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# CUTANEOUS LUPUS ERYTHEMATOSUS: A SYSTEMIC REVIEW TO ITS EPIDEMIOLOGY, PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT

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## ABSTRACT

Information on the etiology of lupus erythematosus has advanced fast in the last decade, bringing with it promising new medicines for the treatment of cutaneous lupus erythematosus (CLE)**.** It is divided into acute, subacute, and chronic subtypes, which are often recognized based on clinical criteria as well as histopathological and laboratory results**.** Although sunlight has been suspected for decades to play a role in the development of cutaneous lupus erythematosus (CLE), only recent research on the effects of ultraviolet irradiation on the skin of CLE patients has resulted in a more comprehensive model for the disease's pathogenesis. Significant progress has recently been achieved in elucidating the mechanisms involved in their development, allowing for the prediction of future targets for more successful therapies. Individual variables may contribute to the heterogeneity of CLE, and we speculate that the predominant inflammatory signature defined by T cells, B cells, PDCs, a strong lesional type interferon (IFN) response, or combinations of the above may be suitable to predict therapeutic response to targeted treatment. Pretherapeutic histological evaluation of the infiltrate could thus stratify patients with refractory CLE for T-cell-directed therapies (e.g., dapirolizumab pegol), B-cell-directed therapies (e.g., belimumab), PDC-directed therapies (e.g., litiflimab), or IFN-directed therapies (e.g., anifrolumab). This review provides an overview of CLE, including its epidemiology, clinical manifestations, pathophysiology, diagnosis, and available treatments, and concludes with the importance of early intervention.

**KEYWORDS**: Cutaneous lupus erythematosus (CLE), Pretherapeutic histological evaluation, T-cell-directed therapies, B-cell-directed therapies, PDC-directed therapies, IFN-directed therapies, Refractory CLE.

## 1. INTRODUCTION

Cutaneous lupus erythematosus (CLE) is an autoimmune illness that can appear as a cutaneous manifestation of systemic lupus erythematosus (SLE) or as an isolated cutaneous lupus lesion with no evidence of SLE (discoid LE (DLE) or subacute CLE (SCLE).[1] There are several subtypes of CLE, each with its pathogenesis. CLE is divided into LE-specific skin lesions, which are distinguished histopathological by interface dermatitis, and LE-non-specific skin lesions, which include urticarial vasculitis and livedo reticularis. LE-specific skin lesions are classified into three primary subgroups based on clinical, laboratory, and histopathological characteristics, as well as the length of time the skin lesions endure. Acute chronic lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE) are the three subgroups(figure 1).[2] The LE tumidus (LET) subtype, which has just lately been identified, is referred to as an intermittent CLE. Discoid lupus erythematosus (DLE), which accounts for 80% of cases, is the most prevalent subtype of CLE. DLE is distinguished by well-defined, atrophic scarring and hypopigmented plaques in the head and/or neck region, whereas SCLE is distinguished by widespread, non-scarring lesions with scaling, depigmentation, and telangiectasis on light-exposed areas of the face, neck, upper trunk, upper back, shoulders, and arms.[3] Papulosquamous lesions and/or annular plaques are the most common symptoms. ACLE causes widespread indurated erythema (on the face, scalp, neck, upper chest, shoulders, arms, and backs of hands) as well as indurated erythematous lesions on the malar areas of the face (a malar rash or butterfly rash), which typically cross both cheeks but spare the nasolabial folds.

Typically, ACLE evolves together with other SLE symptoms.[4]

Diagnosis of these disorders necessitates appropriate subtype categorization using a combination of physical examination, laboratory investigations, histology, antibody serology, and occasionally direct immunofluorescence while excluding systemic disease.

The treatment of cutaneous lupus includes patient education on adequate sun protection as well as topical and systemic medications. In situations of extensive, scarring, or treatment-refractory illness, systemic medicines are suggested.[5]

