a significant impact on patient quality of life (1, 2). Cutaneous lupus erythematosus (CLE) is a set of heterogeneous inflammatory skin conditions with varying morphologies and scarring potential, that for the most part share common histopathologic features. CLE can occur with or without concomitant SLE.

There is substantial need for new therapies to treat CLE. Until very recently, there had been no new approved therapies for SLE since the 1950s. Few clinical trials have been designed to specifically evaluate therapies in CLE despite validated CLE-specific outcome measures such as the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) (3). Quinacrine, a potential first-line therapy for CLE, is in short supply due to an import alert placed on the only manufacturer that once supplied the United States (4). Additionally, second line therapies often involve substantial immunosuppression, monitoring, and other safety concerns. Here, we review

therapies recently approved for SLE, their efficacy/potential efficacy in CLE, as well as emerging therapies in development, and selected therapies that have been studied in CLE but ultimately failed in clinical trials.

THERAPIES APPROVED FOR SLE

Anifrolumab

Anifrolumab is a human, IgG1K monoclonal antibody that binds to type 1 interferon receptor, blocking type 1 interferon signaling. The scientific rationale for its mechanism of action is based on evidence indicating that the type 1 interferon pathway is involved in SLE pathogenesis (5). The FDA approved anifrolumab for SLE (though not lupus nephritis) in July 2021, the first new drug approval for SLE in over 10 years. After an initial phase 3 trial (TULIP-1) failed to meet its primary endpoint, a second phase 3 trial of anifrolumab (TULIP-2) showed that a higher proportion of patients in the treatment group had response at week 52 than those treated with placebo using a different primary endpoint than was used in TULIP-1 (6, 7). In TULIP-2, 362 patients were randomized to 48 weeks of treatment with either placebo or anifrolumab (6). Among patients with at least moderately severe skin disease, 49% of patients in the treatment group achieved the secondary endpoint of reduction in CLASI of 50% or greater compared to 25% in the placebo group, which was statistically significant (6). This data supports findings from TULIP-1 in which secondary endpoints pointed toward a clinical benefit in skin.

Belimumab

Belimumab is a human monoclonal antibody that binds to soluble B-lymphocyte stimulator (BLyS). BlyS levels are commonly elevated in patients with SLE and correlate with increased disease activity (8–10). Binding of BLyS by belimumab leads to decreased survival of B cells and a reduction in the differentiation of B cells into antibody-producing plasma cells (11). Belimumab was the first biologic approved by the FDA for SLE in 2011 and was more recently approved for pediatric SLE in 2019 and lupus nephritis in 2020. Belimumab was studied in a phase 3 placebo-controlled trial of 819 randomized SLE patients and met its primary endpoint indicating a clinical benefit in reducing SLE disease activity (12). However, skin-specific outcomes were not included as endpoints in the study and so its efficacy in treating CLE was not initially evaluated (12). Using the rash component of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), a *post-hoc* study of pooled phase 3 trial data showed approximately a 10% difference in two treatment doses relative to placebo after 52 weeks (13). This analysis also showed that significant improvements of two to three letter scores in the British Isles Lupus Assessment Group (BILAG), a lupus scoring system, were noted in the 10 mg/kg group in the mucocutaneous domain but not in the 1 mg/kg group (13). The change in overall adjusted mean SLEDAI scores from weeks 24 to 52 were significantly better with belimumab vs. placebo, indicating a potentially delayed effect across organ systems (13). Additionally, a number of case series have shown a significant reduction in CLASI-activity (CLASI-A) scores with the use of belimumab indicating a possible benefit (14–16).

THERAPIES IN DEVELOPMENT

Therapies Targeting Plasmacytoid Dendritic Cells

Plasmacytoid dendritic cells (pDCs) are considered one of the most crucial immune cells driving CLE pathogenesis. These cells are found in high numbers in CLE tissue after sun exposure and secrete pro-inflammatory cytokines and chemokines which drive disease progression (17). Two therapies targeting pDCs are currently in development for CLE.

BIIB059 is a humanized IgG1 monoclonal antibody targeting blood dendritic cell antigen 2 (BDCA2), a cell surface protein found exclusively on pDCs. This binding leads to inhibition of the production of pro-inflammatory mediators, including type 1 interferons, as well as decreased levels overall of inflammatory cells in patient tissue (18, 19). In a recent phase 2 trial of 132 patients with CLE, BIIB059 met its primary endpoint with a statistically significant difference in percent change from baseline in CLASI-A score compared to placebo (18). BIIB059 is currently being further evaluated in the phase 3 SLE trial TOPAZ-1 (ClinicalTrials.gov Identifier NCT04895241).

VIB7734 is another monoclonal antibody targeting pDCs currently being studied in patients with CLE. This antibody targets immunoglobulin-like transcript 7, a pDC-specific marker, and mediates depletion of pDCs through antibody-dependent cellular cytotoxicity (20). VIB7734 has been studied in two phase 1 trials and led to a reduction of circulating and tissue-resident pDCs in patients with CLE (20). Most CLE patients experienced clinical benefit as shown by reductions in CLASI-A scores (20). VIB7734 is currently being further studied in a phase 2 trial (ClinicalTrials.gov Identifier NCT04925934).

Therapies Targeting Cereblon

IKZF1 and IKZF3 are susceptibility loci for SLE and encode the transcription factors Ikaros and Ailos (21). Cereblon is a molecule that forms part of a ubiquitin ligase complex which mediates the polyubiquitination and proteasome-dependent degradation of Ikaros and Ailos (22–24). Thalidomide and lenalidomide, drugs that have been used for off-label treatment of CLE, bind to cereblon resulting in increased destruction of Ikaros and Ailos (22–24), leading to decreased B cells, pDCs, and increased T regulatory cells (25, 26). Iberdomide (CC-220) is an oral compound in development for SLE that has been shown to have higher binding affinity for cereblon than lenalidomide resulting in increased Ikaros and Ailos degradation (27). This allows for the use of lower doses, lowering the potential for off-target effects.

Iberdomide did not show a significant difference from placebo in achieving a 50% or more reduction in CLASI-A score in a recent phase 2 trial when including all patients with a baseline CLASI-A score of at least 10 (28). However, the majority of patients in the trial had acute CLE (ACLE) (29). Further analysis by CLE subtype showed that patients with subacute CLE (SCLE) and chronic CLE (CCLE) were more likely to have a reduction in

CLASI-A score of 50% or more when treated with iberdomide 0.45 mg than placebo (29). Additional research is needed to determine the true efficacy of iberdomide in treating CLE and its various subtypes.

THERAPIES THAT FAILED IN CLINICAL TRIALS

JAK and SYK Inhibitors

Janus kinases (JAKs) are involved in the signaling of several inflammatory cytokines that drive the pathogenesis of SLE (30–32). JAK/STAT signaling pathways are also upregulated within lesional CLE skin (33). Baricitinib is an oral selective and reversible inhibitor of JAK1 and JAK2 which has been studied as a potential treatment for SLE. In a phase 2 placebo-controlled trial of 314 SLE patients, baricitinib was found to be superior to placebo with standard of care in treating arthritis and nephritis (34). Improvement in skin disease was assessed as an outcome, but did not show significant difference from the placebo group (34). While many of the SLE patients had cutaneous involvement, the baseline activity scores were low which can make it difficult to demonstrate improvement (35). Baricitinib was also being evaluated in two phase 3 SLE trials, but top-line results led to the decision to discontinue the phase 3 development program in lupus. However, a phase 2 study of topical ruxolitinib, a JAK inhibitor, in discoid lupus erythematosus (DLE) is in development (ClinicalTrials.gov Identifier NCT04908280).

Spleen tyrosine kinase (SYK) activates pathways that increase inflammatory cytokine levels (36). Upregulated SYK activity has been seen in CLE skin and blocking SYK leads to decreased inflammatory cytokine levels in keratinocytes *in vitro* (37). Given the apparent roles of JAK1 and SYK in CLE pathogenesis, a randomized, placebo-controlled phase 2 trial comparing filgotinib, a JAK1 inhibitor, and lanraplenib, a SYK inhibitor, each to placebo was conducted but failed to meet the primary endpoint (38). A topical SYK inhibitor was also studied in a phase 1B trial but failed to show a difference from placebo in skin-specific disease measurement outcomes, perhaps due to low baseline disease activity (39). Another study of a topical JAK/SYK inhibitor had similarly negative results (40).

AMG 811

AMG 811 is a human IgG1 anti-interferon γ (IFNγ) antibody with selectivity for human IFNγ (41). IFNγ is involved in the function of macrophages, B cells, and T cells, and its mRNA is found in higher levels in DLE skin than in normal skin (42). AMG 811 had several trials in patients with SLE which demonstrated acceptable safety and tolerability (43–45). However, a randomized phase 1 trial of 16 patients with DLE failed to show clinical efficacy in improving skin lesions compared to placebo (46).

Ustekinumab

Ustekinumab is a human monoclonal antibody that blocks the p40 subunit of IL-12 and IL-23 and has FDA approval for the treatment of plaque psoriasis, psoriatic arthritis, Crohn's disease, and ulcerative colitis. IL-12 and IL-23 are important mediators of immunity and have been found in increased concentrations in patients with SLE (47, 48). A randomized phase 2 trial of 102 patients with SLE comparing ustekinumab to placebo plus standard therapy met its primary endpoint demonstrating a reduction in SLE disease activity (49). This trial also showed that patients in the ustekinumab group were more likely to achieve a 50% or greater reduction in CLASI-A score than patients in the placebo group, indicating a potential benefit in CLE (49). In a two-year open-label extension of this study, clinical benefits as measured by skin-specific and overall SLE activity outcomes were also seen (50). However, a phase 3 randomized, placebo-controlled trial of ustekinumab in SLE was halted due to lack of efficacy established during the interim analysis.

CONCLUSION

Emerging therapies with clinical trial evidence demonstrating efficacy in some forms of CLE include anifrolumab, BIIB059, VIB7734, and iberdomide. Other pathways involved in lupus pathogenesis, such as tyrosine kinase 2 (TYK2) and serine/threonine kinase IL-1R–associated kinase (IRAK4), represent potential future therapeutic targets of interest. When designing clinical trials to evaluate therapies for potential use in CLE, careful consideration should be paid toward study design to allow for optimal chances of demonstrating clinical benefit; this includes enrolling a sufficient number of patients with moderate to severe baseline disease activity, as highlighted by the skin-specific data from the baricitinib phase 2 and topical SYK inhibitor phase 1B trials. Trials of SLE therapies should also include skin-specific outcome measures as CLE and SLE often demonstrate disparate responses to therapies.

AUTHOR CONTRIBUTIONS

GS, JD, and JM drafted the manuscript. VW supervised the work and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Influence of Socio-Demographic Factors in Patients With Cutaneous Lupus Erythematosus

Amanda M. Walker[1], *Grace Lu*[1], *Shari C. Clifton*[2], *Motolani E. Ogunsanya*[3] *and Benjamin F. Chong*[1]*

[1] Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, United States, [2] Health Sciences Library and Information Management, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States, [3] Department of Pharmacy, Clinical and Administrative Sciences, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States

Cutaneous lupus erythematosus (CLE) is a chronic autoimmune skin disease with potential for systemic involvement, disfigurement, and significant disease burden. The relationships of demographics and socioeconomic status with patients with CLE are emerging topics with important clinical implications. The primary objective of our study is to perform a literature review of studies that have investigated demographic and socioeconomic factors amongst patients with CLE and determine whether these factors influence diagnosis frequency, disease severity and outcomes or health related quality of life. We searched multiple databases to identify literature addressing CLE and concepts such as race, ethnicity, gender, income, education level and geographic location. Information regarding primary research objective was extracted from all full text articles, and a summary of findings was prepared. We found that race and ethnicity can influence CLE diagnosis frequency and disease outcomes. Chronic cutaneous lupus (CCLE) occurs more frequently in Black patients, often with higher overall disease damage. Differences between genders exist in CLE in terms of health-related quality of life, as female gender was a risk factor for worse quality of life in several studies. Lower income, low educational attainment, and lack of health insurance all contribute to poorer overall outcomes in CLE patients. This review will help inform physicians about populations at risk for potentially worse outcomes to guide treatment decisions for patients with CLE and provide important information to design interventions that address modifiable social determinants of health in this population.

Keywords: cutaneous lupus, autoimmunity, race, socio-demographic factors, health equity

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***Correspondence:**
Benjamin F. Chong
ben.chong@utsouthwestern.edu

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INTRODUCTION

Cutaneous lupus erythematosus (CLE) is an autoimmune disorder associated with a broad spectrum of cutaneous manifestations. It may progress into systemic lupus erythematosus (SLE) and involve multiple organ systems (1). CLE can be further classified into acute, subacute, or chronic subtypes according to the clinical characteristics of the skin lesions (2). These CLE subtypes vary in clinical presentation amongst different races and ethnicities.

Prior studies have identified racial and ethnic disparities in dermatological diagnosis frequency, clinical presentation, disease management, and patient outcomes (3, 4). With regards to lupus erythematosus, most of the existing literature has focused on the influence of sociodemographic factors in SLE patients, with limited studies examining the same factors in CLE patients (5–7). This underscores the need for more information on factors influencing CLE outcomes to help guide patient care. The primary aim of our study is to perform a literature review examining demographic and socioeconomic factors that can influence CLE diagnosis frequency, disease severity and outcomes or health related quality of life. Detailed search strategy and methods are available in **Supplementary Figure 1**.

RACE AND ETHNICITY

Studies investigating racial and ethnic inequities in SLE have suggested higher incidence and prevalence in non-White populations (8). Few studies have investigated the incidence and prevalence of CLE in the absence of SLE, with fewer performed in mixed race populations (9–14). These studies suggest that race and ethnicity do affect CLE diagnosis frequency. Several studies found DLE to occur more frequently in Black or Hispanic patients compared to other races and ethnicities (10, 13, 15, 16). A cross-sectional study from the Georgia Lupus Registry showed that the highest age-adjusted incidence rates for DLE were seen in Black women (6.6 for definite DLE and 7.9 per 100,000 person years for definite and probable DLE) (10). These results are also echoed in the Manhattan Lupus Registry, which showed a prevalence of primary DLE that is significantly higher among non-Latino Blacks (23.5 per 100,000 person-years) and Latinos (8.2), and DLE incidence higher among non-Latino Blacks (2.4) (13). A large, multi-ethnic SLE longitudinal cohort study investigating the occurrence of discoid rash found that DLE was more common in Blacks ($p < 0.001$) (15). Black and Hispanic patients were not the only populations shown to be at higher risk of CLE. A study from New Zealand reported that the Maori/Pacific portion of their population had a greater relative risk of all types of CLE combined vs. their European counterparts (2.47, 95% CI 1.67–3.67) and a higher relative risk of DLE overall (5.96, 95% CI 3.06–11.6) (14).

While types of CCLE have been shown to occur more frequently in non-White populations, the opposite is true for SCLE (14, 16). A study examining skin damage and impact on quality of life in CLE patients found that 57 (97%) of all cases of SCLE occurred in White patients and no cases of SCLE occurred in Black patients (16). Jarrett et al. reported that although not statistically significant, the Maori/Pacific population in New Zealand has an overall decreased relative risk of SCLE compared to European participants (14). These differences in subtype distribution also have implications for disease course, as patients with SCLE can expect significant improvements in their skin disease activity over a shorter period of time than those with chronic cutaneous lupus (CCLE) (17).

Racial and ethnic differences can impact CLE disease course and severity. A study from Australia found that non-indigenous patients presented to clinic sooner than indigenous patients (18). Verma et al. found that Black patients develop CLE at an earlier age than non-Black patients and present with greater initial disease damage (16). Not only are non-White patients younger at initial disease presentation but Black patients may be more likely to hospitalized longer than their White counterparts (14.5 days vs. 6.3 days, respectively, $p < 0.02$) (19). When comparing DLE lesion distribution and disease activity and damage scores using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) between Black vs. non-Black patients, Black patients with DLE (median = 10.0, IQR 6.0–14.5) had higher baseline CLASI damage scores compared with non-Black patients (median = 6.0, IQR 3.0–10.0) ($p < 0.001$) (20). Black patients were also more affected by the presence of dyspigmentation in any location compared to non-Black patients (99 vs. 79%, $p < 0.001$). In addition to higher baseline CLASI damage scores, Blacks were less likely to see ≥40% improvement in CLASI damage scores compared to other races (17). Interestingly, Ker et al. found that there was significant improvement in CLASI activity scores over time in patients who were Black ($p = 0.049$), Hispanic or Asian ($p = 0.02$) (21). Additional factors may contribute to disease presentation differences such as disparities in access to health care and insurance status. Non-White patients represent the largest proportion of uninsured patients with 16.7% of Hispanic and 9.6% of Black patients reporting no insurance, while White patients had the highest rate of private insurance at 75.2% (3). Lack of insurance can lead to delays in treatment in non-White patients which may contribute to greater severity of disease at time of presentation. In addition, the burden of disease in uninsured patients is likely higher, which may also influence disease outcomes (22).

Race and ethnic differences were also noted in co-existing medical conditions in CLE patients. A cross-sectional study of CLE patients looking for risk factors for coexistent autoimmune disease in CLE found that CLE patients with at least one coexisting autoimmune condition(s) were more likely to be White (odds ratio [OR], 2.88; 95% CI, 1.00–8.29; $p = 0.0498$) (23). Black patients also have significantly lower 25-OH vitamin D levels compared to Caucasian and Hispanic patients when controlling for CLE disease status, leaving them more vulnerable to vitamin D insufficiency when practicing photoprotective behaviors that often coincide with the CLE diagnosis (24).

Increased disease severity in CLE has been shown to be associated with worse quality of life (25). However, when looking for differences in quality of life by race or ethnicity, neither Klein et al. or Vasquez et al. found any significant associations (7, 25). In contrast, Verma et al., did find that CLASI damage scores in Black patients significantly correlated with SKINDEX-29+3 symptom scores but not in White patients (16). Similarly, a study investigating depression in a primarily Black population in Georgia found that 26% of Black CLE patients reported moderate to severe depression. Higher or worse SKINDEX-29+3 symptoms, functioning, and CLE-specific domain scores were significantly associated with depression as well (26).

GENDER

CLE incidence and prevalence rates are higher in female patients (9, 10, 12–14). These studies report female to male gender ratios ranging from 1.79:1 to as high as 9:1 (9, 12). The exception to this finding comes from a predominately White population study in Minnesota which found the prevalence of CLE to be higher than SLE in men than in women (11). All studies investigating alterations in disease course or severity were predominately female cohorts (16–21, 25). Gender did not play a significant role in predicting progression of disease activity in a multi-center endeavor studying the natural disease course of CLE (21). Similarly, no other studies found significant differences in natural CLE disease course or severity between males and females (16–20, 25).

Studies investigating health-related quality of life and depression in CLE patients report that depression is increased in CLE patients compared to the non-CLE population (27). Most studies in CLE patients found female gender to be a risk factor for poor quality of life or depression (7, 25, 28–30). Klein et al. found that female gender was associated with poor quality of life in all SKINDEX 29+3 subdomains ($p < 0.006$) (25). Results from a multi-center study comparing two different cohorts of CLE patients also found that being female was significantly associated with poor quality of life in all SKINDEX-29+3 subdomains and in SF-36 physical functioning, role-physical, and bodily pain scores (7). A small Japanese cohort found female gender to be a risk factor for poorer quality of life and that functioning and emotions subscales were greater in females compared to males (29). Similarly, Teske et al. found that female DLE patients were significantly associated with poorer QoL in the SKINDEX-29+3 emotions domain, lupus specific scores and symptoms scores (30). Possible reasons as to why females are more susceptible to poorer quality of life may be related to other social factors and increased psychiatric comorbidities related to cosmetic appearance as seen in other skin diseases like acne and vitiligo (31, 32). CCLE can causes significant scarring and hair loss, which may affect women's self-esteem more than men and promote seclusion.

Although most studies show that females are more susceptible than males when it comes to health-related quality of life, two studies found no statistical difference between males and females. This could be related to small sample size of males in each cohort, making robust comparisons difficult. Hesselvig et al. actually found that men with CLE had a higher risk of depression than women (27). However, a small cohort of LE patients in Madagascar did not find any significant correlations between gender and Dermatology Life Quality Index (DLQI) scales (33). Similarly, a CCLE cross-sectional cohort study in Georgia did not find significant differences in risk and severity of depression by gender (26). It is possible that males may be more affected by lack of social support compared to females. A comparison of quality of life in a cohort of SLE patients found that male patients scored lowest in social support domains, and was attributed to differences in communication styles between males and females (34).

INCOME, EDUCATION, AND GEOGRAPHIC LOCATION

Socio-demographic factors including income, education level, and geographic location can affect patients with CLE (7, 19, 28, 30, 33, 35). CLE patients have been shown to experience significantly high healthcare expenditures, particularly if depression is present. In CLE patients with depression, inpatient visits ($p < 0.01$), prescription drugs ($p < 0.001$), and ER visits ($p < 0.05$) were identified as the most significant contributors to medical expenses, respectively (28). Higher levels of poverty were associated with a significantly increased likelihood of rehospitalization within 1 year ($p < 0.0047$) and being female ($p < 0.002$) (19). Income level was also shown to have an inverse relationship with CLASI damage scores ($p = 0.006$), but no significant relationship to CLASI activity scores (35).

In contrast, existing literature has identified variable associations between income and health-related quality of life (7, 30, 33, 35). An annual income <$10,000 was associated with a lower quality of life in the SKINDEX-29+3 functioning and symptom domains in three studies (7, 30, 35). Annual income <$10,000 corresponded to poorer SKINDEX-29+3 symptoms ($p = 0.002$) and lupus-specific ($p = 0.02$) sub-domain scores (7). Joseph et al. also found significant differences in SKINDEX 29+3 lupus-specific ($p < 0.05$), functions, symptoms ($p < 0.01$), and emotions subdomains ($p < 0.001$) between the <$10,000 and >$50,000 annual income categories (35). Within this cohort, Whites comprised the largest proportion in the highest income bracket (58.5%), whereas Blacks comprised a majority of the lowest income bracket (67.1%) ($p < 0.001$). Similarly, when looking at a primarily Black cohort with CCLE, Hong et al. found employment was associated with a lower likelihood of depression (OR = 0.24, $p < 0.01$). Although annual visits with a dermatologist or rheumatologist was not statistically significant, they also found that insured patients and those who visited a PCP in the last year were at lower risk of depression (26). However, Sendrasoa et al. identified an inverse relationship between income and health-related quality of life, with high monthly income associated with increased impairment of quality of life (33). This difference may due to those with higher monthly income having different healthcare expectations than those with low monthly income in Madagascar.

Few studies examined educational attainment (15, 23, 33). Interestingly, CLE patients with at least one coexisting autoimmune condition were less likely to have high school level of education (23). Other studies have also found differences in disease presentation or quality of life depending on degree of educational attainment. In a cohort of SLE patients with CLE, those with DLE were more likely to have fewer years of formal education (15). In addition, patients with a low-level of education had poorer DLQI scores than those with a mid or high education level ($p = 0.008$) (33).

It is well-known that increased sun exposure and ultraviolet (UV) radiation are associated with increased skin flares in those with CLE. Thus, differences in geographic location may have

some influence on diagnosis frequency or disease outcomes in CLE. Only one study has directly compared CLE outcomes between two different locations in the United States (7). Investigators found that although most quality of life measures were very similar between the two CLE populations, there were significant differences in Skindex-29+3 functioning and lupus-specific subdomains and SF-36 physical functioning, role-physical and general health subscales between CLE patients seen in Dallas, Texas, vs. Philadelphia, Pennsylvania (7). CLE patients from the Dallas metroplex expressed an increased tendency to stay inside and were more likely to avoid outdoor activities for fear of increased UV exposure. Despite growing evidence for the effects of UV radiation on CLE lesions, it does not appear that location, and therefore the amount of solar radiation is associated with worse CLE outcomes. Scolnik et al. analyzed cutaneous findings, including DLE, in SLE patients according to latitude and degree of solar radiation and found that living in a city with higher daily solar radiation was not associated with increased cutaneous manifestations during follow up (36).

DISCUSSION

We present a summary of current research findings related to socio-demographic factors in patients with CLE (**Figure 1**). There is strong evidence that CCLE, in particular DLE, more commonly affects non-White patients (10, 13, 15, 16). Physicians are encouraged to be aware of these differences when counseling their non-White patients regarding expected disease course and manage expectations for treatment outcomes. Furthermore, their communication styles with patients about their skin disease may affect their quality of life. Depression in Black patients with CCLE was directly associated with worse reports of staff disrespect and inversely associated in patients who reported that their physicians explained their labs and medications (26).

Differences in disease severity in non-White patients might be partially explained on a genetic level. Recent whole blood transcriptome data identified six patient subsets with distinct molecular phenotypes separated by race and CLE subtype, with increased T-Cell signatures in subsets predominated by Blacks and DLE subtype (37). Further studies are needed with greater CLE subtype diversity and larger sample sizes to investigate the influence of these molecular differences which may help to improve treatment options and outcomes in these groups by developing tailored treatment plans based on molecular subtype.

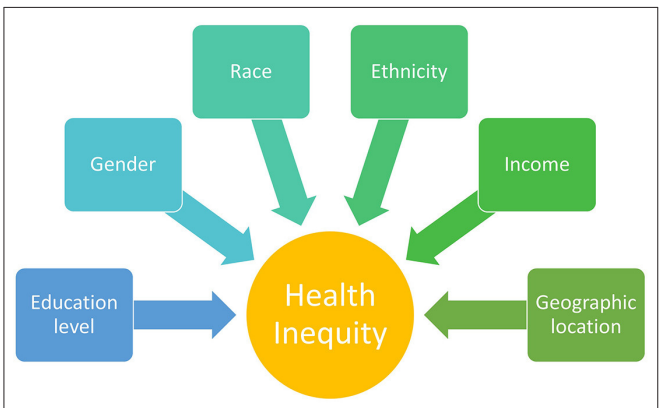

FIGURE 1 | Sociodemographic factors contributing to health inequity that have been investigated in patients with cutaneous lupus erythematosus (CLE).

Like most autoimmune diseases, CLE occurs primarily in female patients; however, it does not appear that female gender is associated with worse CLE disease course and severity. Female patients may differ from males in their attitudes toward their appearance and place emphasis on cosmetic appearance. Further studies with larger sample sizes of male participants are needed in order to accurately compare disease severity and health-related quality of life between these two groups. We recommend that physicians be open to screening for comorbid psychiatric conditions like depression or suicidal ideation so that they may refer them to the appropriate services or online support groups.

Finally, socioeconomic factors like reduced income and low educational attainment have been associated with worse outcomes in patients with CLE (7, 15, 19, 23, 26, 30, 33, 35). A diagnosis of CLE comes with significant financial burden. Inadequate funds or insurance coverage may lead to some patients not being able to afford their treatments, contributing to increased CLE damage and poorer overall outcomes (35). Those with lower socioeconomic status may be more susceptible to social isolation or increased sense of discrimination, contributing to poorer quality of life (35). Furthermore, low educational attainment has been associated with low socioeconomic status which may contribute to low health literacy levels (38). Low health literacy negatively impacts health-related outcomes, use of preventive services, and a patient's overall ability to access care. Possible interventions for improving CLE outcomes in these patients may include increasing physician reimbursement for Medicaid patients, instituting educational videos and patient lectures to improve health literacy, and increasing non-White participation in clinical trials and research to increase representation of these populations.

In summary, differences in CLE diagnosis frequency, disease outcomes, health related quality of life exist depending on the socio-demographic factors present. We have identified that race and ethnicity play a large role in CLE diagnosis frequency and disease outcomes. Although racial and socio-demographic inequities appear to exist in CLE, further investigation is necessary to improve care, increase awareness, and further develop interventions aimed at tackling health inequity in CLE.

AUTHOR CONTRIBUTIONS

AW, MO, and BC contributed to conception and design of the study. AW, GL, and SC contributed to the acquisition and analysis of the data. AW and GL drafted the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.916134/full#supplementary-material

Supplementary Figure 1 | Study selection and screening methods used in present study. Figure was adapted from the PRISMA Flow Diagram 2020 V1. Inclusion criteria included studies with cohorts of CLE patients (with or without SLE) whose primary outcome included CLE diagnosis frequency, CLE disease outcomes or health-related quality of life. Exclusion criteria included non- English studies, conference abstracts, and SLE only cohorts. Searches were completed on February 2, 2022. There were no publication date limits. Covidence review platform was used for study screening and extraction. Two separate reviewers (AW and GL) independently appraised all studies meeting inclusion and exclusion criteria. 1,326 studies were imported to Covidence for abstract and title screening. 302 duplicates were removed and then 1,024 studies were left for screening. 982 articles were excluded based on exclusion criteria. 42 articles were assessed for full-text eligibility and 17 studies were excluded, leaving 25 studies total included in this review. Information regarding primary research objective was then extracted from all full text articles and summarized
in text.

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The Burden of Living With Cutaneous Lupus Erythematosus

Cristina Drenkard[1,2]*, *Kamil E. Barbour*[3], *Kurt J. Greenlund*[3] and *S. Sam Lim*[1,2]

[1] Division of Rheumatology, Department of Medicine, Emory School of Medicine, Atlanta, GA, United States, [2] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, United States, [3] Centers for Disease Control and Prevention, Atlanta, GA, United States

Cutaneous lupus erythematosus (CLE) is a group of heterogeneous autoimmune disorders primarily affecting the skin. Patients with these conditions are mostly young women when they become sick and often suffer from recurrent skin symptoms or longstanding changes in their physical appearance. CLE disorders lead to different levels of morbidity and can impact profoundly patients' quality of life, particularly in the psychological and social health domains. This review provides a summary of recent research investigating the psychosocial burden of living with CLE and the intersect amongst the disease characteristics, patient factors, and social determinants of health. Furthermore, this review provides insight into patient care and research needs that remain unmet to improve the quality of life of patients living with CLE.

Keywords: quality of life, psychosocial impact, racial minorities, cutaneous lupus erythematosus (CLE), disease burden

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***Correspondence:**
Cristina Drenkard
cdrenka@emory.edu

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INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a group of heterogeneous autoimmune disorders primarily affecting the skin and mucosal tissue, showing varying levels of association with systemic lupus erythematosus (SLE). CLE comprises multiple conditions classified into three major subgroups based on the disease morphological characteristics and chronicity: acute (ACLE), subacute (SCLE), and chronic (CCLE) cutaneous lupus erythematosus (1, 2). ACLE consists of transitory erythematosus rashes, which are often localized on the malar area of the face, also known as "butterfly" rash, on UV-exposed areas, or as a generalized rash. SCLE typically presents as an annular or a papulosquamous rash on photo-exposed areas of the trunk and arms. SCLE rashes last longer than ACLE and can cause dyspigmentation. CCLE is the largest subgroup and includes multiple distinctive conditions, including discoid lupus erythematosus (DLE), lupus panniculitis, chilblain lupus, and lupus tumidus. CCLE subtypes can cause scaring and are less likely to be associated with SLE than ACLE and SCLE. DLE, the most common subtype, is characterized by erythematous discoid-shaped, adherent plaques and papules that can be localized in any area of the body, but are more likely to be on the scalp, ears, and face. DLE heals causing dyspigmentation, atrophy, scarring, and permanent hair loss (1, 3, 4).

CLE affects all age groups but is rare in children, and is more common in females with different proportions according to subtype. The female to male incidence ratio ranges between 3:1 and 4:1 for CLE as a group, and between 3:1 and 8:1 for DLE (5–8). Population-based studies indicate that Black people develop the disease at younger age than White people. The mean age at DLE diagnosis was 48.5 and 53 years-old in the predominantly White populations of Olmstead County, Minnesota and Sweden (6, 9), respectively, and 32 years-old in the African-descendent population of French Guiana (10).

There are also racial disparities in the incidence, morphology, and severity of CLE subtypes. While SCLE is more likely to occur in White individuals (11), CCLE, in general, and DLE, in particular, disproportionately affect Black individuals. In the Southeast USA, where the population is evenly distributed between White and Black people, the overall incidence of CCLE and DLE was reported to be at a minimum of 3.9/100,000 and 3.7/100,000 person years, respectively (8). CCLE and DLE incident rates were 3.9- and 4.1-fold higher for Black compared to White people, respectively. Racial disparities were also reported in the prevalence of DLE in Manhattan, with higher rate of cases per 100,000 persons-year among Blacks (23.5) and Latinos (8.2) compared with Whites (1.8) and Asians (0.6). The average age at diagnosis was lowest among Black people (36.7 years old) and highest among White people (63.4 years old), whereas Latino and Asian people were in average 45.8 and 45.3 years old, respectively (7). Among CLE patients at the University of Pennsylvania, Black people had more skin damage at onset and during follow-up than White patients (12), while Black patients with DLE from Texas had significantly worse damage at baseline and greater risk of dyspigmentation at any anatomical location than those of other race/ethnicity (13).

THE BURDEN OF CLE

Patient Perspectives of Living With CLE

Two recent qualitative studies have shed light on how CLE may be perceived by patients and how the disease may affect patients' lives (14, 15). The most salient themes include the negative impact of living with CLE on patients' mental health, which can lead to social anxiety, maladaptive responses, and negative coping strategies such as recreational drug use (14). Issues related to physical signs and symptoms, including scarring and dyspigmentation, fear of disease progression, body image and self-consciousness are often elicited by patients (15). Qualitative findings suggest that the emotional distress caused by living with CLE persists in a large majority of patients, regardless of the disease duration; however; patients' concerns may differ by demographic characteristics (14, 15). White patients reported predominantly fear of disease progression and physical signs and symptoms, whereas Black patients often elicited self-consciousness, alopecia and dyspigmentation. Furthermore, patients aged 60 or younger were more likely to report emotional symptoms than older patients (15).

Individuals living with CLE report that their personal relationships are profoundly affected (14). Patient testimonies indicate high levels of distress about their appearance as well as being socially stigmatized (15). Self-consciousness, one of the most common themes among CLE patients, is intensified by comments made to the patient by other people. These conditions also interfere with outdoor activities due to photosensitivity. Patients often report feelings of helplessness and being restrained by the disease due to the lack of cure and limited cosmetic resources (15). As in other stigmatized diseases, low self-esteem and internalized stigma can have devastating consequences on social interactions, vocational development, employment, and healthcare seeking (16).

Health-Related Quality of Life

HRQL is a multi-dimensional concept that includes domains of physical, mental, emotional, and social functioning, and the social context in which people live (17). In chronic diseases, HRQL has become increasingly important in the assessment of disease severity, the evaluation of interventions, and the allocation of resources. A growing body of research indicates that CLE has a substantial negative impact on the physical, mental, and social health of people living with these conditions (12, 18–20). One of the instruments most commonly used to measure HRQL in CLE is the Skindex 29+3, a skin-specific validated scale that provides separate scores for three skin-related domains (symptoms, emotions, and functioning) and an additional lupus-specific domain to address a patient's worries about hair loss, outdoor activities, and photosensitive-related flares (18, 21). The impact of CLE on the HRQL has been reported to be worse or similar to that seen in patients with other skin diseases, such as acne and non-melanoma skin cancer, as well as in other chronic conditions such as cardiovascular disease and diabetes (18).

HRQL can be influenced by multiple factors, including CLE subtypes and disease characteristics, patient's demographics, social context, and healthcare system. Female sex, older age, low education, low socioeconomic status, smoking, associated SLE, generalized CLE, and higher skin disease activity, have been reported to impact negatively different domains of HRQL in CLE (12, 18–20, 22, 23). Increased disease activity has been associated with poorer quality of life in cross-sectional studies; however, a small longitudinal study among patients with DLE and SCLE pointed to a physician-patient dissociation of the disease assessment, supporting the multidimensional patient-driven nature of quality of life in chronic skin diseases (24). A more recent study used a CLE-specific tool derived from Skindex 29+3 to examine multiple factors potentially associated with the HRQL in a diverse university-based sample of CLE patients from the Southwest US (20). Pain, fatigue, disease activity, body image, and side effects of medications were significantly associated with worse quality of life, with body dissatisfaction having the highest negative impact. These results taken together suggest that treatment evaluation should include measures relevant to the patient, including body appearance.

Depression and Psychiatric Disorders

Psychological health is one of the HRQL domains most negatively impacted in CLE. Patients with CLE have increased prevalence of major depressive disorder, generalized anxiety disorder, panic disorder, suicide risk, and agoraphobia (25). Approximately one-third of people with CLE report moderate to severe depressive symptoms (18, 26–28). Likewise, the risk of depression was found to be 2-fold higher people with CLE compared with the general population in a nationwide Danish study (27). However, mental health challenges are often underdiagnosed and remain untreated in CLE patients and the psychosocial burden of CLE is poorly understood, particularly among patients from minority groups (28, 29).

While the CLE subtype and morphological characteristics are deemed to be primary factors affecting patients' quality of life, recent research suggests that individual characteristics and social

factors also play critical roles (20). A study on illness perception among patients with DLE emphasized that negative emotional reactions to illness are associated with worse quality of life, worse depression and higher activity and damage (30). Furthermore, in a predominantly Black population-based cohort of patients with CCLE, the risk of depression was lower in participants who were employed and insured. Non-depressed patients also reported higher social support, visited a primary care physician more frequently in the last year, and reported better physician-patient interactions (28). Perceptions of stigmatization have been significantly related to both psychological distress and degree of disability among patients with other skin diseases (31–33), and these factors are likely to play a substantial role in the pathogenesis of depression among individuals with CCLE. Despite the high prevalence of depression in patients with CLE, in general, and CCLE, in particular, there is currently sparse work exploring psychosocial pathways in high-risk populations with CLE.

Social Determinants of Health and CLE

The World Health Organization defines social determinants of health (SDH) as the conditions in which people are born, grow, live, work, and age that affects a wide range of health and quality-of life-risks and outcomes. SDH are narrowly correlated to the immediate environment of an individual such as underprivileged social conditions of poverty, lower level of education, unemployment, insecure housing, unsafe home and neighborhood conditions, unsafe employment, childhood experiences (e.g., abuse), poor relationships, and social support (34). Not only do SDH shape individuals' options, choice, and behavior that impact their health, but these conditions also correlate with environmental and social threats that generate unhealthy stress responses. Among patients with chronic skin diseases, social stigma and reduced social connections have been significantly related to both psychological distress and disability (33). However, little is known about the impact of SDH in CLE. Moreover, as Black individuals are at higher risk for chronic disfiguring subtypes and are also more likely to be exposed to social stressors, it is imperative to examine the impact of SDH on the health of this population.

A recent report from the University of Texas Southwestern CLE Registry examined the cross-sectional association of income and quality of life in an ethnically diverse sample of patients with CLE, of whom nearly 80% had DLE and 51% had associated SLE (13). Racial disparities in annual income were evident, with White people representing nearly 60% of participants in the highest bracket (>50 K USD) and Black people representing nearly 70% of those in the lowest bracket (<10 K USD). While Cutaneous LE Disease Area and Severity Index (CLASI) activity scores did not differ significantly across income, CLASI damage scores and income were inversely associated. Moreover, lower annual income was significantly associated with worse quality of life, specifically in relation to symptoms and emotions, and within those in the lowest income bracket, women, patients younger than 40 years of age, smokers, and those with more active skin disease were more likely to have worse quality of life. These findings suggest that CLE conditions place a substantial financial burden on patients, potentially limiting job opportunities and having negative consequences on healthcare access and quality of care. Moreover, low-income individuals reportedly experienced more shame, anger, embarrassment and social isolation related to their skin disease, suggesting that individuals living under the poverty threshold are disproportionately more vulnerable to the psychological and social effects of these stigmatizing conditions.

Burden on the Health Care System

A recent study using administrative data indicated that CLE poses a substantial toll on the healthcare system. The total direct medical cost associated with CLE in the US was ∼$30 billion in 2014, and CLE patients with depression had significantly higher average annual total expenditure, compared to those without depression ($19,854 vs. 9,735) (26).

Cardiovascular Disease

A large body of evidence indicates that SLE and related autoimmune diseases increase the risk of cardiovascular disease (CVD), primarily as a consequence of immune-driven atherosclerotic changes (35–38). Recent research suggests that patients with isolated CLE may also have an increased risk of CVD, although data from various CLE studies are less consistent than in SLE (39–41). An increased cardiovascular risk in CLE can be explained by the chronic inflammatory process that characterize CLE, as well as by the high prevalence of depression in this population, which is a well-known factor associated with atherosclerosis (25, 42). Moreover, traditional risk factors, such as smoking and alcohol intake are coping responses frequently adopted by patients with stigmatized conditions, such as CLE (43). Less known factors, not studied yet in CLE, are related to the chronic exposure to psychosocial stressors, such as social stigma and discrimination. The experience of psychosocial stressors across the life-course contributes to "weathering", or accelerated declines in health due to cumulative burden on biological systems (44–47). Research suggests that chronic stressors elicit a cascade of biological responses that may be functional in the short term, but over time damage the systems that regulate the body's stress response (48–50). Epidemiological studies have shown that psychological stress may significantly contribute to the development and progression of atherosclerosis (51–53).

Relationship of CLE and SLE

ACLE lesions often present as a cutaneous flare within the context of SLE, whereas up to 60% of SCLE patients may have associated systemic features or may transition to SLE (54). In contrast, CCLE conditions in general and DLE in particular are deemed to have a lower risk of associated SLE or disease progression. Still, available data vary widely depending on the demographics and settings of the study population, methods and timing used to ascertain cases, and case definitions. The prevalence DLE lesions in patients with a diagnosis of SLE ranges between 5 and 24% (6, 55, 56), and similar proportions (5–25%) of patients with isolated DLE may progress to SLE (6, 9, 54, 57). Several studies indicate that when systemic manifestations are present in patients with DLE, these tend to be mild and kidneys are less likely to be compromised (56–59). The time from DLE to SLE

progression varies widely, ranging between months to over 30 years (9, 57). One study described that nearly 17% of patients with a diagnosis of DLE developed SLE within 3 years (6), and the highest rates of disease progression within 3 years of DLE diagnosis have been reported for children (26%) and women (20.7%) (6, 55). However, a recent retrospective study underlined a much shorter estimate, with a median interval of 453 days between DLE diagnosis and SLE progression in 34 adult DLE patients who developed SLE (60). The progression from DLE to SLE has been linked to several clinical risk factors, including the presence of generalized DLE lesions, articular symptoms (arthritis or arthralgias), periungual telangiectasias and nailfold abnormalities, autoantibodies, leukopenia and anemia (61, 62). The pathogenic mechanisms for SLE progression are largely unknown. A recent cross-sectional study in a predominantly Black population underlined that the B-cell compartment in some patients with isolated CCLE resembles SLE and is clinically associated with enhanced serological activity and more extensive skin disease, suggesting that SLE-like B-cell changes may help identify CCLE patients at risk for subsequent development of SLE (63). In contrast, another study found a B cell gene signature in the skin of DLE patients, which was more prominent in patients with a lower rate of systemic disease. These findings taken together suggest that B cell phenotypes in the blood and the skin may play specific roles with differential effect in cutaneous lupus and systemic disease activity.