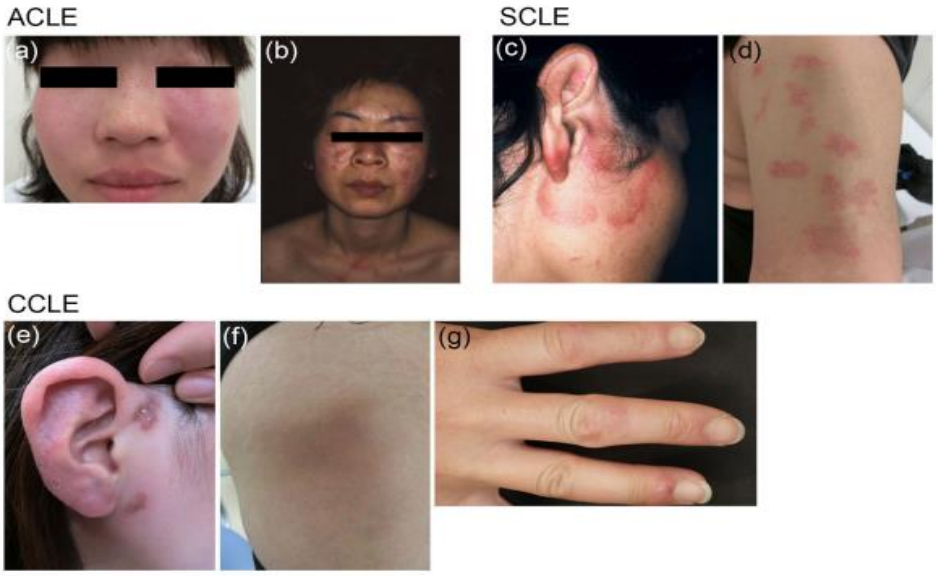


**Figure 1: depicts typical clinical manifestations of three CLE subtypes.** ACLE: (a) Malar rash or butterfly rash on the face; (b) Generalized indurated erythema of the face, neck, upper chest, and shoulders.
SCLE: (c) Papulosquamous or psoriasiform lesions on the upper arm; (d) Annular-polycyclic lesions on the face. CCLE: (e) Scar-causing DLE lesions on the face; (f) Lupus erythematosus profundus on the thigh with depressions; (g) Chilblain lupus erythematosus on the fingers with frostbite-like symptoms.[6]

## 2. EPIDEMIOLOGY OF CUTANEOUS LUPUS ERYTHEMATOSUS

CLE has a comparable incidence rate as SLE, according to studies from throughout the world. SLE patients are estimated to affect 1.5 to 11 per 100,000 people worldwide and 1.5-7.4 per 100,000 people in Europe annually. SLE is most commonly diagnosed in females, with a frequency of 203/100,000 and illness starts in the third or fourth decade of life.[7]

The incidence and prevalence of CLE have been determined by several epidemiological investigations. The population-based incidence of CLE in Sweden was determined to be 4/100,000 per person per year. Similar incidence rates, ranging from 2.74 to 4.36 per 100,000, have been recorded in the US, Asia, and Denmark.[8]

## 3. SIGNS AND SYMPTOMS OF CUTANEOUS LUPUS ERYTHEMATOSUS

Sunlight can cause and aggravate all types of skin lupus. A large rash on the cheeks and nose ("butterfly rash") is the most common symptom of acute cutaneous lupus. Subacute lupus is characterized by a red, raised, scaly rash over sun-exposed parts of the body. It has circular skin lesions or lesions that resemble psoriasis on sun-exposed skin. The symptoms of discoid lupus begin with a red to purple scaly rash on the head, face, ears, and other sun-exposed regions. When the scalp is affected, discoid lupus may heal with colorful scarring and possibly hair loss over time. Patients may experience discomfort or itching at times.[9]

## 4. PATHOGENESIS OF CUTANEOUS LUPUS ERYTHEMATOSUS

The pathophysiology of CLE is intricate and has received a lot of research. In short, a self-amplifying inflammatory loop is generated between cells of the innate and adaptive immune systems in all clinical subtypes of CLE. When environmental stimuli like ultraviolet (UV) light and medicines cause keratinocyte cell death, these cells are recruited to the area.

Smoking may be a risk factor, according to several research(figure 2).[10]

Extracellular release of cytosolic and nuclear debris often results in the activation of danger-related receptors, which subsequently triggers the attraction of certain inflammatory cells. Overexpression of interferons (IFNs), which results in an inflammatory bloop that imitates an antiviral response, is a crucial factor in the pathogenesis of LE. In recent years, there has been growing evidence that, in addition to autoreactive T cells and plasmacytoid dendritic cells (PDCs), B cells may play an important role in the integration of the inflammatory response.[11]

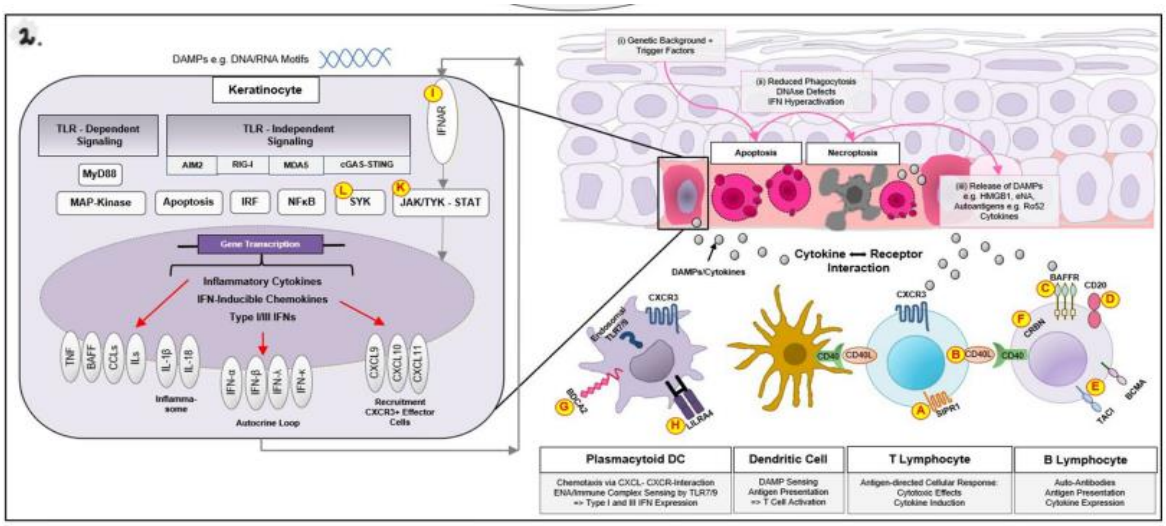


**Figure 2: Overview of cutaneous lupus erythematosus subtypes and schematic representation of CLE pathogenic processes.** (a) Clinical classification of CLE based on lesion chronicity. ACLE, SCLE, ICLE, and CCLE are the most prevalent subgroups, with CDLE being the most common form. (a) An inflammatory signature-oriented, therapy-directed histological evaluation concept. As indicated, CLE is thought to be an IFN-driven autoimmune skin disease characterized by cytotoxic lesional inflammation and activation of predominantly TLR-independent innate immune pathways. Trigger factors, when combined with a suitable genetic background, cause cell stress and, ultimately, apoptosis. Necroptosis occurs as a result of numerous defective processes (reduced phagocytosis, DNAse/TREX1 deficiencies, IFN hyperactivation), resulting in an inflammatory response with DAMP production (e.g. endogenous nucleic acids, HMGB1). Ro52 autoantigens and CXCL chemokines, ILs, and IFNs are examples of cytokines. Potential autoantigens are detected by DCs and presented to lymphocytes in surrounding lymph nodes. This causes lymphocytic differentiation, followed by cytotoxic effector functions against keratinocytes and the formation of autoantibodies.

After recognizing released nucleic acids, recruited PDCs are induced to produce type I and type III IFN, hence enhancing lesional inflammation. Different inflammatory signatures, such as a B-cell- or PDC-rich infiltrate or a high IFN signature, may be examined histologically in the lesional tissue of CLE patients. Targeted therapies are focused on several inflammatory cytokines and their receptors or intracellular targets. T lymphocytes: (A) S1P receptor 1 antagonists (amiselimod); (B) CD40L antagonists (dapirolizumab pegol, frexalimab). B lymphocytes: (C) BAFF receptor antagonists, such as the monoclonal antibody belimumab; (D) CD20 antibodies, such as rituximab; (E) fusion proteins that bind to BAFF and TACI (telitacicept); and (F) the cereblon E3 ligation modulator iberdomide. pDCs: (G) BDCA2 inhibition (litiflimab); (H) anti-LILRA4 antibody daxdilimab. IFN-associated pathways: (I) IFNAR1 inhibition (anifrolumab); (K) JAK inhibition (e.g., flgotinib, tofacitinib, delgocitinib), TYK2 inhibition (deucravacitinib). Other intracellular pathways that have been inhibited include (L) SYK inhibition (lanraplenib). CLE cutaneous lupus erythematosus, ACLE acute lupus erythematosus, SCLE subacute lupus erythematosus, ICLE intermittent lupus erythematosus, CCLE chronic lupus erythematosus, CDLE chronic discoid LE, IFN interferon, TLR toll-like receptor DAMPs are danger-associated molecular patterns, while ILs are interleukins and pDCs are plasmacytoid dendritic cells. BAFF B-cell activating factor, TACI transmembrane activator and CAML interactor, BDCA2 blood dendritic cell antigen 2, LILRA4 leukocyte immunoglobulin-like receptor subfamily A member 4, IFNAR1 interferon-/receptor chain SYK spleen tyrosine kinase, HMGB1 high mobility group box 1, DCs dendritic cells, CD40L CD40 ligand, pDCs plasmacytoid dendritic cells.[12]

## 5. PATHOPHYSIOLOGY AND IMMUNOLOGY

Keratinocytes, which are non-inflammatory cells, aid in lesional inflammation in CLE. Keratinocyte apoptosis is brought on by an initial trigger, such as UV radiation, smoking, or medications.[13]

In keratinocytes, exposure to UV radiation causes an overexpression of autoantigens such Ro52, which induces and activates proinflammatory pathways. Apoptotic keratinocytes contain antigens that individuals who have tested positive for autoantibodies may detect. Given that ribonucleoprotein autoantibodies cause mice to acquire lupus lesions, they may have a separate pathophysiological function.[14] Intriguingly, UV rays or other harmful triggers initially cause keratinocyte cell death and chemokine production throughout the entire epidermal layer, but later in established CLE lesions, keratinocyte apoptosis, and proinflammatory chemokine production are restricted to the dermo-epidermal junction, causing interface dermatitis. Keratinocytes from CLE patients' uninvolved (non-lesional) skin are more susceptible to UV radiation-induced cytotoxicity than keratinocytes from healthy donors, indicating a disease propensity. Secondary necroptosis of