UNMET NEEDS AND RESEARCH OPPORTUNITIES

Qualitative studies among CLE patients revealed important unmet needs related to CLE treatment and care, including insufficient patient education to better cope with the disease and lack of treatments to improve damaged skin (14). Furthermore, Black patients tend to report low satisfaction with dermatologists' knowledge of their skin and hair, as well as lack of culturally sensitive interaction style. Since Black people are more susceptible to DLE than White people and are more likely to develop lesions on the scalp with more severe damage and dyspigmentation, a knowledgeable and culturally competent approach is necessary to better serve these patients. Cosmetic care is another unmet need perceived by patients. Cosmetic procedures are largely avoided by practitioners because the potential side effects that may occur in autoimmune and photosensitive conditions. Moreover, these procedures are expensive and patients with CCLE are often left with permanent skin damage (64).

Despite the heterogeneous spectrum of CLE conditions, as well as the variable disease severity and risk of systemic manifestations across these multiple conditions, most quality-of-life studies tend to approach CLE as a group, with limited data on the potential differences by CLE subtypes. Furthermore, the susceptibility to CLE subtypes and the disease severity differs by individual demographics, with Black patients having higher risks of chronic subtypes, more conspicuous hypopigmentation, and worse skin damage (8, 13, 19). Thus, studies with larger sample size and representation of minority groups are needed to better describe health disparities across CLE subtypes and understand the needs of patients from vulnerable groups.

The study of social determinants has been lacking and is fundamental in CLE, where CCLE, the most prevalent subtype, clearly disproportionately strikes Black minorities. Research addressing social determinants of health is imperative to understand the pathways associated with poor outcomes and inform clinicians, public health agents and general public on interventions and programs that can help to mitigate the negative impact of these conditions in the most vulnerable subpopulations.

AUTHOR CONTRIBUTIONS

CD and SL contributed to the manuscript conception and literature review. All authors were involved in drafting the article and/or critically revising it for important intellectual content, and approved the final version to be published.

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EDITED BY
Victoria Patricia Werth,
University of Pennsylvania,
United States

REVIEWED BY
Yaling Dou,
Texas A&M Health Science Center,
United States
Thiago DeSouza-Vieira,
Universidade Federal do Rio
de Janeiro, Brazil

*CORRESPONDENCE
Benjamin Klein
Benjamin.klein@medizin.uni-leipzig.de

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Current concepts of photosensitivity in cutaneous lupus erythematosus

Benjamin Klein* and Manfred Kunz

Department of Dermatology, Venereology, and Allergology, University Hospital Leipzig, Leipzig, Germany

Cutaneous lupus erythematosus (CLE) represents a complex autoimmune disease with a broad phenotypic spectrum ranging from acute to chronic destructive cutaneous lesions. Patients with CLE exhibit high photosensitivity and ultraviolet (UV) irradiation can lead to systemic flares in systemic lupus erythematosus. However, the exact mechanisms how UV irradiation enhances cutaneous inflammation in lupus are not fully understood. Recently, new molecular mechanisms of UV-driven immune responses in CLE were identified, offering potential therapeutic approaches. Especially the induction of type I interferons, central cytokines in lupus pathogenesis which are released by various skin cells, have become the focus of current research. In this review, we describe current pathogenic concepts of photosensitivity in lupus erythematosus, including UV-driven activation of intracellular nucleic acid sensors, cellular cytokine production and immune cell activation. Furthermore, we discuss activated pathways contributing to enhanced apoptosis as well as intracellular translocation of autoantigens thereby promoting CLE upon UV light exposure.

KEYWORDS

cutaneous lupus erythematosus, UV light, photosensitivity, interferon, DNA damage

Introduction

The human skin is a complex structure consisting of epidermal keratinocytes, melanocytes, dermal fibroblasts, adipose tissue and numerous immune cells. All these compartments are more or less regularly exposed to ultraviolet (UV) irradiation in many areas of the body surface. In healthy skin, UV irradiation has pleiotropic effects and causes a series of cellular reactions that are both metabolically stimulating, pro-inflammatory or even degenerating (1).

Cutaneous lupus erythematosus (CLE) represents a chronic recurrent autoimmune disease with multiple clinical manifestations ranging from isolated cutaneous lesions to systemic disease with systemic involvement (2, 3). UV light can cause a deterioration of skin lesions as well as flares of systemic lupus erythematosus (SLE) (**Figures 1A,B**) (4). Histopathology of CLE lesions shows a perivascular and periadnexal lymphohistiocytic infiltrate and interface dermatitis at the dermo-epidermal border often associated with

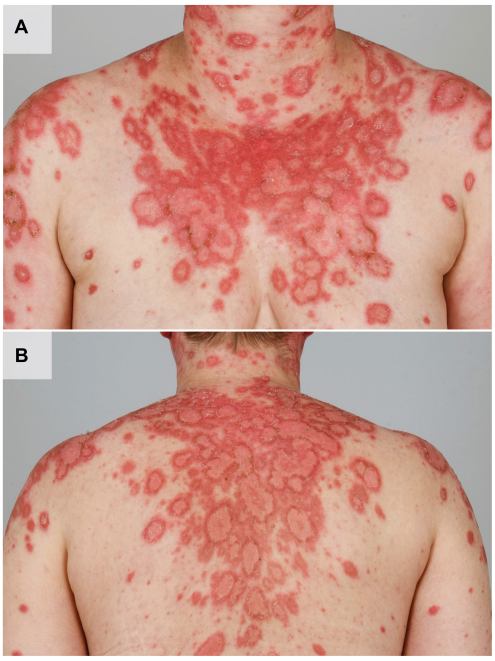

FIGURE 1
UV induced acute flare of subacute CLE in a female patient with SLE. The patient shows multiple disseminated erythematous, angular and scaly plaques in photodistributed areas such as the shoulders, upper arms, cleavage, neck **(A)** and the back **(B)**.

vacuolization of basal keratinocytes (3). Multiple immune cells are involved in the development of CLE lesions after UV irradiation and lead to further recruitment of the adaptive immune system *via* release of various mediators such as type I interferons (IFN). Recently, activation of type I IFNs after UV irradiation has been linked with activation of *cyclic GMP-AMP-synthase* (cGAS) (5). Upon T cell stimulation, B cells are recruited to the dermal compartment and produce autoantibodies. These autoantibodies are directed in particular against nucleic acids and nucleosome components, contributing to disease progression (3). UV light can also lead to increased antigen presentation and increased apoptosis in lupus erythematosus (LE) (6, 7). The cellular debris that develops after exposure to UV irradiation can accumulate and additionally lead to further immune stimulation (8). In this review, we illustrate the effects of UV light on the development of CLE.

Effects of ultraviolet irradiation on healthy skin

DNA damage and cell death

Ultraviolet irradiation represents electromagnetic irradiation characterized by shorter wavelengths than visible light (UVA = 400–320 nm; UVB = 320–280 nm; UVC = 280–100 nm). The uppermost boundary layer exposed to UV irradiation represents the epidermis consisting of several layers of keratinocytes, whose complex role in the pathogenesis of skin injury and development of cutaneous diseases has become increasingly appreciated (9). Whereas short wave UVB is not able to penetrate the epidermis, longer UVA waves reach the dermal compartment of the skin and contribute to photoaging *via* reactive oxygen species (ROS). UV irradiation can cause numerous ways of damage in cells such as DNA damage, impairment of DNA repair, changes in gene transcription and induction of cell death, depending on the wavelength and duration of exposure (10, 11). After absorption of UVB irradiation, direct DNA damage occurs resulting in cyclobutane pyrimidine dimers (CPDs) or pyrimidine-pyrimidone photoproducts (6-PPs) (11). CPDs represent cyclic DNA structures of two pyrimidine bases (such as thymine), which are induced in a dose-dependent manner by UV irradiation and contribute to UV-driven apoptosis, which is mediated by activation of the DNA damage response including p53. UV-driven apoptosis is mediated by caspases 9 and 3 *via* ROS and the release of cytochrome C (12–15). Indirect DNA damage occurs upon exposure to UV irradiation of all wavelengths *via* ROS, which can lead to oxidized bases (8-Oxo-2'-deoxyguanosine, 8-oxo-dG) and single-strand breaks (16, 17). As UV enhances the proportion of ROS *via* different mechanisms including alteration of catalase activity, upregulation of nitric oxide synthase and downregulation of protein kinase C, the cell is under oxidative stress (18). Enhanced oxidative stress further leads to altered signaling pathways or, to a lesser extent than CPDs, to apoptosis upon oxidation of different cellular structures such as the outer cell membrane (12). The DNA alterations induced by UV irradiation can either be repaired by different DNA repair mechanisms or result in apoptosis of the cell through blockage of transcription and replication (19). CPDs and 6-PPs are repaired by the nucleotide excision repair (NER) (**Figure 2**), and oxidative damage is repaired by base excision repair (BER) (12, 19). Once the DNA damage is fully repaired, the cell can continue to perform its original metabolic functions.

Inflammatory responses after ultraviolet in healthy skin

It is not completely understood how UV radiation influences the transcription of genes and recruitment or activation of immune cells in the skin. – Knowledge of whole-tissue responses to UV irradiation is mainly based on gene transcription studies on skin samples and functional analyses of skin cells. One earlier study evaluated the skin response 24 h after narrowband UVB irradiation – which is used in clinical phototherapy – in skin types II and III (20). A total amount of over 1,500 genes were

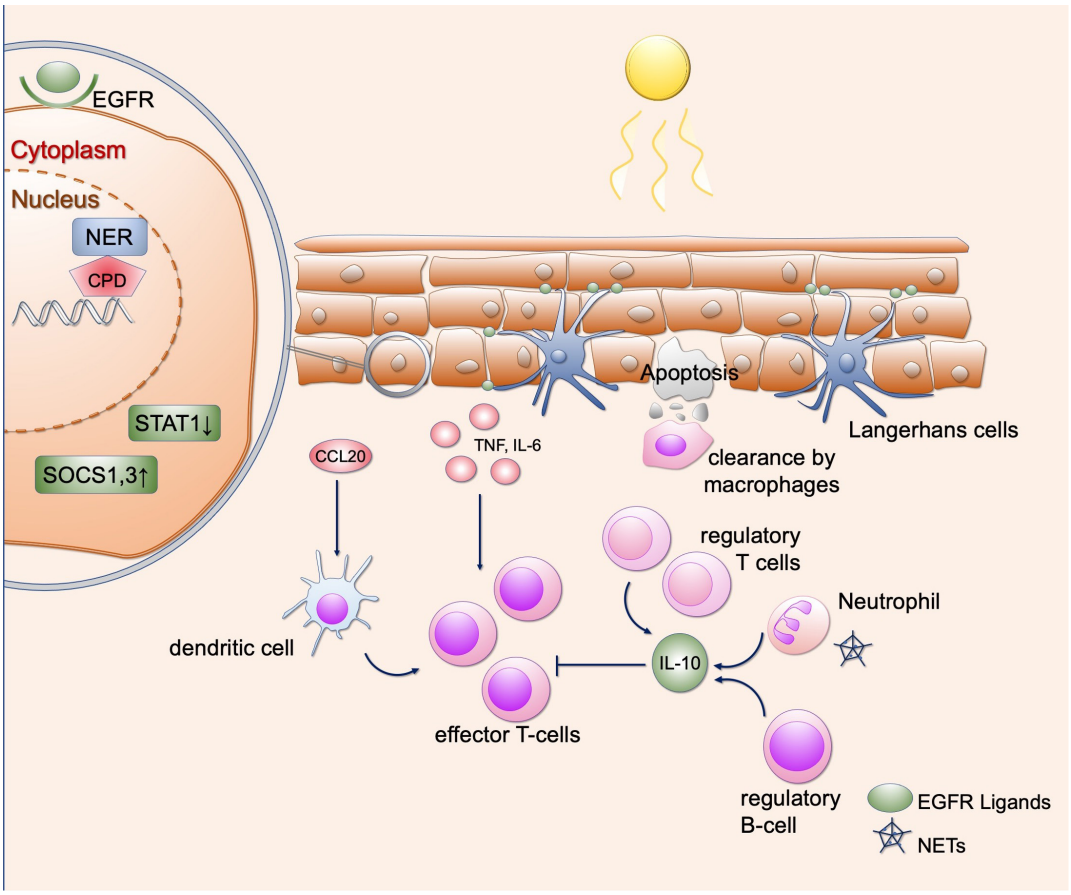

FIGURE 2
Effects of UV irradiation in healthy skin. Shown are various regulatory mechanisms of the skin that can occur as a result of UV radiation. UV causes DNA damage in keratinocytes, which is repaired by various repair mechanisms (here representing the NER). Furthermore, SOCS1 and SOCS3 as well as STAT1 are downregulated so that the response to cytokines is limited. EGFR ligands provided by Langerhans cells lead to epidermal hyperplasia, which in turn results in protection from further UV radiation. UV radiation further recruits various immune cells to the skin, including regulatory T and B cells and neutrophil granulocytes. These lead to an immunosuppressive environment via the secretion of IL-10. Proinflammatory cytokines and chemokines include CCL20, IL-6, and TNF-α, which can be released by keratinocytes. This causes recruitment of dendritic cells and T cells. In addition, neutrophil granulocytes can undergo NETosis after UV radiation, contributing to immune cell recruitment. This equilibrium of immunosuppressive and proinflammatory responses is necessary to maintain self-antigen tolerance. EGFR, epidermal growth factor receptor; NER, nucleotide excision repair; CPD, cyclobutane pyrimidine dimers; STAT1, signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling; IL, interleukin; CCL20, C-C motif chemokine ligand 20; TNF, tumor necrosis factor; NETs, neutrophil extracellular traps.

differentially expressed after UVB irradidation, among which were immune-modulating cytokines, chemokines, leukocyte surface markers and antimicrobial peptides (20).

Ultraviolet irradiation is used as treatment option in a number of chronic-inflammatory cutaneous diseases such as psoriasis and atopic dermatitis, which may be explained by context-dependent effects on cytokine secretion. In keratinocytes, UV irradiation leads to upregulation of *suppressor of cytokine signaling* (SOCS) 1 and 3 expression and downregulation of *signal transducer and activator of transcription* (STAT) 1 expression, which results in reduced responsiveness to IFN-γ (**Figure 2**) (21, 22). Thereby, UVB narrowband irradiation can downregulate inflammatory cytokines such as *Interleukin* (IL)-12, IL-23 and other IFN-γ-associated genes (23). Inflammatory responses to UV are well-known and can result in extensive sunburn after prolonged exposure. *In vitro* studies with keratinocytes treated with UVB irradiation revealed synthesis of inflammatory cytokines such as *tumor necrosis factor* (TNF)-α, IL-1α, IL-6, IL-8 and IL-10 (**Figure 2**) (24–27). Furthermore, dermal fibroblasts release TNF-α when exposed to UVB (28). After treatment by UVB irradiation and IL-1α, synergistic effects for TNF-α secretion were observed in fibroblasts and keratinocytes through enhanced gene transcription, suggesting that IL-1α released by surrounding immune cells may enhance the inflammatory response to UV light (29). Furthermore, the production of TNF-α is stimulated in keratinocytes by the damage of non-coding RNA sequences, which are

subsequently recognized by *toll-like receptor* (TLR) 3 (30). Thereafter, TNF-α is secreted in a *Toll/IL-1R domain-containing adaptor-inducing IFN*-β (TRIF)-dependent manner (30). After photoprovocation, certain nucleosome subunits as well as small nuclear ribonucleoproteins were upregulated, which are known as autoantigens in SLE (31). This shows that expression of autoantigens also occurs in healthy skin after UV light exposure (31). It should be noted that in the latter mentioned study, all samples were taken from female patients, so that a gender biases in transcriptomic changes after UV cannot be excluded.

With regard to immune cells, it has been shown that UV irradiation can result in an immunosuppressive environment. Neutrophils migrate into the skin after UV exposure and maintain an immunosuppressive environment *via* the secretion of IL-10 (**Figure 2**) (32). Regulatory B cells may be recruited by IL-10, which can inhibit a dendritic-cell-induced T cell response (**Figure 2**) (33). However, ROS-dependent induction of human neutrophil extracellular traps (NET) was reported after UV irradiation treatment *in vitro* (34). NETs can activate the immune system *via* intracellular *cyclic GMP-AMP synthase* (cGAS), resulting in type I IFN secretion (35) and thereby promoting a proinflammatory environment.

In T cells, many regulatory mechanisms in the skin after UV irradiation were identified: On the one hand, UV irradiation induces recruitment of $CD4^+$, $CD25^+$ regulatory T cells, which secrete IL-10 and contribute to an immunosuppressive environment (**Figure 2**) (36). Moreover, UV irradiation can lead to polarization of skin resident T cells to IL-17 secreting cells *via* extracellular ATP released by keratinocytes: It has been shown that extracellular ATP in increased by UV radiation. After addition of medium of irradiated keratinocytes on T cells, stimulation of IL-17 production was observed (37). This is mediated by ATP, which after binding to P2×7 receptor leads to the release of IL-1 *via* activation of caspase 1. IL-1 further stimulates IL-17 production in T cells (37). Moreover, different subtypes of CD11c + dendritic cells were shown to be present after UV exposure to narrowband-UVB irradiation (20). The authors identified upregulation of certain chemokines such as CCL20 and CCL2, which are able to recruit dendritic cells and T cells into the skin (20). In summary, context-dependent T cell recruitment occurs after UV irradiation, which may result in an immunosuppressive or proinflammatory environment.

Langerhans cells also play a role in mediating the effects of UV light and limit damage to keratinocytes. They express ADAM17, which is induced after UV irradiation (38). This results in secretion of epidermal growth factors receptor (EGFR) ligands by Langerhans cells, further leading to epidermal hyperplasia, which protects against subsequent UV exposure (**Figure 2**) (38).

As outlined above, the effects of UV light in healthy skin are not exclusively immunosuppressive, but show an interplay of proinflammatory and immunosuppressive cytokines and cell populations. In patients with photosensitivity, as in CLE, the uncontrolled inflammatory response to UV occurs because of numerous mechanisms, which are detailed below.

Lupus erythematosus – mediators of disease

Lupus erythematosus (LE) is a complex autoimmune disease where a combination of genetic susceptibility and promoting environmental factors results in disease exacerbation (39–41). Multiple cytokines such as type I IFN, IL-6 and TNF-α and chemokines such as CXCL10 are involved in the pathogenesis of LE (3, 39, 42). CLE lesions have a strong type I IFN signature and the level of IFN-induced genes correlates with disease activity of SLE (43, 44). Nucleic acids represent potential ligands for type I interferon release that can be recognized by pattern recognition receptors (45). Accumulation of nucleic acids may be caused by a deficiency of nucleases, some of which have been identified as genetic susceptibility genes in LE (45). In addition to type I IFN, impairment in the opsonization of apoptotic cells have been detected in SLE patients (46). Furthermore, numerous immune cells such as myeloid and plasmacytoid dendritic cells, macrophages and T cells are involved in the pathogenesis of CLE and their functions have been studied after UV radiation (39). In the subsequent sections, mechanisms of photosensitivity in lupus are explained in more detail.

Effects of ultraviolet irradiation in the development of lupus erythematosus

Presentation of autoantigens

After exposure to UV irradiation, the localization of certain proteins in the cell changes. These may eventually be recognized as autoantigens as it was shown for the ribonucleoproteins Ro/SS-A and La/SS-B. After UV radiation, these autoantigens are translocated to the outer cell membrane of apoptotic keratinocytes (**Figure 3**) and can subsequently be bound by antibodies, thus forming immune complexes (6, 47, 48). After exposure to UV radiation, these two antigens become oxidized autoantigens through increased generation of ROS, which in turn increase immunogenicity (49, 50). The influence of TNF-α can also increase the surface expression of Ro52/SS-A and La/SS-B on keratinocytes (51). Expression analysis of Ro52 after UV irradiation showed increase in CLE and other inflammatory skin diseases such as psoriasis, lichen planus and atopic dermatitis (52). Increased expression of Ro52 after UV irradiation may be favored by type I IFN and oxidative stress (53). Furthermore, expression of Ro52 is enhanced by the influence of TNF-α, which itself can also be induced by UV

irradiation (54). Evidence to date regarding the translocation of Ro/SSA indicates that this is most likely due to oxidative stress (49). Concerning La/SS-B, recent evidence showed that the translocation from the nucleus to the cytosol is due to redox-dependent conformational changes of La, which can be induced by UV irradiation and is cell-type specific (55). Nevertheless, the exact cellular circumstances under which Ro/SSA and La/SSB presentation at the cell surface arises and how this may be influenced are not fully understood. Ro/SS-A and La/SS-B antibodies are frequently detectable in subacute cutaneous lupus erythematosus (SCLE) and SLE and are also associated with increased photosensitivity (3). These antibodies were initially described in patients with Sjögren's syndrome, and this patient population also exhibits photosensitivity to some extent (56). This is also described for other antigens such as Sm, RNP and Ku, which are also detectable in SLE (57). Once the autoantigen is bound by antibodies, plasmacytoid dendritic cells as well as B cells can be activated or expanded by the formation of immune complexes (58). Therefore, changing of the cellular localization of autoantigens may cause both increased presentation and increased binding to antibodies.

Increased apoptosis and reduced clearance of apoptotic cells

In healthy skin, elimination of apoptotic cells that develop after UV radiation is realized by phagocytes to engulf the cell debris by phosphatidylserine-dependent efferocytosis (59). This elimination together with an anti-inflammatory environment, consisting of secreted TGFβ and IL-10, ensures that self-tolerance remains active (**Figure 2**) (60). Phagocytes recognize membrane components as well as antigens bound by antibodies. The remaining nucleic acids are eliminated by nucleases such as DNase1 (8, 60, 61). However, the capacity of phagocytes is limited and their function of removing apoptotic cells may be impaired, resulting in enhanced amount of autoantigens which can be presented to immune cells (60). In lupus, the number of apoptotic cells measured by TdT-mediated dUTP-biotin nick end labeling (TUNEL)-staining and activated Caspase 3 is already increased in CLE patients without irradiation (7, 62). After UV irradiation, the epidermis of various subtypes of CLE exhibits significantly increased apoptotic cells compared to healthy controls (**Figure 3**) (7). This higher rate of apoptotic cells persists over time, while healthy controls show reduced numbers of apoptotic cells over time, suggesting a delayed clearance in CLE (7, 8). The number of epidermal apoptotic cells was highest in the UVB irradiated population, suggesting a proapoptotic effect by enhanced CPD formation. In addition, epidermal expression of CD95 was found to be increased, suggesting enhanced extrinsic apoptotic pathway (62).