keratinocytes causes the lesional release of nucleic acids and danger-associated molecular patterns (DAMPs) after the original keratinocyte injury.[15] These latter substances include high mobility group box 1 protein (HMGB1), a cytokine that promotes inflammation and can also act as an autoantibody in CLE. Additionally, UV exposure damages DNA and creates immune-stimulatory DNA patterns like 8-hydroxyguanosine. CLE may affect the phagocytic clearance of apoptotic cells and nucleic acids.[16] Pattern recognition receptors (PRRs), such as MDA5, RIG-I, and cGAS-STING, expressed by keratinocytes identify nucleic acids, causing IFN-regulated genes to be produced. Toll-like receptors are involved in the keratinocyte response. (TLR)-independent. The pro-inflammatory cytokines interleukin (IL)-6 and chemokines CXCL9, CXCL10, and CXCL11, which are CXCR3 ligands, are further produced by keratinocytes when IFN and IFN (type I and type III IFNs) are produced. This process is called autocrine secretion. Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling is one way that the IFN response is mediated.[17] By interacting with (autoreactive) cytotoxic T cells through CXCR3-binding, the aforementioned chemokines also encourage keratinocyte cell death by attracting cytotoxic T cells. Nucleic acid motifs also cause melanoma 2 (AIM2) to activate the inflammasome. It's interesting to note that even in the skin of CLE patients that seem to be healthy, baseline phospho-STAT (PSTAT) activity is higher than it is in people with another chronic inflammatory skin condition (psoriasis). As said, there are several inflammatory cells and a complicated interplay between them that contribute to the pathophysiology of CLE. As a result, in the sections that follow, we discuss new findings that take certain cell types into account when describing how inflammation in SLE and CLE is orchestrated (Figure 3).[18]

### 5.1 DENDRITIC CELLS

Antigen-presenting cells (APCs), including dendritic cells (DCs) and PDCs, detect accumulated nucleic acids after the first demise of keratinocyte cells. Through the interaction of the CXCL chemokine with CXCR3, PDCs are drawn to the skin lesions.[19]

PDCs primarily use TLRs, specifically TLR7 and TLR9, to detect nucleic acids. At least in SLE, endocytosis via TLR9 and CD 32 may be used to achieve the uptake of nucleic acids and immune complexes. Large numbers of type I and type III IFNs, cytokines, and ILs are produced by PDCs after PRR activation, further regulating the autoimmune cycle. Type I IFN is required for the development and migration of PDC. PDC infiltrates are found in a high number of skin biopsies and can form clusters in CLE skin lesions; however, PDC infiltrates are not seen in all skin lesions.[20]

Single-cell ribonucleic acid (RNA) and spatial RNA sequencing have recently revealed that even healthy-appearing CLE skin includes a type I IFN-rich environment and that CD16+ DCs undergo IFN priming in the skin, leading to proinflammatory subtypes. PDCs are an appealing therapeutic target because of their important involvement in CLE pathogenesis. The blood DC antigen 2 (BDCA2) receptor, which is only found in PDCs, is one possible target for PDC treatment. BDCA2 inhibits IFN induction.[21]

### 5.2 T CELLS

T cells, B cells, DCs, natural killer (NK) cells, and, on rare occasions, neutrophils make up lesional infiltrates. CXCL10 attracts CXCR3-expressing T cells to skin lesions. T cells identify antigens presented by APCs via interacting with the T-cell receptor (TCR) and the major histocompatibility complex (MHC). TCR interaction activates downstream signaling pathways, resulting in a variety of T-cell activities.[22]

In lupus patients, T cells have a lower activation threshold. The interaction between spleen tyrosine kinase (SYK) with Fc receptor-chain (FcR) resulted in increased phosphorylation of signaling molecules and increased calcium influx, resulting in enhanced TCR downstream signaling. Furthermore, transcription factors influence the expression of several genes, including the CD40 ligand (CD40L), a co-stimulatory protein that promotes B-cell activities such as proliferation, differentiation, antibody production, and class switching. Increased CD40L affects not just on B cells interacting with T cells, but also on APCs. It increases the expression of co-stimulatory receptors on APCs, hence amplifying the TCR signal. several different pathways have been characterized as either deficient (cyclic adenosine monophosphate-dependent phosphorylation, protein kinase C) or enhanced (phosphatidylinositol-3 kinase (PI3K). SLE patients also have an IL-2 deficiency. T-cell polarization is dependent on IL-2, and reduced IL-2 expression promotes the development of inflammatory T-helper 17 (Th17) cells. When activated, cytotoxic T lymphocytes attack keratinocytes in the basal epidermal layer, resulting in interface dermatitis. This is true for CLE subtypes with superficial involvement, but it only plays a minimal role in dermal or subcutaneous CLE subtypes like LE profundus.

Cytotoxic indicators such as granzyme B, which is produced by CD8+ T cells, are seen in CLE skin lesions and are most likely triggered by IFN. Granzyme B expression is greater in scarring lesions of CDLE compared to non-scarring lesions of subacute CLE, indicating a pathophysiologic function in CLE scarring lesions. Th2 cells are likely to initiate cutaneous inflammation, but once established, lesions transition to a Th1-dominated inflammation. Th1 cells boost type I IFN production in cytotoxic T cells and macrophages, thus it is not just cytotoxic T cells that cause keratinocytes apoptosis. Lesional CD4+ T lymphocytes can trigger keratinocytic apoptosis directly via FAS/FAS ligand (FAS-L) interaction.