In SLE patients, a deficit in phagocyte function of macrophages derived from monocytes was demonstrated in earlier reports. *In vitro* macrophages differentiated from SLE patients and incubated in patient serum showed reduced and delayed engulfment of autologous apoptotic components compared to controls (**Figure 3**) (46). However, an intrinsic abnormality in monocyte derived macrophages from lupus patients was not found, as the phagocytosis capacity between patients and controls was not altered with normal human serum (46). Reduced clearance was associated with lower serum levels of complement components (C1q, C3, and C4) (46). In line with this, increased photosensitivity has been reported in patients with complement deficiency of C4A and C2 (63, 64). Furthermore, CD44, an important signaling molecule of the clearance process, was found to be decreased in SLE phagocytes (65). Due to the decreased uptake of apoptotic material, apoptotic components such as nucleosomes can be presented as antigens and stimulate antibody formation by autoreactive B cells. These antibodies (for example anti-double strand (ds)DNA, anti-nucleosomeal, and anti-histone antibodies) are found in numerous patients with LE (3). Apoptotic cells can, when not engulfed by phagocytes, undergo secondary necrosis (8). Cell material derived from secondary necrosis, may increase immunogenicity *via* post-translational modifications (8).

Another mechanism of cell death represents necroptosis, which was shown to be associated with interface dermatitis, a common histopathologic feature in CLE and other inflammatory skin conditions such as lichen planus (66). Whether UV irradiation can enhance necroptotic cell death in lupus keratinocytes has not been shown so far.

DNA damage, nucleic acid metabolism and type I interferons

As mentioned above, UV irradiation induces DNA damage in a dose-dependent manner. DNA damage itself may contribute to the pathogenesis of LE, as explained by the example of oxidative DNA damage. Oxidized bases such as 8-oxo-dG represent a consequence of UV-mediated damage through ROS induction (12). This damage is normally eliminated by base excision repair (BER) (19). An initial enzyme of BER represents Oxoguanine glycosylase 1 (OGG1) (19). Interestingly, defects in OGG1 increase IFN expression as well as cutaneous inflammation including alopecia in a murine lupus model (67). In addition, decreased expression of this enzyme has been demonstrated in discoid LE (67). To further understand the role of DNA damage in photosensitivity, it might be helpful to take a look at DNA damage syndromes such as Xeroderma pigmentosum, Bloom syndrome or ataxia telangiectasia. These syndromes are caused by defects in proteins of the DNA repair apparatus, and patients can also exhibit enhanced photosensitivity (68–70). Furthermore, some of these DNA damage syndromes exhibit autoimmune phenotypes such as ataxia telangiectasia, where

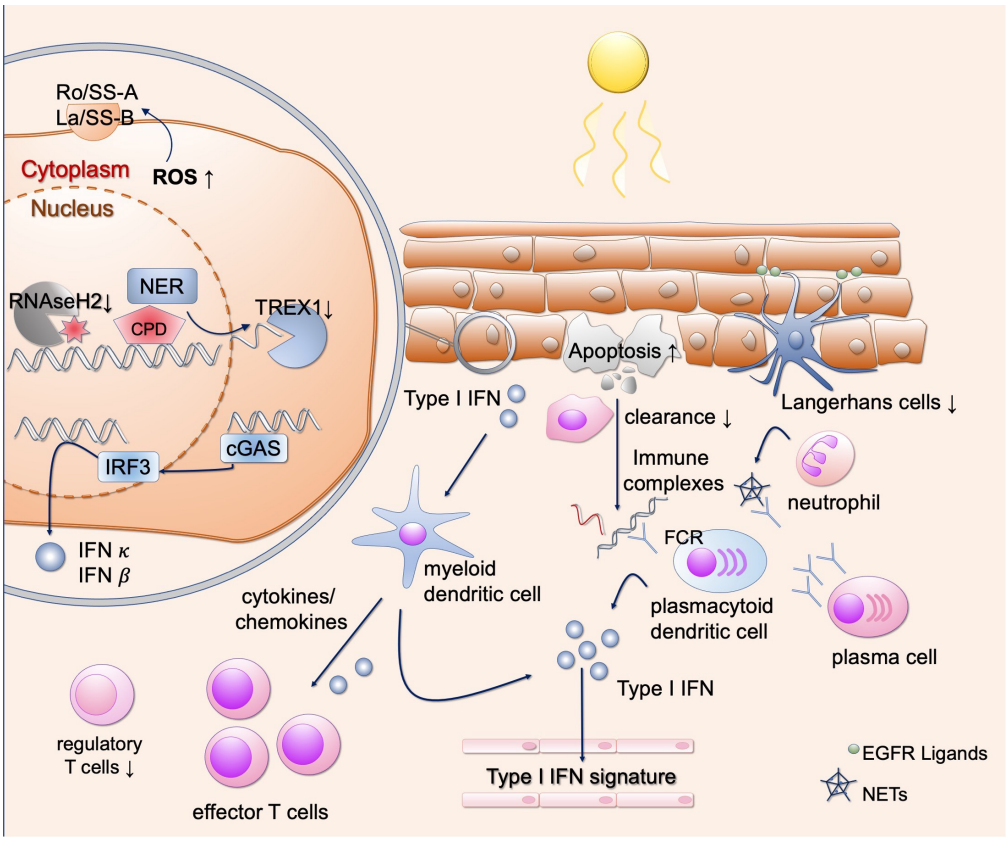

FIGURE 3
Different mechanisms of photosensitivity in lupus. Upon UV-light, enhanced apoptosis occurs in lupus patients. These apoptotic cells are incompletely engulfed by phagocytes, resulting in secondary necrosis and immune complex formation after binding to autoantibodies. This results in Fc-dependent production of type I IFN, contributing to the interferon signature in blood in lupus patients. Keratinocytes, present autoantigens such as Ro/SSA on the outer surface after UV irradiation. They show DNA damage and enhanced ROS production after UV irradiation, inducing oxidated DNA which is resistant against TREX1-mediated degradation. Free nucleic acids induce cGAS activation and production of type I IFNs. Subsequently, different types of immune cells are recruited to the skin, further activating a strong T cell response. Langerhans cells produce EGFR ligands to protect keratinocytes from UV induced damage, but they are reduced in lupus skin. Neutrophils undergo NETosis after UV irradiation, contributing to the development of immune complexes. EGFR, epidermal growth factor receptor; ROS, reactive oxygen species; NER, nucleotide excision repair; CPD, cyclobutane pyrimidine dimers; TREX1, three prime exonuclease 1; cGAS, cyclic GMP-AMP synthase; IFN, interferon; IRF3, interferon regulatory factor 3; FCR, Fc receptor; NETs, neutrophil extracellular traps.

rheumatoid arthritis and the development of autoantibodies were described (71–73). How DNA damage can lead to secretion of cytokines (in particular type I IFN) has been studied in ataxia telangiectasia. A defect in the ataxia-telangiectasia mutated (ATM) gene results in increased activation of the DNA damage response, mainly in the presence of DNA double-strand breaks, induced by genotoxic stress (71). During the repair of DNA double-strand breaks, single-stranded DNA is initially excised (*end resection*) (19). It was shown that in the case of ATM deficiency, single-stranded DNA accumulates in the cytosol and activates the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) (71). Subsequently, signaling of cGAMP *via* interferon regulatory factor (IRF) 3 leads to the release of proinflammatory cytokines (71). The release of type I IFN after DNA damage has been described in different cutaneous DNA damage syndromes (74). Also in lupus, the effects of UV irradiation on type I IFN activation has been investigated.

In healthy murine cells, UV irradiation was able to activate cGAS and the stimulator of interferon genes (STING) and also induce a neutrophil-dependent kidney inflammation (5, 75). The substrate of cGAS activation was not specifically identified in the latter study. But these findings could potentially explain the link between photosensitivity and lupus nephritis. cGAS represents an important mediator and eventually a therapeutic target for photosensitivity (**Figure 3**). The downstream signaling of this protein will further be discussed below.

Cyclic GMP-AMP synthase represents a cytosolic enzyme and is activated by free cytosolic nucleic acids (76–78). However, under steady state conditions, the nucleus together with the nucleic acids is well-separated from cytosolic cGAS. Furthermore, various intra- and extracellular nucleases prevent

endogenous nucleic acids from being recognized by DNA and RNA sensors (79). If defects in nucleases occur or the concentration of cellular nucleic acids increases, recognition of these endogenous nucleic acids may occur. As mentioned above, defects of the extracellular exonuclease DNAse1 as well as the intracellular exonuclease three prime exonuclease 1 (TREX1) have been described in various forms of lupus (**Figure 3**) (80–82).

After double-stranded DNA or single-stranded DNA with stem loop, is recognized by cGAS, cyclic GMP-AMP (cGAMP) is produced (76). cGAMP can activate STING as a second messenger (**Figure 3**), which stimulates Tank binding kinase 1 (TBK1) and IRF 3 as well as inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) (83). IRF3 acts as a transcription factor on the expression of type I IFN, which binds in an autocrine and paracrine manner to the IFN-α receptor (IFNAR) (42). Activation of NF-κB results in the release of other proinflammatory cytokines (84). Interestingly, oxidative DNA damage (8-oxo-dG as described above) is resistant to TREX1 degradation, thereby potentiating STING-mediated inflammation (**Figure 3**) (85). The sources of cytosolic DNA may consist of excised DNA strands during DNA repair, reduction of DNA binding proteins in the nucleus, viral or mitochondrial DNA, micronuclei and senescent cells (86).

It has been shown that in murine cells, type I IFN increases both locally and systemically after exposure to UV irradiation (5). By inhibiting the hydrolysis of cGAMP, the UV-induced release of type I IFN is enhanced (5). Furthermore, UV irradiation-induced IL-1β expression was shown to be cGAS-dependent. However, the production of TNF-α and IL-6 was not dependent on cGAS in murine cells after UV irradiation (5). Increased immune cell infiltrates consisting of neutrophils, monocytes, and γ/δ + T cells were detected after UV irradiation, which infiltrate the skin in a cGAS-dependent manner, in a murine model of skin inflammation. In cGAS-deficient mice, less CCL2 chemokine expression was detected after UV irradiation, which may explain the infiltration of monocytes and T cells in wild type mice (5). cGAS-dependent photosensitivity was recently shown in human TREX1- deficient cells from patients with lupus (87). Here, activation of cGAS with subsequent release of type I IFNs also occurred after UV light (87). The authors revealed enhanced CPD formation after UV irradiation due to TREX1 deficiency. This is caused by enhanced ssDNA fragments within the cell, which are more susceptible for CPD formation after UV irradiation (87). Recently, it has been shown that CPDs are released in extracellular vesicles of keratinocytes in a caspase-dependent manner after UVB-radiation (88). Whether these structures activate STING downstream and if these extracellular vesicles are altered in CLE remains a target of research. A potential source of cGAS activation represent DNA fragments which occur in the cytosol during DNA repair and replication (89). This was recently shown in another study which revealed that during NER small oligonucleotides are released, which are then degraded by TREX1 at the 3′end in HeLa cells (90). Nevertheless, it should be noted that TREX1 deficiency plays a role only in some forms of CLE and the mechanisms of photosensitivity seem to be more complex. Whether exclusively cGAS and STING are induced after UV irradiation in lupus is currently not clear. The involvement of other nucleic acid sensors such as retinoic acid inducible gene 1 (RIG1) in mediating UV-induced inflammation in CLE has not yet been elucidated in detail and needs further investigation.

In SLE, apoptosis-derived membrane vesicles containing dsDNA could be identified as ligands cGAS activation. These were increased in the serum of the patients and contained significantly more dsDNA, which can activate cGAS (91). Whether the UV-induced activation of skin cGAS is also caused by apoptosis-derived membrane vesicles is not fully understood and requires further experiments.

Epidermal derived IFN-κ additionally acts as an important cytokine in the pathogenesis of CLE and SLE and is induced by UV irradiation (**Figure 3**) (92). IFN-κ drives a proinflammatory response of keratinocytes with recruitment of immune cells to the skin, which may contribute to the cellular infiltrate observed histologically in lupus skin (92). Additionally, IFN-κ enhances signaling of other type I IFNs such as IFN-α, suggesting a priming of human keratinocytes. Specific inhibition of IFN-κ reduces the effects of other type I IFNs, making it a potential therapeutic target in CLE and SLE (92). How exactly UV light stimulates IFN-κ secretion and which signaling pathways are involved, warrants further investigation.

Another risk factor for the development of SLE is a mutation in the ribonuclease RNaseH2 (**Figure 3**) (93). This enzyme removes ribonucleotides from DNA during replication events (94). It has been shown that a lack of removal of ribonucleotides favors the development of CPDs and leads to an activation of type I IFN after UV radiation (93). It is still unclear whether the CPDs themselves or the following DNA damage response lead to type I IFN activation.

Taken together, several genetic alterations can lead to different forms of LE with increased photosensitivity. The exploration of genetic alterations on a cellular level has unraveled mechanisms of photosensitivity.

Immune cell recruitment

Besides abnormal cytokine release after exposure to UV irradiation, the production of chemokines plays a substantial role in the recruitment of immune cells in lupus patients. As outlined above, UV irradiation triggers the secretion of proinflammatory cytokines such as TNF-α, IL-1, IL-6 (95). Moreover, after solar simulated irradiation, the UV-induced

type I IFN response in the skin elicits the secretion of Th1-associated chemokines such as CXCL9, CXCL10, and CXCL11 in T cells, which contribute to the further recruitment of T cells (**Figure 3**) (95, 96). The secretion of chemokines such as CCL5 and CCL8 is promoted, resulting in skin inflammation. These cytokines are found to be differentially expressed in CLE (95). Furthermore, CCL27, is upregulated after stimulation by TNF-α and IL-1β, resulting in CCR10-dependent T cell recruitment (95, 97). In line with this, histopathology of lupus lesions specifically shows a T-cell dominated inflammatory cell infiltrate at the dermo-epidermal junction zone. In addition, increased expression of the adhesion molecule ICAM-1 was detected in dermal endothelia after UV irradiation in lupus erythematosus tumidus, CDLE and SCLE, supporting recruitment of immune cells after tissue injury induced by UV radiation (98). UV light is considered to be a trigger of interface dermatitis in the context of photoprovocation. Interestingly, regulatory T cells are decreased in CLE (99). This is mediated by type I IFN-dependent suppression of regulatory T cells and upregulation of effector T cells which are induced by UVB in lupus-prone mice (**Figure 3**) (100). This indicates that UV irradiation dysregulates the T cell response in CLE. An enhanced effector T cell response also results from the production of cytokines and the presentation of autoantigens, both of which are increased after UV irradiation, as described above.

In mice, monocytes were identified as a source of type I IFN production after UV irradiation (101). This type I IFN production is mediated by colony stimulating factor (CSF)-1, which is produced by keratinocytes, resulting in phagocyte infiltration in the skin and development of CLE-lesions (102). Importantly, infiltration of monocytes after UV irradiation is correlated with type I IFN gene expression, highlighting the role of monocytes in the UV-driven immunopathogenesis of lupus lesions in SLE patients (103). Another source of type I IFN in the development of lupus lesions represent plasmacytoid dendritic cells (pDCs), which are enriched in subtypes of CLE (104). pDCs are able to sense immune complexes containing dsDNA by toll-like receptor (TLR) 9, subsequently leading to type I IFN production (**Figure 3**) (105). Furthermore, modified mitochondrial DNA, generated after exposure to mitochondrial stress and enhanced ROS production, is able to activate pDCs and induce IFN secretion (106, 107). Oxidized mtDNA is enriched in neutrophil extracellular traps of SLE patients and mitochondrial ROS contributes to lupus-like disease in mice (108). Mitochondrial components such as mtDNA and mtRNA can activate specific cytosolic nucleic acid sensors such as cGAS (mtDNA) and thus contribute to UV-mediated inflammation (109). Currently, it is unclear to what extent UV irradiation contributes to the generation of oxidized mitochondrial nucleic acids in the epidermis and whether their recognition results in increased production of type I IFNs. Hence, mitochondrial stress responses after UV irradiation need further investigation.

Neutrophils appear in UV-irradiated skin and contribute to an immunosuppressive environment through secretion of IL-10. They undergo NETosis after UV irradiation and thereby contribute to immune complex formation (8, 34). Neutrophil activation and subsequent cGAS-dependent neutrophil infiltration of the skin and kidney is IL-17-dependent (75). It is unclear which conditions are necessary for neutrophils to produce IL-10 in a limited manner, paving the way for increased inflammation after UV irradiation.

B cells are also involved in the pathogenesis of LE *via* differentiation to plasma cells and production of autoantibodies (**Figure 3**) (3). However, the extent to which B cells are directly involved in mechanisms of photosensitivity of lupus patients is poorly understood. Different B cell signatures have been detected in different subtypes of CLE, and it remains intriguing to what extent UV induces or influences this signature (110). Mast cells represent another component of the cutaneous immune system, and their function is particularly important in IgE-mediated diseases (111). However, mast cells also proliferate in lupus lesions after UV irradiation (112). These cells are producers of matrix metalloproteinases (MMPs), which are involved in UV-induced cellular aging (112, 113). Increased levels of MMP-2 and MMP-9 could be detected in lupus patients and also correlated with disease activity (114). However, how exactly MMPs contribute to the inflammatory response in CLE warrants further investigation.

Perspective

As described above, the various mechanisms that contribute to photosensitivity in LE are manifold. Based on this knowledge, the question arises of how to interfere therapeutically with these mechanism to either prevent or treat this disease. Continuous photoprotection is essential for lupus patients (115). A particular target in LE is the type I IFN pathway and its individual regulating factors. Anifrolumab, an antibody directed against IFNAR, was recently approved for the treatment of SLE and also showed efficacy in cutaneous lesions (116, 117). Furthermore, inhibitors of blood dendritic cell antigen 2 (BDCA2), a C-type lectin, and a number of other compounds are currently tested in in clinical trials and show promise in interfering with the pathogenesis of LE and photosensitivity (117). Currently, a study of the JAK inhibitor tofacitinib is being conducted to investigate photosensitivity in lupus patients before and after therapy (NCT05048238, clinicaltrials.gov). With positive results, a milestone for the therapy of lupus patients with photosensitivity could be created. Since cGAS is a key mediator in the effects of UV light (5, 87), exploration of the mechanisms of the cGAS-STING pathway will lead us to better understanding of photosensitivity in lupus. Recently, R-loop structures have been identified in the context of genomic instability and represent a potential source of cGAS

activation (118). In Escherichia coli, R-loop structures occurred significantly higher after UV, highlighting their potential role in UV mediated stress responses (119). Hence, the inhibition of cGAS may also have beneficial effects on photosensitivity. The discovery of human-cGAS-specific small-molecule inhibitors such as G108, G140 and G150 has been recently reported based on high-throughput drug screenings (120). These substances require further clinical testing and may be of benefit for patients suffering from photosensitivity.

Taken together, the pathogenic mechanisms of lupus photosensitivity have been a focus of research in recent years. The major findings of these investigations have not only led to a better understanding of lupus pathogenesis but also to a translation into early clinical trials.

Author contributions

BK had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Both authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Robert Gniadecki,
University of Alberta, Canada

REVIEWED BY
Serena Bergamo,
ULSS2 Marca Trevigiana, Italy
Priscila Giavedoni,
Hospital Clinic of Barcelona, Spain

*CORRESPONDENCE
Alice Verdelli
alice.verdelli@hotmail.it

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An update on the management of refractory cutaneous lupus erythematosus

Alice Verdelli[1]*, Alberto Corrà[2], Elena Biancamaria Mariotti[2], Cristina Aimo[2], Valentina Ruffo di Calabria[2], Walter Volpi[1], Lavinia Quintarelli[3] and Marzia Caproni[3]

[1]Section of Dermatology, Azienda USL Toscana Centro, Florence, Italy, [2]Section of Dermatology, University of Florence, Florence, Italy, [3]Rare Dermatological Diseases Unit, Department of Health Sciences, Azienda USL Toscana Centro, University of Florence, Florence, Italy

Management of cutaneous lupus erythematosus (CLE) involves a combination of preventive measures, topical and systemic drugs, fairly similar for the different subtypes. Although guidelines exist, to date, no specific drugs have been specifically licensed for CLE. Antimalarials remain the first-line systemic treatment, but many patients do not respond, making refractory lupus a challenge for clinicians. The choice of alternative medication should be based on effectiveness, safety and cost. Most of the available drugs for CLE have been adapted from systemic lupus erythematosus (SLE) treatment but the existing literature is limited to small studies and evidence often lacks. As knowledge of pathogenesis of both CLE and SLE is improving, promising new therapies are emerging. In this review, we discuss the available medications, focusing on the novelties under development for CLE.

KEYWORDS

cutaneous lupus erythematosus (CLE), management, anifrolumab, refractory, belimumab, rituximab, JAK inhibitors, therapy

Introduction

Cutaneous lupus erythematosus (CLE) is a chronic, autoimmune, inflammatory disease comprising several subtypes, e.g., acute CLE (ACLE), subacute CLE (SCLE), chronic CLE (CCLE) and intermittent CLE (ICLE) (1). CLE can be isolated or associated to a systemic involvement. Up to 70–80% of patients with systemic LE (SLE) develop muco-cutaneous lesions during the course of the disease and up to 25% of patients with systemic LE (SLE) show muco-cutaneous involvement at diagnosis (2, 3). Thus, a systemic involvement should always be assessed at diagnosis and at follow-up (4).