T-helper cells generate IL-21, which increases the expression of granzyme B in PDCs and encourages NK cells to target keratinocytes. Type I IFNs, on the other hand, suppress granzyme B synthesis by PDCs.[23]

In SLE, Th cells can respond to nucleosomes produced by dying cells, causing B cells to produce (anti-DNA-) antibodies. In lupus, Th clones generate IL-2, IFN, and IL-4, and CD4+ T cells overexpress perforin, which is epigenetically controlled by DNA methylation. When compared to other inflammatory skin disorders or healthy persons, the amount of CD4+, CD8+ regulatory, and -T cells are significantly reduced in CLE, and impairment of regulatory immunosuppressive function contributes to the autoimmune cycle. Furthermore, growing research suggests that the composition of the inflammatory infiltrate varies amongst CLE subtypes. CD4+ T cells and FOXP3+ T cells are much lower in subacute CLE skin lesions compared to CDLE, as is the CD4/CD8 ratio.[24]

### 5.3 B CELLS AND PLASMA CELLS

B cells play an important part in LE pathogenesis through the production of autoantibodies against nuclear components and their intricate interactions with T cells. Different IFNs increase B cells' ability to generate antibodies; nevertheless, persistent type I IFN exposure stimulates autoantibody synthesis. A novel mouse model established the importance of IL-21 and TLR7/9 in B-cell recruitment to inflammation sites in CLE lesions and localized antibody production. In SLE, IL-17 attracts immune cells and boosts B-cell antibody production.[25]

Antinuclear antibodies (ANAs) are common in SLE patients, although only a small percentage of CLE patients have detectable autoantibody levels in the blood. Various investigations found a variety of autoantibody presence and CLE subtypes. In SLE, the presence of antibodies corresponds to the HLA-DR3 phenotype, and the presence of other antibodies (e.g., Ro or LA) is related to disease severity. In SLE, IL-17 attracts immune cells and increases B-cell antibody production. B-cell motility, receptor engagement, antigen presentation, cytokine responsiveness and production, survival, differentiation, and class switching are all IFN-dependent.[26]

Since substantial B-cell signatures and lesional B-cell infiltrates were documented in individuals with autoantibody-negative CLE, our view of the pathophysiological significance of B cells in LE has evolved. Aside from antibody production, B cells can contribute to the autoimmune response through a variety of methods. For example, new research suggests that B cells have an antigen-presenting and T-cell activating activity. Lesional B-cell infiltration differs amongst LE subtypes. B lymphocytes can group and create lymphoid-like structures in the skin known as tertiary lymphoid organs/structures (TLO). The establishment of dense B-cell clusters or TLOs has been documented in many subtypes of CLE, such as LE profundus or CDLE. B cells, in addition to producing antibodies, can contribute to the autoimmune response in a variety of ways. The new study, for example, reveals that B cells may both convey antigens and activate T cells. Lesional B-cell infiltration varies according to LE subtype. B cells can form lymphoid-like structures in the skin called tertiary lymphoid organs/structures (TLO). The formation of dense B-cell clusters or TLOs has been seen in various CLE subtypes, including LE profundus and CDLE. B cells undergo immunoglobulin class switching and somatic hypermutation during maturation to differentiate into antibody-secreting plasma cells; these processes can occur in germinal centers or extrafollicular sites, and both have been documented in SLE.[27]

CD40 and IL-21 are required for somatic hypermutation and isotype switching. The cells help to differentiate plasma cells. After naive B cells are activated, plasma cells are formed and continue to make antibodies while getting survival signals from surrounding cells via the BAFF axis and IL-6.

Plasma cells can collect and stay at the site of inflammation. Plasma cells can generate antibodies even in the absence of antigens because they get survival signals from BAFF or IL-6.[28]

### 5.4 NATURAL KILLER CELLS

Peripheral NK cell levels in SLE have an inverse relationship with disease activity. Lupus NK cells release more IFN than healthy controls, and their cytotoxic activities are compromised. In CLE skin lesions, NK cells are abundant and have the ability to proliferate. terms of CLE pathophysiology, the definitive involvement of NK cells remains unknown.[29]

### 5.5 NEUTROPHILL GRANULOCYTES

Neutrophil granulocytes are early responses to tissue injury. Neutrophils generate antimicrobial peptides (AMPs; for example, LL-37) and reactive oxygen species (ROS), as well as neutrophil extracellular traps (NETS), which are nets composed of chromatin, histones, and other intracellular material. The process of NET creation, known as 'NETosis,' can be a source of immunogenic materials and, coupled with the release of AMPs, has been related to autoimmunity. Recent research found a significant level of molecular variability in pathogenic neutrophil subsets in SLE (so-called low-density granulocytes [LGS]) with differences in NET formation and responsiveness to type I IFNs, as well as a large number of IFN-induced genes. In SLE, LGS has been linked to increased vascular inflammation and arterial dysfunction. Not only are neutrophils susceptible to NETosis, but poor NET breakdown owing to enzymatic blockage or antibody production can also enhance SLE activity.[30]

Complexes produced by double-stranded DNA (dsDNA) and LL-37 are taken up by pDCs via endocytosis and

detected by TLR9 after NET formation and the release of other immune cells in SLE, resulting in activation and type I IFN production. Autoantigens can be LL-37/dsDNA complexes. Higher amounts of LL-37 and other AMPs have also been seen in CLE skin lesions as well as SLE skin lesions when compared to healthy controls. Furthermore, NETs are seen in numerous CLE subtypes (panniculitis, ACLE, DLE); nonetheless, it is unknown if and to what degree such subsets of neutrophils and AMPs have a pathophysiologic function in CLE.[31]

### 5.6 MACROPHAGES

Monocytes and macrophages perform different biological functions, such as phagocytosis and cytokine synthesis. Monocytes play an antigen-presenting role in SLE.