To monitor CLE progression and treatment response, two scores have been validated, e.g., the *Cutaneous Lupus Erythematosus Disease Area and Severity Index* (CLASI) and, more recently, the *Revised CLASI* (RCLASI), which are able to provide disease activity (CLASI-A) and damage (CLASI-D) in CLE patients (5, 6).

According to current guidelines (7–9), management of CLE involves a combination of topical and systemic drugs, fairly similar for the different subtypes. Although consensus over the treatment and guidelines have been succeeded over the years, to date, no specific drugs have been approved by the *Food and Drug Administration* (FDA). Most of the medications for CLE have been adapted from SLE treatment but the existing literature is limited to small studies and evidence often lacks. As drugs that have proven to be effective in systemic disease may not be effective in cutaneous disease, the treatment of refractory CLE is particularly challenging, as it is difficult to achieve a consensus on the appropriate progression of treatment beyond first- and second-line treatment options. Moreover, since many of these treatments are immunosuppressants, with possible side effects, a thoughtful approach is mandatory in order to better select the most appropriate drug (10).

General recommendations include sun protection, smoking cessation and vitamin D implementation as well as withdrawal of photosensitizing drugs and avoidance of isomorphic trigger factors (9, 11–13). Female patients are also recommended to avoid hormonal contraception containing estrogens and estrogen replacement therapies. These measures are crucial to prevent refractory CLE. In fact, studies on the photoprotective habits of lupus patients have shown an increased frequency of sunscreen utilization during years (14, 15). However, not all patients with CLE use daily sun protection, not all apply the right dose and not all re-apply sunscreen during the day. Yang et al. found that especially males, patients with dark Fitzpatrick skin types, and patients between the ages of 31–50 use less frequently sun protection than necessary (16). Accordingly, active smoking has been associated with CLE severity, with a lower risk of long-term CLE remission (17). Although it is known that it decreases the efficacy of systemic treatment, the impact of tobacco on the efficacy of antimalarials may be caused by an increase in the severity of the disease more than by resistance in smokers (18).

Topical corticosteroids remain the first-line treatment of all CLE subtypes, both in localized and widespread form (7–9). They should be applied for a short time or intermittently to reduce side effects, such as atrophy, telangiectasia and steroid-induced dermatitis. Alternatively, as first-line or second-line topical treatment, calcineurin inhibitors (0.03% or 0.1% tacrolimus and 0.1% pimecrolimus ointment) could be used, showing a better safety profile and low side effects, especially in active, edematous CLE of the face. Topical retinoids could be considered as second-line treatment in verrucous LE and other hyperkeratotic lesions of CLE, especially in cases refractory to topical corticosteroids or topical calcineurin inhibitors.

The first-line systemic treatment for all types of CLE includes antimalarials, namely hydroxychloroquine (HCQ), chloroquine (CQ) and quinacrine (Q), with HCQ being the most studied and used agent even in pregnancy and pediatric patients. However, long-term use (i.e., $\geq$ 5 years) and high-dose HCQ (i.e., $>$ 5 mg/kg/day) are both risk factors for the development of HCQ retinopathy (19). Accordingly, dose should be calculated on body weight with a maximum daily dose of 5 mg/kg of real bodyweight for HCQ and 2.3 mg/kg of real bodyweight for CQ to reduce side effects. However, in contrast with current guidelines, a recent survey demonstrated that about 70% of patients uses a fixed dose of antimalarials independent of the patient's weight. In both Europe and the USA, HCQ is often prescribed as 200 mg film-coated tablets, while 100 mg HCQ tablets are available in China, not yet approved by the US FDA. The most commonly reported daily dose of HCQ was 400 mg. An inappropriate dose of antimalarials could be one of the reasons for refractory skin manifestations (19). Antimalarials are also burdened by low therapeutic adherence (20–22), especially in younger patients and in patients not convinced of the efficacy of antimalarials in the management of their disease (19). In fact, 17.3% of CLE patients skip HCQ once a week or more often. Non-adherence to HCQ could potentially lower the risk of retinopathy in the individual patient but has been associated with an increased risk of flares and may partly explain cases of refractory CLE. Thus, in case of refractory CLE should be evaluated the adherence and eventually, dosed HCQ blood levels. The need for alternative therapies in refractory CLE has been also emphasized by the limited access to quinacrine that in recent years has restricted its combination with HCQ and CQ.

In case of refractory CLE, Q could be added either to HCQ and CQ with good results, whereas the combination of HCQ and CQ should be avoid because of the risk of irreversible retinopathy. In addition, systemic corticosteroids are recommended as first-line treatment in highly active and/or severe CLE. They should be used for short periods, gradually tapering until withdrawal, to reduce corticosteroids-associated side effects (7–9).

Second- and third-line systemic treatments include immunosuppressants and immunomodulants. Over the last years, increasing knowledges in the pathogenesis of CLE and SLE also led to several new therapeutic options, such as B-cell- or interferon (IFN) α-targeted agents. Herein we reported a review on the current drugs available for refractory CLE.

Immunosuppressants and immunomodulants

Systemic corticosteroids are recommended as first-line treatment in highly active and/or severe CLE. Recommended second and third-line systemic immunosuppressant treatments for CLE include methotrexate (MTX), dapsone, systemic retinoids, mycophenolate mofetil and thalidomide/lenalidomide. Herein, we reported the recommended dose and summarized the evidence of efficacy.

Systemic corticosteroids

Systemic corticosteroids are recommended as first-line treatment in highly active and/or severe CLE, in addition to antimalarials. The usual oral dose of systemic corticosteroids is 0.5–1 mg/kg bodyweight per day for about 2–4 weeks followed by tapering of the dose to a minimum (≤7.5 mg/day) with the aim to discontinue the application. During pregnancy or breastfeeding systemic corticosteroids (prednisone and methylprednisolone) should be given in a dose of not more than 10–15 mg per day (9).

Systemic corticosteroids are generally avoided in CLE patients due to the well-known side effects. However, in addition to antimalarials, they are recommended as first-line treatment in highly active and/or severe CLE (8, 9). Besides being beneficial in association to other therapies that may require time for onset of action, in a prospective, cross-sectional, multicenter study performed by EUSCLE, systemic corticosteroids showed the highest efficacy in comparison with all other systemic drugs used for CLE therapy, providing to be effective in 94.3% of the 413 treated patients. Moreover, systemic corticosteroids were most frequently (in 58.1%) and most successfully (in 96.8%) applied in cases of ACLE, probably due to the frequent association with SLE. The usual oral dose of systemic corticosteroids is 0.5–1 mg/kg bodyweight per day for about 2–4 weeks followed by tapering of the dose to a minimum (≤7.5 mg/day) with the aim to discontinue the application to avoid side-effects. In fact, LE patients are particularly susceptible to the side effects of steroids, as they are at increased risk of developing avascular necrosis at baseline (23). The continuation of treatment with antimalarials or other corticosteroids-sparing agents is recommended during the tapering and after discontinuation of systemic corticosteroids. Moreover, to reduce the risk of corticosteroids-associated side-effects, it is recommended to avoid long-term maintenance treatment with corticosteroids in CLE patients without systemic involvement. Systemic corticosteroids are also administered in association to rituximab ($2 \times 1{,}000$ mg/m^2 IV rituximab in combination with 100 mg IV methylprednisolone at an interval of 2 weeks) in patients resistant to other therapeutic agents, such as antimalarials, thalidomide, immunosuppressive drugs, and high-dose of intravenous immune-globulin (IVIg) (24).

Methotrexate

MTX, up to 20 mg per week, is a second-line treatment for refractory CLE, preferably subcutaneously, and in addition to antimalarials. Folic acid at a dose of 5–10 mg/week, the day after MTX injection, should be added to reduce MTX side effects.

In a recent study on 73 patients with antimalarial-refractory CLE, MTX was found to be the second most effective alternative option after thalidomide, with fewer side effects, showing a partial or substantial resolution in 69% of the 19 treated patients (25).

In a retrospective study, 10 of the 12 analyzed patients with CLE receiving weekly administrations of 10–25 mg MTX showed significant improvements of their skin lesions within 6 weeks (26).

Another study of 43 patients with CLE, MTX, as both monotherapy and adjunctive therapy, resulted in significant improvement in activity of cutaneous lesions in 98% of patients, especially in SCLE (27). MTX was administered intravenously at initial 15–25 mg/weekly dose, then tapered to 7.5–1 5 mg/weekly in 8 patients and 10–20 mg/weekly in 7 patients. Severe side effects necessitating discontinuation of MTX treatment were recorded in seven patients (16%), solved after MTX discontinuation.

Both studies supported the use of low dose MTX for management in refractory patients.

In a retrospective study comparing MTX with MMF, MTX was successfully administrated in 72% of 18 SCLE patients and 46% of 13 DLE patient measured by CLASI improvement, with side effects reported by 28% of SCLE patients, among which nausea/diarrhea was the most common cause of discontinuation, and by 19% of DLE patients, with increased transaminases as the main cause of withdrawing (28).

Cyclosporine has been used in combination with MTX with good result and allowing lower dosing when used in combination (29).

A randomized controlled trial (RCT) study on 41 SLE patients with skin involvement comparing the efficacy and safety of MTX and CQ showed significant improvement in both groups, with no significant differences, demonstrating that low-dose MTX can be as effective as CQ (30).

Although CLE patients can benefit from MTX treatment, the drug can cause adverse sequelae, including hematologic, pulmonary, gastrointestinal, and hepatic side effects. Therefore, the drug should be administered under careful physician supervision (31).

Dapsone

Dapsone is the first-line treatment for bullous LE and a second-line treatment for refractory CLE, preferably in addition to antimalarials. Low dose treatment (50 mg daily) should be used with an increased to a maximum of 1.5 mg/kg daily based on clinical response and side effects, monitoring the glucose 6-phosphate dehydrogenase (G6PD).

The European League Against Rheumatism (EULAR) recommended dapsone, 100 mg daily, in SLE with skin lesions,

especially bullous manifestations, in non-responsive cases or cases requiring high-dose corticosteroids (32, 33).

Concerning CLE, dapsone seems to work especially on SCLE, DLE and lupus erythematosus panniculitis (LEP) (34–36).

Lindskov and Reymann treated 33 DLE patients with dapsone with satisfactory results in 48% of patients (37).

In a retrospective analysis, Klebes et al. analyzed 34 CLE patients treated with dapsone (median dose: 100 mg/day) as monotherapy or combined with antimalarials, for a mean duration of 16 months. Authors reported a complete remission in 18% ($n = 6$) of the patients and an improvement in 41% cases ($n = 14$) while in 18% ($n = 6$) patients the drug was ineffective. The best effect was seen in SCLE patients with either disease remission or improvement in 75% of the patients, similarly to other reports. Dapsone was discontinued in 4 cases due to reversible side effects and in 5 patients due to poor efficacy (38).

Coburn and Shuster treated 11 patients with DLE showing good result in 8 patients (39).

In a study by Ruzicka and Goerz on the effects of dapsone in 7 patients (4 with DLE and 3 with a widespread rash of SLE), SLE patients had remission of discoid lesions, oral lesions and urticarial vasculitis. However, 2 patients with SLE and generalized acute skin lesions as well as 1 patient with disseminated DLE remained unresponsive to dapsone (40). With a dapsone dose of 25 mg in combination with 500 mg vitamin C, Ruzicka and Goerz observed healing of DLE.

Successful treatment of LEP with dapsone was also seen in 11 cases. Disease remission was noted in all patients between 1 and 8 weeks (mean 4.6 weeks) (36).

Overall, the risk of dapsone-dependent side effects is very low. Dapsone is not recommended in patients with G6PD deficiency to avoid one of its severe side effects, hemolytic anemia, in these individuals. It is not recommended in individuals carrying the HLA-B*13:01 allele, which is associated to the development of dapsone hypersensitivity syndrome, a fatal side effects of this drug (41).

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a third-line option for refractory CLE in addition to antimalarials. Recommended starting dose is 500 mg × 2 daily, that can be increased up to 3 gr daily.

Mycophenolic acid (MPA) could be an alternative choice to MMF.

MMF has been shown to be effective in different CLE subtypes, in combination with HCQ and (or) systemic corticosteroids, in small series (28, 42–44).

A prospective, non-randomized, open pilot study assessed the efficacy of mycophenolate sodium, the enteric-coated form of MMF, in 10 patients with SCLE refractory to antimalarial therapy (45). Remarkable results with significant CLASI improvement were achieved with 1.440 mg/day MMF monotherapy for 3 months. No serious side effects were reported. A retrospective analysis of 24 patients with recalcitrant CLE showed some clinical response in all patients and resolution or near resolution of disease activity in 62% of patients (46). The average final dose of MMF was 2.750 mg/day. Therapy was well tolerated and the mean time to initial response was 2.76 months. The beneficial effects of MMF in combination with HQ are highlighted in a recent case series of three patients with recalcitrant CLE. Doses of MMF from 1,000 to 1,500 mg/day were effective within 5.6 weeks (47).

Azathioprine, cyclosporine, cyclophosphamide

Guidelines do not suggest azathioprine, cyclosporine and cyclophosphamide for CLE without systemic involvement, since few data are available in the literature with no control trials to support routine use in CLE (7–9).

Interestingly, azathioprine has proven good results in non-specific cutaneous LE manifestations, especially recalcitrant leukocytoclastic vasculitis (48).

Retinoids

Retinoids are a second-line treatment in selective CLE patients unresponsive to other treatment, especially hyperkeratotic lesions and verrucous LE, preferably in addition to antimalarials. The recommended daily dose of acitretin and isotretinoin in treatment for CLE is 0.2–1.0 mg/kg body weight. It usually takes 2–6 weeks for patients to achieve treatment response.

Retinoids, including acitretin, isotretinoin and alitretinoin, have been used in refractory CLE with satisfactory results.

In a double-blinded RCT, acitretin 50 mg/day was found to be effective as HCQ 400 mg/day, with improvement or clearance of skin lesions in 48% of the patients receiving acitretin and 50% of patients receiving HCQ. However, acitretin was less tolerated (49).

Both isotretinoin and alitretinoin have been used successfully in small case series (50–52).

For verrucous LE and (or) hypertrophic lesions of CLE, sporadic case reports have also shown significant therapeutic effects of either acitretin or isotretinoin (53, 54).

The main clinical side effects associated to retinoids are skin and mucous membrane dryness, gastrointestinal symptoms, muscle weakness and arthralgia. Due to their teratogenic effects, counseling and contraception must be given to women of

childbearing age. They may alter liver function and lipid profile, thus regular blood tests are mandatory.

Immunoglobulins

Intravenous immunoglobulins (IVIG) therapy in refractory CLE has response ranging from partial to almost complete resolution of lesions (55, 56). However S2k guidelines do not suggest use of IVIG for CLE due to flare of lesions and side effects documented in various case series (57, 58).

One of the main concerns is the high cost of the treatment, which limits its widespread use.

Fumaric acid esters (monoethylfumarate and dimethylfumarate)

Fumaric acid esters have been successfully used in CLE in small series (59, 60).

A recent open-label phase II study showed an improvement in disease activity in 11 patients receiving monoethylfumarate and dimethylfumarate, but the primary endpoint, corresponding to 50% reduction in RCLASI score, was not achieved (61). Side effects include mainly gastrointestinal symptoms, e.g., abdominal cramping, nausea, and diarrhea.

Thalidomide/lenalidomide/iberdomide

Guidelines recommend thalidomide as second-line treatment for refractory CLE, especially DLE and SCLE, preferably in addition to antimalarials, whereas lenalidomide is not suggested for the treatment of CLE.

Thalidomide

Thalidomide is an immunomodulatory, anti-inflammatory and anti-angiogenic drug, successfully used to treat CLE in severe refractory cases (62, 63). It also shows photoprotective properties, inhibiting UVB-induced keratinocytes apoptosis (64).

The first studies on thalidomide in CLE date back to 1983, when 60 patients with DLE were treated with high dose of the drug (400 mg/day), obtaining a response in 90% of cases. However, relapses after drug withdrawal were developed by nearly all patients, even if less severe (65). Subsequent case series or small sized studies reported similar results with doses of mainly 50–100 mg daily (63, 65–69).

In a Brazilian study on 65 CLE patients, 98.9% patients reported complete or partial improvement with thalidomide 100 mg daily. However, 82% of them had cutaneous relapse and 43.2% patients presented neuropathy symptoms, which limited the use of the drug (70). Similarly, a prospective study on 60 patients with refractory CLE reported a 98% clinical response rate to 100 mg of thalidomide daily, with flares in 70% patients after drug withdrawal (71). This high relapse rate was confirmed in a recent meta-analysis of 21 studies that used thalidomide for the treatment of CLE, showing a pooled response rate of 90% but a high relapse rate of 71%. After cessation of treatment, 16% of patients manifested peripheral neuropathy but only in 4% the symptoms were persistent (72).

A recent Chinese study of 69 patients demonstrated optimal response rate (71%) at 50 mg daily (73). The same dosage was administrated by Frankel et al. in 5 patients with refractory CLE, 4 (80%) of whom showed a partial or total response after 4–8 weeks of treatment (74).

Overall, thalidomide has been used primarily in the treatment of DLE and SCLE with responses in about 98% of cases: Less frequently, ACLE, LEP, LET, or non-specific lesions, such as pyoderma gangrenosum, obtained remission under thalidomide treatment, with response rate of 50%. None of the previous studies used CLASI (63). It seems that relapses generally occurred between 4 and 8 weeks after drug interruption, but all cases responded to drug reintroduction (72). The rate of relapse after thalidomide withdrawal was 71% compared with 34% with a maintenance dose. DLE forms tended to relapse most often and required a long-term maintenance dose of thalidomide while SCLE forms showed a sustained remission after withdrawal (63).

The main limitation of thalidomide in all the studies were severe side effects, especially peripheral polyneuropathy, thromboembolic events and teratogenicity (75, 76). According to meta-analyses, 24% of patients developed side effects with the need to discontinue the drug, including 16% patients with peripheral neuropathy and 2% with thromboembolic events (72).

Peripheral polyneuropathy may occur early during the first 4 weeks of treatment and is not always reversible even after the withdrawal of the drug. Low maintenance thalidomide-dose (50 mg/day) could reduce the risk of this adverse event.

In a retrospective study of 139 CLE patients, thromboembolic events were found in 8 cases. The risk was higher for patients with a history of arterial thrombosis and hypercholesterolemia. Authors recommend a starting dose of 50 mg/day of thalidomide in association with HCQ. As some patients had high anti-phospholipid antibodies (aPL) titers, low-dose aspirin could prevent thromboembolic events.

Another limitation of thalidomide is its high cost, that affects the choice of alternative drug (77).

Lenalidomide

Lenalidomide (LND), a synthetic thalidomide analog, has proved efficient and well-tolerated in small case series of refractory CLE, both in adults and children, even after thalidomide failure, with lower side effects (78–84).

In a recent multicenter retrospective study on 40 CLE patients, mostly with concomitant systemic involvement, LND was found to be effective in 98% of the patients with a 4-point or 20% decrease in CLASI-A and a complete remission in 43% of patients (85). Authors underlined the long-term efficacy of the treatment. A median 10 month-follow-up was performed (range 07–147 months). Asthenia was the most common side effects (23% of cases) and in 12.5% of patients cardiovascular diseases and cancers were reported, leading to drug discontinuation. In another retrospective study on 19 CLE patients, of whom 12 with DLE, oral LND at starting dose of 5 mg daily, associated to an antiaggregant (acetylsalicylic acid or clopidogrel), determined a complete or partial resolution in 12 (63%) and 5 (26.5%) patients, respectively. Adverse reactions appeared in 17% cases and permanent LND withdrawal occurred in 12% of patients (86).

Totally, considering this latter study and the previous literature, 76 CLE patients (66 adults and 10 adolescents) were treated with LND with complete resolution in 88% cases, of whom 53% had a complete remission. Relapses occurred in about 26.4% (range 0–64%), especially upon dosage reduction (87).

Seven small-sized studies reported complete/partial response in all SLE/CLE treated patients with a mean time to response of 3 months. Comparing to thalidomide, LND was better tolerated with no cases of polyneuropathy or worsening of previous thalidomide-induced neuropathy. However, most of these studies did not perform nerve conduction tests. Flare rate varied from 25 to 75% occurring 0.5–10 months after drug withdrawal (87). As for thalidomide, a high teratogenicity risk was reported.

According to current studies, lenalidomide therefore appears as a valuable option in refractory CLE even after failure or limiting toxicity of thalidomide.

Iberdomide

Iberdomide, a thalidomide derivative, may degradate Ikaros (*IKZF1*) and Aiolos (*IKZF3*), two transcription factors involved in immune cell development and homeostasis. These molecules are overexpressed in SLE and play a role in B-cell, T-cell and monocyte regulation (86). In a phase IIa study on 42 SLE, iberdomide was efficient in reducing the Physician's Global Assessment (PGA) and CLASI-A, being a promising therapeutic strategy in CLE (88).

Biologics and small molecules

Targeting plasmacytoid dendritic cells and interferon signaling

Plasmacytoid dendritic cells (pDCs) are a subset of immune cells linking innate and adaptive immunity. They are well-known for being a major source of type I interferon (IFN) in response to viral infections or self-nucleic acids through signaling pathways involving pattern-recognizing receptors (PRR). pDCs have therefore a primary role in the pathogenesis of several autoimmune diseases with IFN-signature, such as lupus erythematosus. However, pDCs' spectrum of action appears to be much wider since the description of various interactions with T, B and NK cells. In fact, the expression of proinflammatory cytokines and costimulatory molecules enhance plasma cells differentiation, antibody secretion, Tregs and Th17 lymphocytes commitment, NK cells activation and immune cells recruitment (89). Type I IFN and pDCs represent a central paradigm not only in SLE but also in CLE pathogenesis, as highlighted by lesional skin infiltration from pDCs (90). This evidence poses the basis for a potential therapeutic option in targeting IFN and pDCs in CLE.