There have been conflicting findings on whether there are differences in monocyte and macrophage counts in lupus patients vs healthy controls. Several investigations have found a deficiency in apoptotic material absorption and extended phagocytosis, resulting in the buildup of possible autoantigens and additional immunological stimulation lupus.[32]

One study found that the phagocytosis ability of macrophages from SLE patients was decreased only when the patient's serum was present. Macrophages from SLE patients have a reduced ability to adhere. Furthermore, macrophages may be divided into M1 macrophages, which have inflammatory and destructive capabilities and are activated by IFN, and M2 macrophages, which have regulatory features, are engaged in tissue healing, and are activated by IL-4 or IL-13. Polarization in SLE favors M1 macrophages since M1 genes (e.g., STAT1 and SOCS3) were shown to be differentially expressed in SLE patients' monocytes. In a mouse model, adoptive M2 macrophage transfer reduced the severity of SLE.

One research discovered FAS-L-expressing macrophages enriched around hair follicles in CLE patients, perhaps responsible for lupus-associated scarring alopecia via a direct FAS/FAS-L interaction with hair follicle keratinocytes. More information on the potential roles of macrophages in SLE may be found elsewhere. Recent research revealed that the microRNA (miRNA) miR-4512 has a pathophysiologic, inflammatory role in SLE monocytes and macrophages via the TLR4-CXCL2 axis.[33]

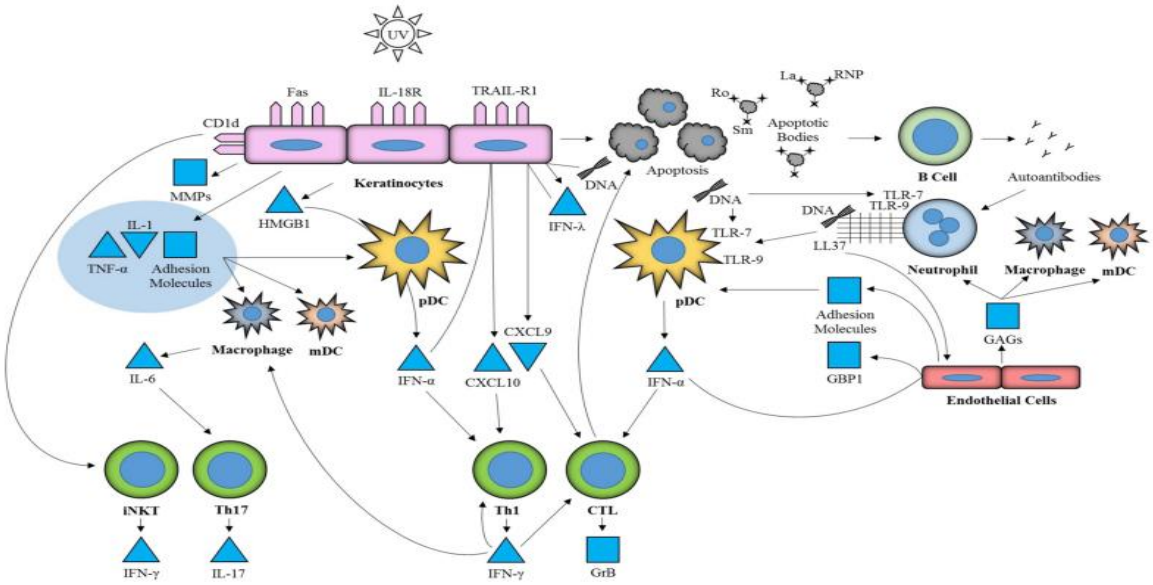


**Figure 3**: In reaction to UV radiation and other damage, keratinocytes (KCs) generate cytokines and pro-inflammatory chemicals. These cytokines attract and activate innate immune system cells such as macrophages, myeloid dendritic cells (mDCs), and plasmacytoid dendritic cells (PDCs). Endothelial cells use adhesion molecules and glycosaminoglycans (GAGs) to recruit cells from the innate immune system. PDCs produce more cytokines when they are exposed to endogenous DNA from apoptosis and neutrophil extracellular traps. PDCs generate interferon (IFN)-, which attracts adaptive immune system members such as Th1 and cytotoxic T lymphocytes (CTLs). Th1 cells release IFN-, which activates macrophages and CTLs while also increasing their production. CTLs prepare KCs and other cells for death by activating caspases in the target cells via granzyme B (GrB). Through increased production of the antigen-presenting protein CD1d, KCs attract invariant natural killer T cells (iNKTs). IFN- and other cytokines are produced by iNKTs. Through the secretion of IL-6, several immune cells enhance the development and activation of Th17 cells. IL-17 is produced by Th17 cells. The activity of these cells and cytokines results in the creation and continuation of cutaneous lupus erythematosus lesions. MMP stands for matrix metalloproteinase, while TLR stands for Toll-like receptor.[34]

## 6. DIAGNOSIS

To determine the clinical subtype, the diagnosis of CLE is based on information gathered during the history-taking and physical examination, as well as histopathological findings and, if necessary, immunohistopathology of the cutaneous lesions.[35]

Depending on the subtype of CLE, which is determined based on clinical and histological findings, the kind and extent of the laboratory study must be customized to each patient. Routine biochemical tests, in addition to particular tests based on the planned therapy, should be done before beginning the medication and monitoring any potential side effects.

After confirming the diagnosis and defining the CLE subtype, additional tests may be required, such as serological tests to characterize the autoantibody profile and tests to evaluate the disease's systemic activity, as well as complementary tests to investigate the involvement of specific organs, which may aid in determining the prognosis.[36]

### 6.1 HISTOPATHOLOGY

Except for lupus profundus and tumid LE, different types of CLE share histological features, making a comprehensive clinicopathological correlation essential for establishing the subtype. The development and stage of the lesions influence histopathological differentiation.[37]

The most prominent features include perivascular and peri adnexal lymphocytic inflammatory infiltrates in the superficial and deep dermis, as well as interface dermatitis, which is defined by lymphocyte aggressiveness at the dermo-epidermal junction. As a result, further changes occur, such as basal layer vacuolar degeneration and keratinocyte necrosis in the lowest layers of the epidermis, followed by basement membrane thickening. The epidermis thins out, and the epithelial ridges flatten. Mucin deposition in the dermis is a common observation in LE, albeit it is non-specific and varies in degree depending on the kind of lesions.[38]
In addition to the modifications already mentioned, hyperkeratosis, follicular corneal plugs, and epidermal thinning are highly visible in DLE, the prototype of fully established diseases. DLE in its late, cicatricial stage is characterized by pigmentary incontinence, vascular ectasia, dermal fibrosis, and adnexal loss.

The abnormalities in ACLE are often milder, although there may be edema and bleeding in the superficial dermis.

The lymphocytic infiltration is minimal, perivascular, and superficial, with neutrophils present in the most recent lesions. The TEN-like variety of ACLE has significant hydropic basal degeneration, resulting in dyskeratosis, subepidermal cleft, and total epidermis necrosis.

The interface dermatitis in SCLE is frequently severe, with many cytoid bodies. The lymphocytic infiltration is mostly perivascular and superficial. The presence of epidermal thinning, hyperkeratosis, follicular plugs, mucin deposition, and basement membrane thickening is less pronounced than in DLE.

Bullous LE has a prominent neutrophilic infiltration that is commonly aligned with the dermo-epidermal junction and causes microabscesses in the dermal papillae, as well as subepidermal cleavage and bullae with neutrophils within them.[39]

### 6.2 ANTINUCLEAR ANTIBODIES

Antinuclear autoantibodies are immunological markers that are used to diagnose and monitor LE. The antinuclear antibody (ANA) screening test is the most often utilized. It is an indirect immunofluorescence approach that uses HEp-2 cells as a substrate. In ACLE/SLE, ANA is more important, being seen in virtually all patients (94% to 100%), generally at high titers larger than 1/160. Even at high titers, they are not specific for SLE since they may be discovered in a variety of disorders, including various connective tissue diseases, hemo- tological and liver diseases, viral infections, after the use of numerous drugs, and even in healthy persons. In other types of CLE, ANA is shown to be a lower level, in 52% to 80% of SCLE patients and 5% to 17% of DLE patients. Because they are specific for SLE, anti-native DNA, and anti-Sm antibodies are the most relevant, although having lower sensitivity of 56% to 70% and 19% to 25%, respectively. In addition to diagnostic usefulness, the anti-native DNA antibody can be used to monitor the illness since serum levels tend to reflect disease activity, particularly nephropathy, especially when the anti-Sm antibody is present. Anti-native DNA and anti-Sm antibodies are uncommon in SCLE patients and almost non-existent in CCLE patients. Anti-Ro/SS-A and anti-La/SS-B antibodies are not specific for LE and are frequently seen in patients with Sjögren's disease.[40]

They occur in 36% to 64% and 8% to 33% of SLE patients, respectively, and are associated with cutaneous and hematological symptoms such as cytopenias. Anti-Ro/SS-A and anti-La/SS-B antibodies are detected in 70% to 90% and 30% to 40% of SCLE cases, respectively, and up to 25% and 5% of DLE cases, respectively. Anti-Ro/SS-A antibodies, in particular, are regarded as SCLE indicators and are linked to the severe photosensitivity of this subtype of CLE. Furthermore, when these antibodies are present in a pregnant woman, they pass the placental barrier and can induce neonatal LE.

Antibodies directed particularly against the 52 kD component of the Ro/SS-A antigen have been linked to an increased risk of congenital heart block. Adults who have these antibodies may also have QT prolongation,

which puts them at a higher risk of developing cardiac arrhythmias.

Anti-RNP antibodies are typical of mixed connective tissue disease, however, they can be found in 23% to 49% of SLE patients and do not correlate with any clinical signs. They may occur in 8% to 10% of SCLE instances and only in very rare cases of CLE.[41]

## 7. TREATMENT

Pharmacological and non-pharmacological treatments are used to treat CLE. Choosing the most successful therapy for each instance can be difficult, requiring attention to clinical symptoms as well as familiarity with current medicines. It is crucial to examine patient adherence to treatment at each medical appointment, Although the US Food and Drug Administration (FDA) has only approved three medications for use in SLE --- corticosteroids, hydroxychloroquine, and none particularly licensed for CLE, there is data on the literature that allows justifying the treatment strategy.[42]

### 7.1 GENERAL MEASURES

Sunscreens help prevent the emergence of lesions in CLE patients, therefore photoprotection is an important component of therapy. Other patient care measures, including behavioral adjustments and the use of helmets and long-sleeved clothes, preferably with UVR skin-protection technology, are also required.