BIIB059 is a humanized IgG1 monoclonal antibody which binds BDCA2, a pDCs' specific receptor which inhibits the production of type I IFN. In a recent phase I, randomized, double-blind, placebo-controlled clinical trial, 8 CLE patients were treated with single doses of BIIB059 resulting in reduction in CLASI-A scores, reduced level of IFN-related genes in blood and reduced immune infiltration in skin lesions Doses were reported to range from 0.05 to 20 mg/kg. Most of the adverse events related to the drug were mild to moderate in severity, mainly consisting in upper respiratory tract infection. One treated patient developed herpes zoster on day 141 (91). A phase II trial for the treatment of SLE and CLE is currently ongoing (NCT02847598) (92).

Immunoglobulin-like transcript 7 (ILT7) is a surface molecule selectively expressed by human pDCs. VIB7734 is a monoclonal antibody properly designed to target ILT7 in order to reduce pDCs functions and count. It showed positive preliminary results in depleting circulating and lesional pDCs in CLE patients in phase I trials, with parallel improvement in disease activity and local type I IFN activity.

In two phase I studies in patients with autoimmune diseases, VIB7734 demonstrated an acceptable safety profile, comparable to that of placebo (93). Phase II clinical trial to study the treatment of moderate to severely active CLE (RECAST SLE)

is now recruiting. Patients have been divided into three groups with three dosing intervals.

Among the emerging treatments for CLE, the most promising approach is represented by anifrolumab, a fully humanized, IgG1κ monoclonal antibody targeting IFN-α/β/ω receptor (IFNAR) which disrupt signaling pathways of all type I IFNs. Following the preliminary evidence of efficacy, in July 2021 the FDA approved the use of anifrolumab in SLE patients with active disease under standard therapy in USA. Contemporary, several trials investigating the efficacy and safety of the drug are ongoing in Europe and Japan (94).

A phase IIb trial comparing intravenous anifrolumab vs. placebo in SLE patients demonstrated significant improvement of cutaneous involvement in the high IFN gene signature subgroup (95). More recently, results of the second phase III RCT comparing anifrolumab 300 mg vs. placebo showed a statistically significant difference in CLASI response (49 vs. 25%, respectively, $p = 0.039$) (96). In another phase II study on the efficacy of subcutaneous anifrolumab in SLE with active skin disease, significant reductions in CLASI activity score were observed in anifrolumab groups (97).

Sifalimumab is a human igG1κ monoclonal antibody targeting IFN-α molecule. A phase IIb trial evaluated efficacy and safety of several fixed intravenous dosages in adults with moderate to severe active SLE with inadequate responses to standard-of-care treatments. Three doses' intervals were administered to the participants (200, 600, 1,200 mg). Although the 1,200 mg dosage provided the most consistent results, no clear sifalimumab dosage effect was observed in the study. Apart from the success in reducing SLE activity, improvements in CLASI score were greater for all sifalimumab dosages compared with placebo, suggesting an interesting option for SLE and CLE. The percentages of patients with at least one adverse event, serious adverse event or adverse event leading to discontinuation were similar across the groups. The most common adverse events were worsening of SLE, urinary tract infections, headaches, upper respiratory tract infections and nasopharyngitis (98).

Besides type-I IFN, other cytokines of the interferon family are involved in CLE pathogenesis (99). Accordingly, IFNγ showed a potential central role since high levels of IFNγ mRNA were found in DLE lesional skin, while immunohistochemical analyses found statistical difference in staining of receptor between DLE skin samples and normal skin (100).

AMG 811 is a human anti-IFNγ antibody (IgG1 isotype) that selectively targets human IFNγ. The activity of AMG 811 was assessed in a phase I RCT comparing AMG 811 therapy with placebo in DLE patients, showing changes in biomarkers associated with IFNγ in the blood and skins of DLE patients. However, these findings did not reflect significant changes in CLASI score. In fact, although a single subcutaneous dose of 180 mg was well tolerated it did not lead to statistically significant improvements in any of the efficacy outcome measures (101).

CLE lesional skin showed an activation pattern of spleen tyrosine kinase (SYK), a key regulator of cell proliferation and inflammatory pathways which was suggested as a promising target for CLE treatment (102). In a double-blind Phase Ib study the maximum applied GSK2646264 dose at any time point was 10 mg/cm^2 over 90 cm^2 (900 mg cream containing GSK2646264 9 mg). Topical application of the SYK inhibitor GSK2646264 to active chronic and subacute CLE lesions was well tolerated over 28 days of treatment and no new safety concerns were identified. However, the trial failed to demonstrate a change in disease activity, while a modest decrease in IFN-related genes expression was found (103).

The SYK inhibitor lanraplenib (GS-9876), administered at a dosage of 200 mg, has been tested in a phase II trial in parallel with filgotinib 30 mg via oral administration in female patients with moderate-to-severe CLE, showing greater efficacy than placebo while the higher median decrease in CLASI-A was reached in the group treated with filgotinib. Most adverse events were mild or moderate in severity. Two serious adverse events were reported with lanraplenib and one with filgotinib (104).

B cell- targeted therapies

Among B cell-targeted therapy, rituximab and belimumab have been the most studied drug in cutaneous lesions (7–9). The role of B cells in SLE pathogenesis has been well described (105), whereas their role in CLE is still controversial. A recent study by Abernathy-Close et al. identified a B cell gene signature in the skin of DLE patients, highest than in ACLE and SCLE patients and, interestingly, in patients with DLE without associated systemic disease. These data indicate that while type I IFNs are known to contribute to the recruitment and activation of B cells in autoimmune disease (106), they may not be critical drivers in the differential recruitment of B cells observed in DLE skin. Interestingly, patients with skin lesions and positive autoantibodies tend to have a lower B cell enrichment score in the skin. The role of B cell in CCLE has been also evaluated in a study conducted by Jenks et al. They reported that while most of the patients with primary CCLE are more likely to have a B cell independent disease, 38% of them exhibited a highly activated SLE-like B cell profile providing a possible marker of progression to SLE (107).

Rituximab

Dosages commonly used are two 1,000 mg IV administered 2 weeks apart. Among adverse events reported to the FDA, the most common are febrile neutropenia, pyrexia, pneumonia, and anemia. Serious side effects that can lead to death, include infusion-related reactions, severe skin and mouth reactions,

Hepatitis B Virus (HBV) reactivation, Progressive Multifocal Leukoencephalopathy (PML).

Rituximab is a monoclonal antibody directed against the CD20 antigen, leading to B cell depletion.

According to current SLE guidelines, in refractory SLE or in case of intolerance/contraindications to standard immunosuppressive agents, rituximab can be introduced (30).

Concerning skin manifestations, in two large RCTs on patients with SLE (EXPLORER and LUNAR trials) rituximab failed (108, 109). However, prospective registry data showed cutaneous improvement in 70% of rituximab-treated patients with a partial or complete remission of mucocutaneous lesions (107). Study findings suggest that rituximab may be effective in treating severe CLE in some patients with systemic disease, especially those with acute and non-specific types (110). Bullous lupus and LEP have also improved after rituximab (111–116).

Recently, Mumford et al. reported the resolution of refractory isolated DLE with rituximab, suggesting a possible role of B-cell even in this subtype of CLE (117).

Thus, rituximab may have efficacy in patients with SLE and severe active CLE; however, outcomes may vary with SCLE and CCLE subtypes and may reflect the variation in co-medications (93). Its use could be considered when treating severe CLE in some patients with systemic disease, especially those with acute and non-specific types.

Belimumab

The recommended dose for SLE and lupus nephritis is 200 mg once weekly, administered subcutaneously, regardless of weight. Therapy should be interrupted after 6 months if no improvement is obtained. Adverse reactions more frequently reported (> 5% of SLE patients) were viral infections of superior respiratory tract, bronchitis and diarrhea.

Belimumab is a monoclonal antibody that reduces B lymphocyte survival by blocking the binding of soluble human B lymphocyte stimulator (BLyS) to its B cell receptors.

It is approved for SLE whereas no clinical trials have formally studied its effect on CLE (32).

The S2K guidelines do not recommend the use of belimumab for CLE (9); on the contrary, Lu et al. suggested belimumab as fourth-line treatment for widespread, refractory CLE lesions in patients with active SLE, especially those who have repeated recurrence of ACLE lesions during tapering of systemic corticosteroids (8). Accordingly, in a *post hoc*, pooled analysis of two phase III trials on belimumab in SLE (BLISS-52 and BLISS-76) the treatment, in combination with standard therapy, was associated with statistically significant improvement in mucocutaneous manifestations vs. placebo as assessed by both Safety of Estrogens in Lupus Erythematosus National Assessment– Systemic Lupus Erythematosus (SLE) Disease Activity Index (SELENA-SLEDAI) and British Isles Lupus Assessment Group (BILAG) scale (118). CLASI was not validated until 2011 and therefore was not studied in these randomized controlled trials.

Belimumab was associated with significant improvements in maculopapular eruption (mild), alopecia and active discoid lesions (119).

Recently, a study on 67 Italian SLE patients treated with belimumab, including 19 with mucocutaneous involvement, demonstrated a significant reduction of median CLASI activity score at 24 months, from 5 (range 1–14) to 0.5 (0–6) (120).

Vashisht et al. reported a dramatically improvement of median CLASI activity scores [from 17 (range: 9–31) to 3 (range 2–14); ($p = 0.043$)] in 5 patients with SLE with recalcitrant CLE after belimumab (121).

Dresco et al. also found a significant clinical improvement in 83% out of 7 patients with CLE with or without SLE, based on the CLASI and RCLASI activity score as well as their quality of life (DLQI) (122).

In a multicentric, retrospective observational study on 16 patients with CLE, of whom 13 with concomitant SLE, 50% of cases responded to belimumab, administered intravenously at 10 mg/kg every 2 weeks for 3 doses and then monthly, with a reduction in CLASI score, although an overall statistical improvement was not observed. Authors suggested that belimumab may be beneficial in some patients, mostly those with mild persistent activity and phototypes IV to VI. Interestingly, a clinical response was observed in all the 3 patients with isolated CLE (123). However, to date, the evidence about the effectiveness of belimumab in CLE not associated with SLE is scarce. Only isolated refractory cases of CLE successfully treated with belimumab have been recently reported.

Janus kinase inhibitors

Ruxolitinib or baricitinib (JAK1/JAK2 inhibitors) and tofacitinib (primarily JAK3 inhibitor), have been reported to clear recalcitrant CLE lesions. Commonly reported adverse effects are infections associated with herpes virus (herpes simplex labialis, reactivation or primary infection with varicella zoster virus, VZV), nasopharyngitis, as well as infections of upper respiratory tract and urinary tract. Manifestation of acne and gastrointestinal side effects, such as nausea and diarrhea, have also been observed. For topical applications, acne and pruritus have been described. Furthermore, patients treated with JAK inhibitors should perform strict contraception until at least 1 week after the end of treatment (124).

The Janus kinases (JAKs) are intracellular tyrosine kinases involved in a broad variety of inflammatory cascades participating in the pathogenesis of both SLE and CLE (107). Particularly, interferon-associated JAK activation is thought to play a key role in CLE lesions, since a significant

upregulation of JAK signaling in cutaneous lesions was demonstrated (125).

Two studies have described the use of JAK inhibitors in the treatment of CLE, using the SLE Disease Activity Index 2000 as the main end point which is not specific to skin disease (126, 127). Baricitinib showed complete remission of a refractory papulosquamous rash in an SLE patient (128) and complete clearance of subacute CLE and no further progression of the FFA in a patient who was started on baricitinib 4 mg for 2 months, followed by ongoing maintenance therapy with baricitinib 2 mg (129).

Ruxolitinib, at the full dose of 20 mg twice daily, baricitinib and tofacitinib have been trialed as therapeutic options for familial chilblain LE (130–135). Elman et al. also reported successful response to tocilizumab in non-familial refractory chilblain LE (136).

Bonnardeaux and Dutz showed an improvement in CLASI score in 3 patients with different refractory CLE subtypes treated with tofacitinib administered orally at a dosage of 5 mg twice daily (137). Moreover, topical tofacitinib 2% ointment was found to solve recalcitrant periorbital DLE in a case report (138).

Targeting cytokines and their receptors

Ustekinumab

Ustekinumab is a monoclonal antibody targeting IL-12 and IL-23. Although it seems to be effective in SLE, its role in the management of CLE is still debated (139). Few case reports of successful treatment of SCLE and DLE with ustekinumab, administered at a dosage of 45 mg or 90 mg with subcutaneous injection as for psoriasis (140–142) were reported in literature, while in a recent phase II RCT, ustekinumab in addition to standard therapy resulted superior to placebo in SLE patients with a baseline CLASI-A $\geq$ 4, showing a 50% improvement of CLASI-A in 17/32 (53%) patients under ustekinumab vs. 6/17 (35%) of the placebo group ($p = 0.032$) (143). However, the extension study involving 24 subjects in ustekinumab group vs. 14 patients under placebo showed $>$ 50% improvement in CLASI-A score in 79 and 100% of the subjects groups, respectively, at week 112 (144). Moreover, some reports of ustekinumab-induced SCLE are available, generating debate over its use in CLE (145, 146).

Low-dose IL-2

In a recent phase II study of 40 SLE Chinese patients receiving a 12-week treatment with 1 million IU subcutaneous IL-2, skin lesions and alopecia improved according to SELENA-SLEDAI and BILAG scores. However, assessment of disease activity with CLASI score was not performed (147, 148).

Conclusion

Current treatment regimens for CLE generally comprise antimalarials, systemic corticosteroids, immunosuppressive and immunomodulant drugs, while cytotoxic agents are reserved for severe cases. However, available drugs are not always effective and side effects may occur following long-term use. Moreover, chronic steroid exposure and wide spectrum immunosuppression are major triggers of organ damage. As the skin greatly contributes to the burden of disease in terms of personal and psychological wellbeing, occupational disability and therefore medical and social costs, the development of new treatment protocols for severe and refractory cases is necessary.

In the last years, research on the pathogenesis of SLE and CLE had improved, and several new biologics and small molecules-based treatments have been proposed with promising results on skin disease. However, the lack of large clinical data and of standardized and homogeneous score to assess disease activity such as CLASI and RCLASI is a major impediment to improve management strategies in CLE.

Therefore, future prospective studies on this field should be proposed, with the contribution of expert dermatologists.

Author contributions

AV concepted the whole work, drafted and submitted the manuscript. AC, EM, CA, VR, WV, and LQ contributed to literature revision, manuscript production, and pictures collection. MC concepted the work and revised carefully the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Devinder Mohan Thappa,
Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India

REVIEWED BY
Ricardo Ruiz-Villaverde,
Hospital Universitario San Cecilio, Spain
Jan Peter Dutz,
University of British Columbia, Canada
Adam Reich,
University of Rzeszów, Poland

*CORRESPONDENCE
Joseph F. Merola
JFMerola@bwh.harvard.edu

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Cutaneous lupus erythematosus disease assessment: Highlighting CLE outcome measures

Rebecca G. Gaffney[1], Victoria P. Werth[2,3] and Joseph F. Merola[1,4]*

[1]Harvard Combined Dermatology Program, Boston, MA, United States, [2]Department of Dermatology, University of Pennsylvania, Philadelphia, PA, United States, [3]Corporal Michael J. Crescenz Veteran's Administration Medical Center (VAMC), Philadelphia, PA, United States, [4]Division of Rheumatology, Department of Dermatology and Medicine, Brigham and Women's Hospital, Boston, MA, United States

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Introduction

Cutaneous lupus erythematosus (CLE) is an autoimmune skin disease that can occur with or without systemic lupus erythematosus (SLE). This potentially disfiguring disease can have significant impact on patient's quality of life (QoL) and is often refractory to many first- and second-line therapies. Despite the need for new treatments in CLE, patients are often excluded from clinical trials with SLE due to disease heterogeneity and previously difficult to measure disease activity and QoL. Standardized outcome measures for CLE are essential for trial design and regulatory approval of novel treatments. In this review, we aim to explore and highlight the various outcome measures for physician reported outcomes and patient reported outcomes for CLE.

CLE is an autoimmune skin disease that can occur with or without features of SLE. Even skin-limited disease can have a significant impact on patient's QoL and patients are often refractory to standard topical treatment and antimalarials. Despite this, there have been no skin-directed therapies approved by US Food and Drug Administration (FDA) in the past 50 years, and only two new biologics for SLE during this time frame (1, 2). Patients with CLE are often excluded from clinical trials for SLE, likely due to disease heterogeneity and previously difficult to measure disease activity and QoL in these patients. More clinical trials focusing on CLE are emerging and CLE specific outcome measures are important in identifying promising medications in this potentially disfiguring disease.

Owing to the challenges with outcomes research in this heterogeneous disease, there is currently a lack of standardized outcome measures in CLE to be used in clinical trials. This represents a barrier to trial design, problematic heterogeneity across studies, and a regulatory hurdle to approval of much-needed novel drugs. Our group recently published a multistage literature review of CLE and SLE studies to develop a working core outcome set (COS) for CLE to be used in clinical trials as an interim guide until standardized outcomes are established (3). Proposed core domains include skin-specific disease activity and damage, investigator global assessment of disease activity, symptoms (encompassing itch, pain, and photosensitivity), health related quality of life, and

patient global assessment of disease activity. In this review, we aim to highlight our recommended outcome measures for each core domain and summarize other various physician reported outcomes and patient reported outcomes that have been used for CLE.

Physician reported outcomes

Skin-specific instruments

Cutaneous lupus disease area and severity index

The CLASI was developed by an international group of experts in dermato-rheumatology who met multiple times to discuss and review descriptors, as a responsive CLE disease measurement tool to be used in clinical trials. Patients were also interviewed to make sure the CLASI captured what was important to them. Subsequent qualitative studies confirmed the items chose for the CLASI reflected concerns to patients (4). It was designed to capture various CLE subtypes, but excluded more rare entities like lupus panniculitis and bullous lupus. The CLASI has two scores: activity and damage. Each anatomic location is scored (from scalp to toes), with highly photo-exposed areas listed separately in addition to sections focusing on mucous membrane involvement and alopecia. For the activity score, points are given for mucous membrane lesions, recent hair loss, diffuse hair loss attributed to active SLE, inflammatory scalp alopecia, as well as the presence of erythema and scale in multiple different body surface areas to allow for determining the extent of disease without relying on Body Surface Area (BSA), which may be quite low, even in extensive active disease. Separate composite scores for activity are calculated by simply summing the individual component scores. Disease activity is scored to a maximum of 70 points. For damage score, points are given for presence of dyspigmentation and scarring including scarring alopecia to a maximum of 80 points. Dyspigmentation score is doubled when it has been present for more than 12 months (1, 5).

The CLASI has shown excellent content validity, construct validity, and inter/intra-rater reliability in multiple studies and has been validated for use in the pediatric population (1, 6). Additionally, the CLASI has shown to correlate with QoL. A severity and responsive analysis showed that higher numerical score indicated more severe disease. Therefore, a reduction in CLASI score corresponds to a reduction in disease activity which makes it an excellent organ-specific outcome measure to use in clinical trials (7). Our prior literature review showed that the CLASI was used in 54.5% ($n = 18$) of CLE and SLE randomized control trials that evaluated skin with a skin-specific outcome measure and 66.7% of CLE and SLE studies published in PubMed or ClinicalTrials.gov since it was developed and validated. The CLASI-A and CLASI-D were therefore recommended instruments for the core domains of skin-specific disease activity and skin-specific disease damage in our proposed working core outcome set (3).

Unlike the Psoriasis Area and Severity Index (PASI), which is the gold standard to measure severity and extent of psoriasis, the CLASI does not take surface area into account in scoring (8). Affected areas are weighed equally regardless of surface area or number of lesions, but scores are assigned based on the most severe representative lesion in each anatomic area. However, in CLE, surface area is often small and may not reflect true disease severity. Patients may have numerous small lesions that significantly impact QoL without adding up to a large BSA. Like the PASI, the CLASI uses erythema as a hallmark of disease activity by reflecting the hyperemia that accompanies inflammation. Since erythema can be transient or reflect underlying telangiectasia, using the CLASI requires training to be able to accurately score patients (1). Finally, in the original validation studies, it was found that the CLASI takes an average duration of 5.25 min to conduct (ranging from <1–11 min). There was no significant variation over time as experience with the instrument increased (5).

The CLASI works for most subsets of CLE, with the exception of lupus panniculitis and tumid LE if there is no erythema, which is quite rare. The activity of lupus panniculitis is difficult to assess and thus is not included in the CLASI except as relates to the lipoatrophy from resolved panniculitic activity. The RCLASI is partially validated and has demonstrated good inter/intra-rater reliability, but its practicality is limited by the extensive nature of this instrument. The less user-friendly nature of the RCLASI has drawn into question its feasibility for use in clinical trials (9).

Cutaneous lupus activity-investigator global assessment

The FDA previously released a document for the development of drugs for SLE with emphasis on treatment measurement of disease activity and damage and are now encouraging disease-specific global assessment tools for many inflammatory skin disorders (1, 10). Per our prior literature review performed, there was no standardized IGA for CLE (3). Thus, the CLA-IGA was recently developed by experts in dermato-rheumatology to fill this unmet need. It is currently undergoing reliability studies and therefore its validity and applicability is not yet determined.

Scoring is based on severity of morphologic features of CLE. Like other IGA instruments, it consists of a 5-point scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe) that evaluates the severity of the CLE disease activity. Scoring is based on the severity of the morphologic features averaged across all body lesions. Morphologic features include erythema, scale, edema/infiltration, the extent of follicular plugging/follicular hyperkeratosis of the scalp, and secondary

changes of CLE plaques such as presence of vesicles, erosion, and crusting.

Item generation across the breadth of CLE subsets was derived from a large international consensus exercise and was subsequently drafted by experts in connective tissue dermatology. Its content validity was further developed by involvement by a larger panel of dermato-rheumatology experts over several rounds of input to refine morphologic features and review content descriptors. Like the CLASI, it uses erythema as a driver for final score and morphologic characteristics were selected to reflect severity of CLE disease activity and be sensitive to change over time.

The CLA-IGA offers a CLE-specific global assessment tool that can provide a snapshot of overall disease activity and is highly feasible to perform. Because an IGA is a more global assessment with an ordinal scale, it also allows for disease severity to be readily and easily interpretable by clinicians and patients alike. It offers complementary data to the CLASI, focusing on lesion morphology activity severity, without the need for extent of disease considerations. This may be particularly relevant in the most common subsets of CLE where BSA extent is often limited but still carries high burden on patients. It may additionally be considered for studies with lower BSA and/or for assessing target lesions. Analogies may be drawn between the common use of concurrent PASI and psoriasis IGA in the conduct of psoriasis trials. Given the heterogeneity of CLE presentation, often with more than one subtype in the same patient, assignment of features such as specific level of erythema or more subtle changes in activity may be challenging to capture with the CLA-IGA where regional variation may exist. Nevertheless, global assessment tools are supported and encouraged by the FDA and the CLA-IGA offers a complement to the CLASI in clinical trials. We therefore recommend the CLA-IGA as a possible endpoint for CLE pending results of validation studies (3).

SLE instruments that measure skin involvement

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) is a global index that measures disease activity through 24 questions regarding clinical manifestations of SLE (physical findings and laboratory values) that are weighted by type of manifestation, not severity of the manifestation. For example, preferential weighting is given to vasculitis, central nervous system involvement, and active renal disease. The maximum score achievable is 105, but even patients with very active disease rarely exceed a score of 20. "Inflammatory-type rash," "alopecia," and "oral or nasal ulcers" are the only representations of skin findings in this tool. Additionally, because the SLEDAI only measures the presence or absence of features, skin disease needs be completely resolved to indicate improvement, making it insensitive to incomplete resolution of changes. The SLEDAI-2K was developed as a modification to the SLEDAI to reflect persistent, active disease in scoring and has been validated against the original SLEDAI as a predictor of mortality and measure of disease activity (11, 12).

Similar tools to the SLEDAI/SLEDAI 2K are the Lupus Activity Criteria Count (LACC), the British Isles Lupus Assessment Group (BILAG), and the Systemic Lupus Collaborative Clinics/American College of Rheumatology Damage Index for SLE (SLICC/ACR Damage Index for SLE) which also only document the presence or absence of CLE manifestations, and are therefore not adequate tools to evaluate CLE disease activity (1, 12, 13).

Patient reported outcomes

Health related quality of life

The Dermatology Life Quality Index (DLQI) is a widely-used dermatology-specific questionnaire consisting of ten questions about the previous 1 week. The total DLQI ranges between 0 (no impairment) and 30 (maximum impairment). The ten questions in the DLQI can be subdivided into six domains that relate to different aspects as follows: symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment (14). There is just one question related to the impact on emotional QoL, and emotions are greatly impacted in CLE (14). We found just one validation study for the Brazilian version of the DLQI for CLE (3, 15).

The Skindex-29 is a validated measure of the effects of skin disease on QoL. There are 29 items that form three domains: symptoms, emotions, and functioning. The symptoms subscale measures pain, itch, burning, or sensitivity. The emotional subscale measures depression, anxiety, embarrassment, or anger. The functioning subscale evaluates changes to daily life, such as work, sleep, or relationships with others. In the Skindex+3, there is a fourth subscale that assesses CLE-specific issues such as photosensitivity and alopecia. Patients are asked to assess how often (never, rarely, sometimes, often, all the time) they experience a given effect and scores are assigned to each question. Domain scores and overall score are expressed on a 100 point scale with higher numbers indicating worse QoL (16).

The CLE-QoL was recently developed with input from patients with CLE. It combines the Skindex-29+3 with four questions from the vitiligo-specific quality of life (VitiQoL) instrument. The four additional questions correspond to an additional subscale in body image/cosmetic issues. It has shown strong reliability and structural and convergent validity in a single validation study, and future studies will determine if additional questions meaningfully improve the capture of QoL features (17).

Interestingly, a study was performed in patients with psoriasis and eczema (n = 28) to compare the DLQI and Skindex-29. Interviews on content and format of both tools showed that participants preferred the Skindex-29 for ease of understanding and incorporation of various emotions. Patients were overall satisfied with format and length of both tools (18).

Other generic QoL indices identified in our literature review include the EQ-5D and the Short Form Health Survey (SF-36), which have not been validated in CLE (3).

Patient global assessment of disease

The PtGA is an instrument that allows for a subjective overall evaluation of disease severity from the patient's perspective. It is a widely use PRO across multiple diseases, including skin-specific entities. There are multiple scoring systems, but most PtGA instruments use an ordinal scale to rate severity of disease on a 5-point scale where 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe. A 10-point linear VAS scale has been used for a number of studies. Despite feasibility of use, there is currently no validated PtGA for disease activity in CLE (3).

Patient reported symptoms

While the Skindex-29+3 and CLE-QoL both include questions about itch, pain, and photosensitivity, there are no CLE-specific measurements found dedicated to these symptoms (16, 17).

The 12-Item Pruritus Scale (12-PSS) has been shown to be a valid and reliable tool to assess generic dermatologic itch. It is a one-page instrument that consists of 12 items to assess different aspects of pruritus. Though it was not originally developed for patients with CLE, severity bands were later defined for CLE (19).

Commonly used and practical scales in clinical trials, though not formally validated in CLE, are the pain and pruritus Visual Analog Scales (VAS) and Numeric Rating Scales (NRS). For the VAS, patients are asked to mark a position along a 10 cm long line that corresponds to a single question about pain or itch and severity is assigned based on length. Similarly, for the NRS, patients are asked to rate their symptoms on a defined scale between 0 and 10.

In our proposed core outcome set for PROs, we were unable to recommend one clearly superior instrument due to lack of validation data and the vast number of instruments identified. However, suitable instruments include the CLE-QoL, Skindex29+3, DLQI, SF-36, and EQ-5D for HRQoL domain and the 12-PSS, CLE-QoL, Skindex29+3, DLQI, itch VAS/NRS, and pain VAS/NRS for the symptoms domain. Given the lack of CLE-specific PtGAs, there is no specific outcome measure that could be recommended for the patient global assessment domain (3).

TABLE 1 Lupus outcome measurements.

Outcome measurements	
Physician reported outcomes	**Patient reported outcomes**
Skin specific instruments	The Dermatology Life Quality Index (DLQI)
Cutaneous Lupus disease Area and Disease Severity Index (CLASI)	Skindex-29
Cutaneous Lupus Activity-Investigator Global Assessment (CLA-IGA)	Cutaneous Lupus Erythematosus-Quality of Life (CLE-QoL)
	Patient Global Assessment of Disease (PtGAs)
SLE instruments that measure skin involvement	12-Item Pruritus Scale (12-PSS)
The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)	Visual Analog Scales (VAS)
	Numeric Rating Scales (NRS)

A summary of commonly used outcome measurements can be found in Table 1.

Conclusion

CLE represents a set of conditions with heterogeneous presentation, variably associated with underlying SLE. The heterogeneity in both CLE presentation and CLE outcome measures has previously hindered trial design and drug development. To help overcome this barrier, we recently developed a working core outcome set for CLE and our recommended outcome measures for each core domain are reviewed above. This COS can serve as an interim guide for upcoming CLE trials but large-scale consensus exercises are ideal to develop standardized outcome measures. The previous lack of focus on skin outcomes in trials was significantly improved by the CLASI, and validation studies for the FDA requested CLA-IGA are underway. This review identifies a paucity of validated CLE-specific patient reported outcomes, particularly a PtGA. The CLE-QoL is a newer and promising instrument that should be included in future studies to further evaluate its validity and responsiveness.

In this review, we identify the current CLE outcome measures and highlight unmet needs that will hopefully inform the agenda for future studies to allow a regulatory pathway forward to develop novel drugs for CLE.

Author contributions

RG, JM, and VW made substantial contributions to the conception or design of the work, or the acquisition, analysis, or

interpretation of data for the work, drafting the work or revising it critically for important intellectual content, provided approval for publication of the content, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Mohammed Osman,
University of Alberta, Canada

REVIEWED BY
Toshihiro Matsui,
National Hospital Organization Sagamihara National Hospital, Japan
Marzia Caproni,
University of Florence, Italy
Nikolaos Patsinakidis,
University of Oldenburg, Germany

*CORRESPONDENCE
Julia Elmgren
julia.elmgren@stud.ki.se

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Clinical aspects of cutaneous lupus erythematosus

Julia Elmgren[1,2]* and Filippa Nyberg[1,2]

[1]Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Department of Dermatology, Karolinska University Hospital, Stockholm, Sweden

Lupus erythematosus (LE) is an autoimmune inflammatory disease with a wide clinical spectrum from life-threatening multi-organ inflammation in systemic lupus erythematosus (SLE) to limited skin disease in cutaneous LE (CLE). The etiology of CLE is still not fully understood but a multifactorial genesis with genetic predisposition and certain environmental factors as triggers for the development are generally accepted features. Lesions can be induced and aggravated by UV-irradiation and smoking is linked to more severe forms of skin disease and to co-morbidity. Drugs, including many common medicines like antihypertensives, are known to induce subacute CLE (SCLE). The mechanisms involved have recently been shown to be part of the IFN-I pathway and new, specific treatments are currently in clinical trials. CLE is currently classified in subtypes based on clinical presentation and duration into acute CLE (ACLE), SCLE, and chronic CLE (CCLE). Distinct subtypes can be seen in individual patients or coexist within the same patient. Because of the confluent and overlapping picture between these subsets, serology, and histopathology constitute an important role guiding towards correct diagnose and there is ongoing work to update the classification. The Cutaneous Lupus Area Severity Index (CLASI) is a validated tool to measure activity and damage both in clinical trials but also for the clinician to evaluate treatment and follow the course of the disease among patients. CLE is known to have substantial impact on the life of those affected. Several tools have been proposed to measure QoL in these patients, currently Skindex-29 is probably the most used. Patient education is an important part of prevention of flares, including UV-protection and smoking cessation. First-line treatment includes topical corticosteroids as well as topical calcineurin inhibitors with the addition of systemic treatment with antimalarials in more severe or therapy resistant cases. Treatment specifically targeting CLE has been lacking, however novel potential therapies are in later phase clinical trials. In this review we aim to describe the different subsets of the cutaneous form in LE with focus on clinical aspects.

KEYWORDS

cutaneous lupus erythematosus, histopathology, classification of CLE, skin inflammation, lupus

Introduction

Descriptions of lupus (= wolf in Latin) can be found as early as the Middle Age. The first to describe Lupus Erythematosus in modern time was the Swiss dermatologist Laurent-Theodore Biett. In 1833 his work was published through his student Cazenave, giving it the name Erythema Centrifugum. Cazenave was among the first one to describe morphologically what today is known as discoid lupus (1). Two distinct forms of lupus were later described by Kaposi as erythematosus *discoides* and lupus erythematosus *disseminate*, which refer to a state of generalized lesions, i.e., manifestations below the neck (2).

Classification of subtypes of CLE

In 1981 Gilliam and Sontheimer created a classification mostly based on clinical presentation of cutaneous characteristics in patients with lupus erythematosus (LE), and subdivided it into acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE) (3) **Table 1**. Different updates, additions and suggestions have been discussed widely. Other suggestions and additions such as the Düsseldorf classification proposed addition of a fourth type, named intermittent CLE (ICLE) (4). Further, suggestions of categorizing cutaneous LE (CLE) specifically based on histopathologic picture i.e., level of skin-involvement have also been proposed for classification (5). A Delphi process with international experts suggested 12 criteria for discoid LE (DLE), including morphology, histopathology and location, with ambition to reach homogeneity on the most common subset of CLE (6). These suggested criteria have been evaluated and found to probably be more applicable to disease damage than to evaluate disease activity. The clinical usefulness is still not clear, but these new criteria are considered to be of value when recruiting patients to clinical trials (7, 8). Management of CLE as well as clinical research is dependent on clear classification criteria and further work is needed to elucidate accurate and complete classification criteria.

TABLE 1 Classification of cutaneous LE suggested by Gilliam and Sontheimer (3) (modified) (3).

Chronic cutaneous LE
Clinical forms
1. Discoid LE (most common form)
• Localized DLE
• Generalized DLE (lesions above and below the neck)
2. LE profundus (panniculitis)
3. LE tumidus
4. Chilblain LE
5. Lichen planus overlap syndrome
Clinical features of DLE
Usually localized, chronic, scarring lesions of head and/or neck region lasting months to years. Usually no extracutaneous disease.
Subacute cutaneous LE (SCLE)
Clinical forms
1. Papulosquamous (psoriasiform)
2. Annular-polycyclic
Clinical features
Usually widespread, non-scarring lesions with associated scaling, depigmentation, and telangiectasis distributed on photo-sensitive areas.
Acute cutaneous LE (ACLE)
Clinical forms
l. Localized, indurated erythematous lesions (malar areas of face-"butterfly rash")
2. Widespread indurated erythema (face, scalp, neck, upper chest, shoulders, extensor arms, and backs of hands)
Clinical and laboratory features
Multisystem disease and antinuclear antibodies are usually present.

Epidemiology

Investigations from different parts of the world have shown CLE to have similar incidence figures as SLE. The global incidence of SLE is approximated as 1.5–11/100,000 per person-year, and in Europe 1.5–7.4/100,000 per person-year (9). The majority of those diagnosed with SLE are females with onset of disease in their third or fourth decade of life with a prevalence of 203/100,000 (10, 11).

Several epidemiological studies have been performed to determine the incidence and prevalence of CLE. In a study by Grönhagen et al. the population-based incidence of CLE in Sweden was found to be 4/100,000 per person years (12). Similar incidence rates have been reported from the US, Asia, and Denmark with a range of 2.74–4.36/100,000

Abbreviations: ACLE, acute cutaneous lupus erythematosus; ACR, American College of Rheumatology; AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; BAFF, B-cell activating factor; BSLE, bullous systemic lupus erythematosus; CCLE, chronic cutaneous lupus erythematosus; CLASI, Cutaneous Lupus Area Severity Index; CLEQoL, cutaneous lupus erythematosus quality of life; CQ, chloroquine; DI-SCLE, drug-induced subacute cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; DLQI, dermatology life quality index; DM, dermatomyositis; ENA, extractable clear antigen; HCQ, hydroxychloroquine; ICLE, intermittent cutaneous lupus erythematosus; IFN, interferon; IVIg, intravenous immunoglobulin; LBT, lupus band test; LP, lichen planus; MAb, monoclonal antibody; MMF, mycophenolate mofetil; NLE, neonatal lupus erythematosus; PPI, proton pump inhibitor; RA, rheumatoid arthritis; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaboration Clinic; SS, Sjogren's syndrome; anti-TNF-alfa, anti-tumor necrosis factor-alfa.

per person-year (13–15). The ratio between biologic sex is overrepresented among females with a ratio of 2–4:1 (12, 14, 15). CCLE is overrepresented among racial/ethnic minority groups, particularly individuals with skin of color (16–18).

Discoid LEis the most common clinical presentation and is generally estimated to 62–83% of all CLE patients (12–15, 19). Also, DLE and SCLE are currently the only subtypes with specific ICD codes (L.93.0 and L93.1) while all other are classified as L93.2 "other localized cutaneous LE" making registry studies on a large scale impossible as tools to identify other, more rare subtypes.

A recent study found that signs of disease damage, particularly ear dyspigmentation, scalp dyspigmentation and scarring alopecia, can more frequently affect patients with skin of color with DLE (16).

Association to SLE

Many shared features point to regarding CLE and SLE as being part of a disease spectrum: shared histopathological, clinical, and serological features as well as the presence of overlap and development from cutaneous to systemic disease. The risk for progression to SLE in DLE patients is estimated between 5 and 30%. The generalized form of DLE has a higher potential of progressing to SLE compared to those with localized lesions (12, 19–22). Potential risk factors for progression to systemic disease are suggested to be anemia, arthritis and positivity for ANA (19). DLE patients statistically have a lower risk of progression to or coexisting SLE compared to both ACLE and SCLE (23, 24).

However, there are also clinical differences to support regarding CLE as a distinct disease entity: underscoring this view is the low risk of DLE progressing to SLE and differences in genetic background, age and sex distribution.

Recently, lesional and serological B-cell expressions have been suggested to differentiate between cutaneous and systemic LE. B-cell activating factor (BAFF), a cytokine linked to activation of B-cells, seems to play an important role in SLE and has been elevated in 30% of patients. Increased expression of BAFF in lupus lesions compared to healthy controls has also been reported and theories suggest that levels of BAFF can correlate to disease activity (25). B-cell signature in lesions varied between the different subsets of CLE with the highest expression found in DLE lesions, suggesting that a gradient of expression can be identified (26, 27).

Of great interest for prognosis and management of CLE patients is to identify potential biomarkers. Biomarkers suggested to reflect a higher risk of progression from CLE to SLE are ANA, anti-ds- DNA-, anti- Sm-, anti-U1-RPN antibodies and higher erythrocyte sedimentation rate (ESR). For DLE, ANA positivity and anti-ds-DNA seem to be markers of risk for progression to SLE (28). Both SLE and CLE patients show elevations of IFN, therefore IFN-upregulation such as IFN-gamma may predict progression in SLE and could as well serve as a biomarker to predict progression among CLE patients (29). The IFN-regulated cytokine CXCL13 correlate with both disease activity in SLE and renal involvement. Widespread lesions are associated with a higher abundance of the ligand to CXCL13 and could therefore serve as a biomarker in the future (30). A suggested biomarker to evaluate response to treatment is vascular endothelial growth factor (VEGF) (31).

At the present state of knowledge, the two groups CLE and SLE are best regarded as closely related but distinct and different diseases. Correlation between SLE and CLE indicates that the overall risk of progressing to SLE is significantly higher within the first 3 years from CLE diagnosis (12, 13, 23). Studies from different parts of the world largely confirm the finding, that in case of systemic progression it occurs within a few years from cutaneous lupus diagnosis (14, 15). Epidemiologic findings therefore clearly underscore the importance of alertness for development of systemic disease, especially during the first years after diagnosis of CLE.

Subtypes of CLE

Acute CLE

This subset occurs mostly in a patient with SLE and can be presented in a localized or a generalized form, with the former most recognized as an erythematous rash and edema over the malar eminences and bridge of the nose, although saving the nasolabial folds. This manifestation is usually triggered by UV irradiation although not exclusively. This so called "butterfly eruption" typically lasts from days to weeks and heals without scarring (24, 32). The rare, generalized form is presented as a morbilliform widespread eruption (24, 33). ACLE is often seen as a prodromal symptom of systemic disease and patients are usually positive for ANA (80%) and anti-dsDNA (30–40%) by this time (34). The lesions heal without scarring or dyspigmentation (20). Steven Johnson/Toxic Epidermal Necrolysis-like Lupus Erythematosus is a hyperacute manifestation of ACLE. It presents as a widespread erythema with epidermal detachment (20, 35). Other manifestations appearing with ACLE are telangiectasias, oral ulcerations, poikiloderma, scales, and erosions (24, 32).

Bullous SLE (BSLE) is a rare form of ACLE that was recognized by Hall et al. who reported about patients with vesiculobullous eruption with unknown etiology to disease and with poor response to corticosteroids. They instead used Dapsone and achieved significant results with remission close to administration (36). BSLE is considered a rare form and is mostly affecting adults between their thirties and forties and like SLE, this form predominately affects women. Clinical features of this form are widespread non-scarring blistering arising on erythematous or normal skin mostly affecting areas such as neck,

trunk, and extremities. Histopathologic examination shows neutrophilic and interpapillary micro abscesses with a picture resembling those seen in dermatitis herpetiformis. Presence of autoantibodies against collagen type-VII have also been reported from several studies (37–40).

Subacute CLE

In 1979 Gilliam and Sontheimer proposed that this entity should be considered a distinct subset of LE (41). This subset is mostly described in Caucasian females and lesions usually occur in UV-exposed area such as neck, chest, back and arms but are rarely seen in the face (33). The classic presentation of SCLE lesions usually comes with an erythematous papules or macules that later progress to and become annular-polycyclic lesions or-, less common, hyperkeratotic papulosquamous lesions in the rarer psoriasiform type (42). A majority (about 80% depending of sensitivity of method) express autoantibodies anti-Ro/SSA- and often also anti-La/SSB antibodies (30–40%) (43). The lesions usually heal without scarring although dyspigmentation occurs (24). Among SCLE patients, around 50% present with a mild form of SLE reporting myalgia and arthritis as common symptoms but in contrary to systemic disease, few of these have manifestations in kidneys or central nervous system (44, 45). In a recent study, prevalence of AMA-M2 antibodies among patients with SCLE had an increase in cholestatic liver enzymes, suggesting patients with newly diagnosed SCLE to be screened for AMA. If present, the authors to this study recommend avoidance of drugs with potential liver toxicity in order to prevent a progression to primary biliary cholangitis (46).

Drug-induced SCLE

Since the first description of SCLE induced by thiazides in 1985 by Reed et al. the association with numerous drugs and drug-induced SCLE (DI-SCLE) is now well described and new drugs are added. Recently, the mRNA-COVID-19 vaccine has been associated to both induction and exacerbation of SCLE (43, 47–51).

Drug-induced SCLE is estimated to constitute about one third of all the SCLE and over 100 drugs have been associated to subacute DI-SCLE (43, 52). Of importance for clinicians to be aware of this condition when seeing patients with SCLE for the first time since it is identical to idiopathic SCLE (53).

However, some differences between idiopathic SCLE and DI-SCLE have been reported: Age of onset has been suggested to be higher in DI-SCLE, with a mean of 60 years compared to SCLE with a peak around 40 years (54). Reports of unique findings in DI-SCLE suggest characteristics as lesions with bullous and erythema multiforme type, more widespread, older age of onset and findings in histopathology described as leukocytoclastic vasculitis. The serologic findings of anti-Ro/SSA- and anti-La/SSB antibodies in most cases do not seem to differ between idiopathic and drug-induced form (52, 54).

Existing criteria for drug-induced SLE proposed by Borcher et al. have been proposed for application also in DI-SCLE (52, 55):

- sufficient and continuous exposure to a specific drug
- at least one symptom compatible with CLE
- no history suggestive of CLE before starting with drug
- resolution of symptoms within weeks after discontinuation of putative offending agent.

More rarely drug-induced CCLE has been reported, with typical discoid lesions in photo distributed areas (54).

Although this strong association, the relationships and pathomechanisms are not fully understood. Time from exposure to a new drug to onset can vary from days to years but median latency is approximated to 6 weeks. Most of these cases resolve once discontinuation and patients mostly improve clinically within 1–3 months (56). Depending on drug type, the improvement seems to vary in time from discontinuation ranging from months to years. Drugs with strong association include terbinafine, anti-tumor necrosis factor alfa (TNF-alfa) -inhibitors, PPIs, and monoclonal antibodies (MAbs) (43, 54, 57, 58). For the drug-induced discoid form of CLE association with 5-FU and anti-TNF-alfa are described (52). Recently a systematic review, covering therapy with MAbs, reported incidence of DI-SCLE, where the most common indication for MAb-treatment was inflammatory arthritis 40%, advanced melanoma 12% and psoriasis/psoriatic arthritis 10% (57).

Chronic CLE

Discoid LE

The majority of patients within the CCLE group, have the discoid form (DLE) which can be presented as localized and generalized lesions (12–15). DLE are often coin shaped, erythematous, hyperkeratotic chronic lesions leaving scar behind mostly localized to head and neck with a lasting of months to years (3). In a review by Walling et al. the natural course of a DLE lesion starts as a macule or papule with a well demarked line with scaling that later progress to become a discoid plaque (59). DLE plaques are most often indurated and this has been suggested to be a criterion for DLE, however it is difficult to evaluate in a homogenous way and is not included in the current evaluation tool Cutaneous Lupus Area Severity Index (CLASI) (60). Histopathology is the gold standard for diagnosis, in typical cases it shows a hyperkeratosis and follicular plugging and interface dermatitis and a perifollicular lymphocytic infiltrate. Changes in basal layer of epidermis include membrane thickening as well as a more profound inflammatory infiltrate compared to ACLE and SCLE (4, 61). However, it is considered very difficult to discriminate between subtypes by histopathology alone. The

histopathological finding of follicular hyperkeratotic plugs is also the most common finding by dermoscopy in DLE lesions as well as absence of follicular openings. Non-scalp lesions displayed a slightly higher frequency of hyperkeratotic plugs and red dots at dermoscopy compared to scalp lesions (62).

LE profundus (panniculitis)

This rare form of CCLE occurs in <5% of CLE and more seldom in SLE (53). It is of great importance for clinicians to recognize and treat this form since lesions can progress quickly and heal with subcutaneous atrophy scarring and dyspigmentation. An area affected by panniculitis often presents as a depression in the skin seemingly unaffected skin with palpable subepidermal nodules. The lesions can also present with a DLE plaque and erosion in the overlying skin. Lesions is usually located to proximal extremities, trunk and face but less commonly found in distal extremities (63). Histopathological changes in LE profundus show characteristics of panniculitis with mucin but there is no consensus in specific biopsy findings for LE profundus (64).

LE tumidus

This uncommon form of CLE was first reported in 1909 by dermatologist Erich Hoffman. This subtype is characterized by photosensitivity and "succulent" edematous erythematous plaques that heal without scarring, often in the face and more often prevalent in male patients than other forms of CLE. Locations that are most commonly affected is face, V-neck and back. A diagnose of LE tumidus is supported by histopathological findings of mucin and a lymphocytic infiltrate. Treatment is similar to other forms of localized CLE. Since 2012 LET is included in the SLICC as other forms of chronic CLE (65, 66).

Chilblain LE

This more rare subtype can occur both with and without SLE. It is most commonly found on the toes and fingers of females but can sometimes be more widespread. A history of cold-induced or aggravated lesions should be obtained (24). Patients are often anti-Ro/SSA antibody positive and some patients also display cryoglobulins at serological analysis (67). They also often have concomitant Raynaud's phenomenon and are smokers. The lesions are tender, bright red to reddish-blue papules, nodules or plaques (24, 68).

Familial chilblain LE is a rare presentation caused by heterozygous mutations in the genes encoding 3'repair endonuclease (TREX1) or corresponding protein. Familial chilblain LE typically begins in early childhood, and is associated with increased risk for SLE (69).

Chilblain Lupus is an example of a subset that has been linked to mutations in the genes *TREX1* and *STING*, i.e., a mutation in these regions will result in an IFN-1 immune response and disease activity (23, 70, 71).

LE-lichen planus overlap syndrome

This rare variant has clinical, histopathologic and immunofluorescence finding of both LE and LP (72).

Neonatal LE (NLE)

Neonatal LE is a condition affecting offspring when maternal anti-Ro/SSA- and anti-La/SSB antibodies, and less common anti-U1 ribonucleoprotein is passed over placenta with the potential of inducing an inflammatory response (73). The exposure to antibodies is associated with an increased risk of autoimmune congenital heart block, skin rash, thrombocytopenia, leukopenia, anemia, and hepatobiliary disease. In concordance with theories of etiology to other autoimmune mediated diseases, NLE is a multifactorial disease with an interplay of genetic susceptibility within the child and the environment (73, 74). The skin manifestation associated with NLE is characterized of an erythematous rash with central clearing sometimes with scaling, resembling those seen in lesions of SCLE (75). It is typically located in periorbital area of the eyes, sometimes referred to as racoon sign. A histological examination would mainly show an interface dermatitis and accumulation of IgG in dermal-epidermal junction (DEJ). The lesions can be distributed in the face with a majority of 80%, but is also found in the scalp, trunk, and extremities. It is usually not present by time of delivery instead appearing weeks later lasting for months (75–77). The lesions may heal with hypopigmentation and telangiectasia but rarely leaving scars behind (75). The skin manifestation itself is harmless and with good prognosis of disappearing in correlation with clearance of antibodies. However, the more severe outcome associated with NLE are autoimmune mediated congenital heart block. This is, when occurring, an irreversible state and therefore require intervention with pacemaker (76). Among 0.20–0.86% of females are thought to be positive for anti-Ro/SSA antibodies, although a great number of these do not have manifestations and are therefore not aware of their positive serology/expression (78). In a prospective study performed by Jaeggi et al. they noted that high titers of anti-Ro/SSA- and anti-La/SSB antibodies correlated with an increased incidence of NLE in the child, thereby implicating that the levels of antibody titers exposure correlate with severity of symptoms in the child (74). Considering NLE a rare disease, a high number of women are not aware of their positive serology and approximately 1–2% of those with positive serology will give birth to a child with NLE therefore screening for antibodies is a topic that have been up to discussion among clinicians (79). Today diagnose is based on serology of the mother and clinical presentation in the offspring. According to practical guidelines, potential prevention tools are discussed such as prenatally treatment of mother with hydroxychloroquine (HCQ) and immunoglobulin. Pregnant

TABLE 2 LE non-specific skin manifestations.

Raynaud's phenomenon –
Cutaneous vasculitis
Non-scarring alopecia
Livedo reticularis
Digital manifestations
Photosensitivity

women diagnosed with SLE are recommended to continue with HCQ preconceptionally and throughout their pregnancy (73, 80, 81).

For images of presented subtypes, we are referring to Rook's textbook of Dermatology (82).

Cutaneous manifestations in SLE and classification criteria

Classification criteria for SLE were developed in 1982 by the American College of Rheumatology (ACR). SLE diagnosis was initially based upon fulfillment of ≥4/11 criteria. The ACR criteria allow a patient with mainly mucocutaneous features of the disease, to fulfill 4 criteria (e.g., photosensitivity, malar rash, mucous ulcers, cutaneous lupus and ANA) (83). In 2012 the criteria were revised by The Systemic Lupus International Collaboration Clinic (SLICC) and were extended with additional 6 criteria. The 17 SLICC criteria gave a higher sensitivity in particular in an early phase of disease, although not higher specificity (84). In 2019 the EULAR/ACR criteria were further revised with adding a positive ANA test as an entry criterion, although of importance for clinicians to know that a negative test cannot exclude an SLE diagnosis (85). SLICC and EULAR/ACR both share high sensitivity (85–87).

Cutaneous manifestations in SLE are often divided into specific and non-specific, referring to specific histopathological picture or not (23). The non-specific manifestations can be seen in other systemic inflammatory diseases as well and is therefore not considered to be pathognomonic for CLE (88) (**Table 2**).

Mucosal lesions in SLE and CLE

In the EULAR/ACR classification criteria for SLE diagnosis, mucocutaneous lesion include oral ulcers as an additive criterion for an SLE diagnose (85). Mucosal lesions in lupus have been described with a variety of descriptive terms with no unified terminology. The prevalence of oral mucosal lesions and the various morphological presentations with possible correlation to disease activity was recently described and underscore the clinical importance of mucosal lesions also in a dermatological setting (89).

Diagnosis and management of CLE

The diagnosis is based on clinical evaluation and confirmed with histopathological investigation of skin biopsy. Serology is routinely obtained at baseline to assess systemic involvement as well as guidance among the subsets of CLE.

Dermapathology/histopathology

Histopathological picture for diagnosing CLE is considered the golden standard combined with clinical and serological picture. A biopsy will not be able to confidently discriminate between the three main subsets of CLE since these will all show an interface dermatitis. In the subsets of the less common forms of chronic CLE, especially tumidus and panniculitis, different histopathological features especially presence of mucin, have been widely discussed but consensus in criteria exist as of today (20). Moreover, the histopathological picture in cutaneous lesions of dermatomyositis, is identical to the picture seen in CLE (90).

Immunofluorescence

The lupus band test (LBT) is not routinely performed in CLE, but it can be helpful in the differential diagnosis of different inflammatory conditions in the skin. Non-lesion LBT is recommended as a diagnostic adjunct for diagnosing SLE in inconclusive cases (91). LBT consists of Immunoglobulins, predominantly IgG but also IgM and IgA together with complement factors C1q and CR in a linear pattern at the dermal-epidermal junction shown by immunofluorescence techniques on skin biopsies. They are reported to occur in lesional and sunexposed skin in DLE and SLE in more than 80% of cases. A positive LBT in non-exposed (e.g., gluteal) skin is seen in approximately 50% of SLE patients, but when it is found it is regarded as a specific criterion for SLE (59, 92, 93).

Serology

A serological test of ANA and extractable nuclear antigens (ENAs) should be performed at baseline to assess possible systemic involvement. A routine blood and biochemistry test including urinanalysis for proteinuria should be performed. If antimalarials are considered, a visual check should also be performed before start of medication.

ANA positivity is commonly present in ACLE together with anti-ds-DNA, but in less than 50% of DLE. Anti-Sm- as well as anti-ds-DNA positivity is not commonly present in DLE or SCLE but occur more frequently in ACLE (8).

Differential diagnosis

Dermatomyositis (DM) is an important differential diagnosis, and in cases without or with minimal myositis can be very similar to SCLE both clinically and histopathologically (94). In a recently published study, proteomic analyses were conducted through skin biopsies with lesions both from DM and CLE. Findings in this study was expression of IL-16, which was highly abundant and detectable in CLE lesions while in DM not detectable. Interpretation of this novel finding into the clinic could assist clinicians to differentiate between DM and CLE since the histopathologic appearance is similar in these two entities (95).

Sjögren's syndrome (SS), is primarily associated with Sicca symptoms, dry eyes and mouth, caused of an autoimmune reaction to lacrimal and salivary glands (96). Patients diagnosed with SS are frequently positive for anti-Ro/SSA-antibodies and sometimes SCLE and SS is seen in the same patient. It is, however not known why some patients with anti-Ro/SSA antibodies have increased frequency of photosensitivity and SCLE, and some are not photosensitive and display SS. The so-called annular erythema of SS is sometimes considered to be the Asian counterpart of SCLE, but there is no consensus in criteria or possible differences (97, 98).

Quality of Life, general symptoms, and comorbidity

It is today well known that patients with various skin disorders experience a great burden on their mental wellbeing (99). Consequently, a diagnose with CLE will have impact both on the physical appearance and on the mental health. The prevalence of depression among SLE patients is higher compared to the general population and studies on patients with CLE also implicate that mental illness as well as depression is increased (18, 100). Pruritus is a contributing factor to the impaired QoL in a variety of skin conditions and systemic disorders including autoimmune connective tissue diseases. Studies have shown that pruritus is a common subjective symptom in CLE and even appeared to be comparable to the itch experienced in chronic idiopathic urticaria and late-stage T-cell lymphoma. Pruritus may be an underrecognized symptom in CLE and may be a marker for disease activity both in CLE and SLE (101). Regarding this fact, early diagnosis, adequate treatment, and close collaboration among clinicians underscore the importance to enable a holistic treatment (102). An increase of depressive symptoms has been found also in patients with DLE and skin of color although not correlated to disease-activity but rather due to socioeconomic factors (17, 18).

The question of an increased risk of cancer among CLE has been studied, although the incidence of cancer has been reported to be higher among CLE patient compared to the general population, studies have not been able to exclude potential confounders such as exogenous factors, e.g., smoking (103, 104). Patients with CLE also seem to have higher risk in diseases such as embolism and thrombosis (105).

Guidelines of care

Current guidelines for management are based on clinical experience and consensus work as well Cochrane reviews (106–108). Before start of treatment, clinical assessment should be complemented by assessment of severity of activity and damage.

Cutaneous Lupus Area Severity Index was developed in 2005 as a tool for practicing clinicians to be used for measure damage and disease activity in cutaneous LE. Average time duration for assessment of CLASI is 5.25 min which makes it to a tool that is not time consuming and would therefore not interfere with time limit for appointment. Activity is defined as erythema (0-3p) and scale/hypertrophy (0-2p) and based on anatomic location. Damage is defined as scarring/atrophy/panniculitis (0-2p) and dyspigmentation (0-1p). Lesions in mucous membrane, alopecia and dyspigmentation are also part of scoring in CLASI (109). This tool has been validated against physician-reported and patient-reported outcomes in SLE (110). CLASI seems to contribute to a more comprehensive measurement as well as objective measure of the improvement in disease activity.

Ideally, patient reported measures of quality of life, using tools as DLQI, Skindex-29 and CLEQoL should also be checked at baseline before treatment and regularly followed up. At present there is no specific, standardized measure of QoL in CLE although some have been proposed (111–114).

Information including prophylactic measures such as smoking cessation and UV-avoidance are mandatory. A structured follow up of treatment results using CLASI as a tool, will help in guiding the clinician in the individual patient as well as creating knew knowledge and room for quality improvement work. Among CLE patients the prevalence of smoking is higher compared to the general population and according to Bartels et al. smoking exposure in pack years showed an increase in cutaneous manifestation among patients with SLE (115, 116). Smoking also seem to affect response to antimalarial agents resulting in worse response among patients whom receiving antimalarial treatment and smoke compared to non-smoking patients (117, 118). However, the mechanism is not fully understood, and important to be aware of smokers that among with CLE also tend to have more disease activity and therefore might be more challenging to monitor.

Currently, first line treatment is sunscreens, topical or intralesional corticosteroids or topical calcineurin inhibitors. In more widespread cases or if local treatment is not sufficient, antimalarial drugs are helpful in more than half of cases of CLE. Recently, a practical algorithm was published as a part

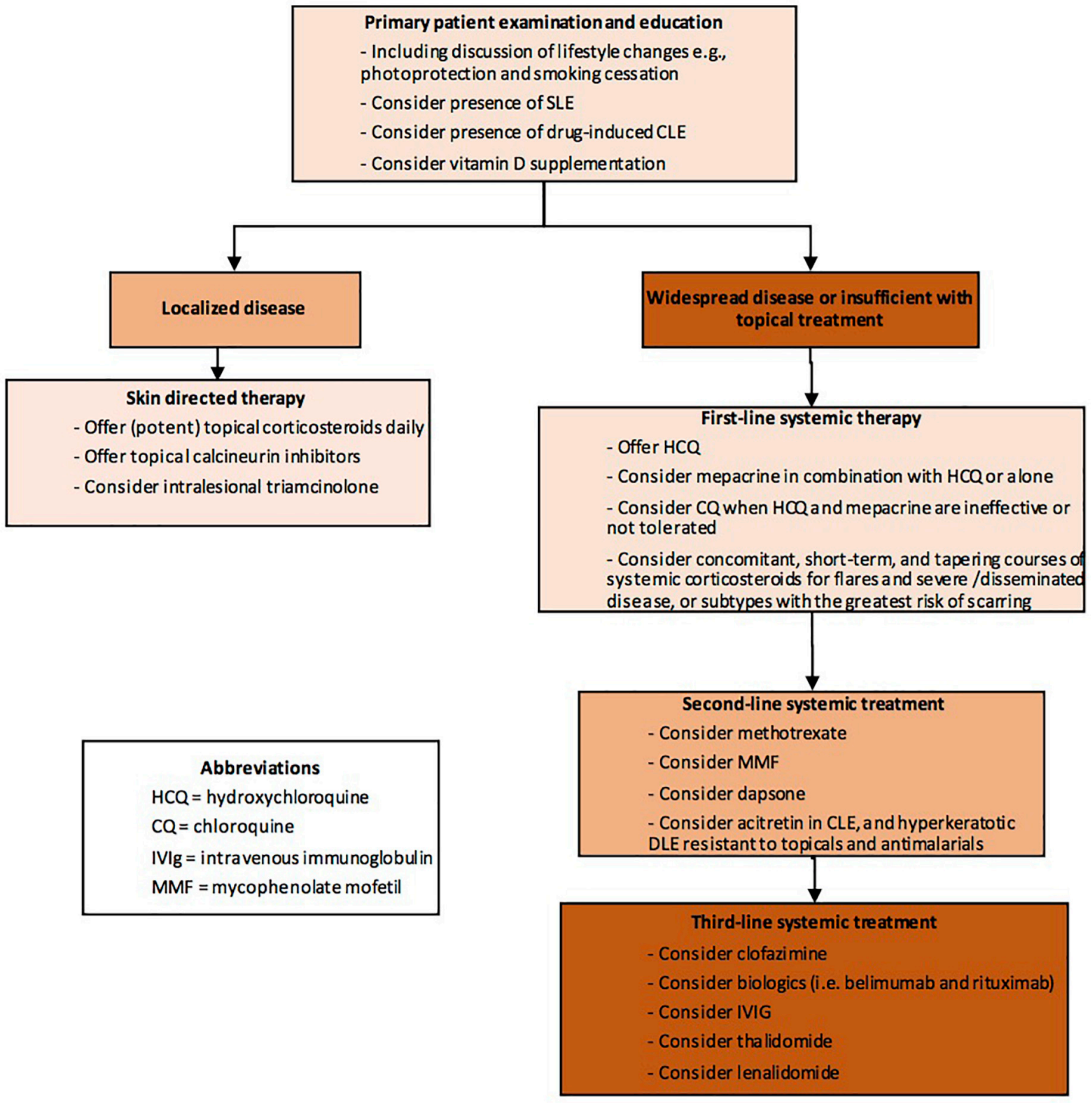

FIGURE 1
Patient management pathway Cutaneous Lupus Erythematosus (abbreviated) from Wiley Library © 2021 British Association of Dermatologists (119).

of British Association of Dermatologists guidelines—"Patient management pathway" (**Figure 1**) (119).

Although hydroxychloroquine is regarded to be very safe concerning potential retinal toxicity, recent data suggest that a longer treatment time than 7 years should be monitored (120).

Patients not responding to antimalarials, may respond to other immunomodulatory agents such as oral corticosteroids, retinoids, dapsone, methotrexate, mycofenolate mofetil (MMF), acitretin, clofazimine, biologics, intravenous immunoglobulin (IVIg), thalidomide and lenalidomide (59, 119).

Clinical trials on specific treatment aimed at the recent knowledge of immunopathogenesis in the IFN-I pathway and different ways to block interferon production and effects, are ongoing (121–123). Recently, the use of anti-BDCA2 antibody Litifilimab in CLE patients in a phase-two study was reported to be superior to placebo. In this study the treatment target used was CLASI-activity score (124).

The therapy strategy treat-to-target (T2T) has gained recognition as an efficient therapeutic strategy for management of chronic diseases in terms of both medical outcome and patient satisfaction. The aim is to achieve remission or the absence of symptoms by identifying a treatment target followed by frequent controls and, if needed, modifications of therapy. This requires validated scoring systems to evaluate therapy outcome. SLE has been proposed as a condition with potential for the T2T strategy with promising results (125, 126).

In CLE, structured use of T2T would require further validation of present tools for long-term disease outcomes such as CLASI and QoL instruments.

Conclusion

Strict, accepted, and meaningful classification and treatment targets along with efficient new treatments will eventually lead to better outcomes for this patient group.

Author contributions

JE performed literature search and writing. FN edited and commented and wrote parts of the text. Both authors contributed to the article and approved the submitted version.

Conflict of interest

FN has been consultant for Biogen, AstraZeneca and Serono.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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