At each appointment, smoking cessation should be assessed and promoted, preferably with a referral to support programs and treatments. Vitamin D supplementation may be effective for illness management in those who are deficient. In the event of drug-induced CLE, the suspected medication should be stopped immediately.

When utilizing teratogenic medicines, it may be required to use contraception. If there is no history of thrombosis or high levels of antiphospholipid antibodies, women with CLE can take combination oral contraceptives; otherwise, an intrauterine device or isolated progestogens should be used.

Scars and alopecia can be concealed using cosmetic camouflage and hair prostheses, increasing patients' quality of life and self-esteem. Because of the danger of kernelization, patients with CLE should be encouraged to avoid procedures that traumatize the skin.[43]

### 7.2 TOPICAL TREATMENT

Because of its anti-inflammatory impact, corticosteroids are considered the first line of topical treatment. They can be used to treat localized lesions or as adjuvant therapy in patients receiving systemic therapy. Potent corticosteroids, such as clobetasol, are more successful than low-potency ones in regulating the condition. However, due to their action on fibroblasts and blood vessels, respectively, both medications are linked with a higher incidence of side effects, such as striae and telangiectasias, in addition to rosaceiform perioral dermatitis. As a result, powerful topical corticosteroid treatment should be utilized for as little time as feasible. For isolated hypertrophic lesions, intralesional corticosteroid injections may be employed.[44]

Topical calcineurin inhibitors, such as tacrolimus 0.03% or 0.1% ointment and pimecrolimus 1% cream, can be used instead of corticosteroids in situations when therapy is extended or there is a higher risk of adverse effects, such as lesions on a child's face. They are not as effective as strong topical corticosteroids. The usage of these drugs can cause a burning sensation, pruritus, and erythema at the site of application. Some trials have demonstrated promising outcomes when clobetasol 0.05% and tacrolimus 0.03% were used together.[45]

When taken as a 0.5% cream, R-salbutamol is a 2-adrenergic receptor agonist that reduces IL-2 and IFN-production and may ameliorate CLE lesions. It is not, however, commercially accessible for topical usage. Topical retinoids have been used effectively in a few modest case studies.

### 7.3 SYSTEMIC TREATMENT

Patients with localized lesions that are resistant to topical treatment or with widespread lesions typically require systemic therapy.

**Table 1: Drugs used for treatments.**

| DRUG | LEVEL OF EVIDENCE | DEGEE OF RECOMMENDATION |
|---|---|---|
| Hydroxychloroquine | 1 | A |
| Acitretin | 2 | B |
| Isotretinoin | 2 | B |
| Methotrexate | 4 | |
| Dapsone | 4 | |
| Thalidomide | 2 | A |
| Mycophenolate mofetil | 2 | B |
| Azathioprine | 4 | |
| Belimumab | 2 | B |

Evidence Level: 1 -- Systematic Reviews (SR), Randomized Clinical Trial (RCT) meta-analysis; 2 - Cohort studies and cohorts; 3---SR of Case-control studies (case-control studies), 4 -- case series, poor cohort studies, and case-control research; 5 — Professional opinion.

Degree of recommendation: A --- more consistent observational or experimental studies (meta-analyses or RCT); B --- less consistent observational studies (other non-randomized or observational clinical trials and case-control studies); C--- Case studies or series (uncontrolled studies); D --- uncritically evaluated view based on consensus, physiological investigations, or animal models.

Table 1 displays the amount of evidence and degree of recommendation for the key medications used in systemic therapy of CLE.[46]

### 7.3.1 ANTIMALARIALS

Antimalarials (AM) are the first-line systemic treatment, and they are likely to prevent CLE from progressing to systemic illness. They can reduce type I IFN production by decreasing antigen presentation by PDC, the formation of antigen-antibody complexes, and signaling via toll-like receptors. When compared to chloroquine (CQ), hydroxychloroquine (HCQ) has a higher safety profile in terms of ocular toxicity. According to some sources, the suggested dose of HCQ is 6.5 mg/kg/day. However, the American Academy of Ophthalmology suggested in 2016 that dosages of HCQ larger than 5 mg/kg/day and CQ greater than 2.3 mg/kg/day be avoided due to an elevated risk of retinopathy.[47]

AM causes nausea, vomiting, skin pigmentation, dizziness, headache, ototoxicity, and peripheral neuropathy. The most common adverse effect is retinopathy, which occurs in up to 1% of patients. Patients should be evaluated at baseline and yearly after the fifth year of medication usage if they do not have any additional risk factors. Patients using HCQ at dosages greater than 5 mg/kg/day, those with renal impairment, those taking tamoxifen concurrently, or those with pre-existing retinal maculopathy are at higher risk for retinopathy and should be checked more often.[48]

### 7.3.2 METHOTREXATE

For patients who are unresponsive to AM therapy or who have any other contraindications, methotrexate (MTX) is the primary option among second-line medications. It is a dihydrofolate reductase inhibitor that interferes with cell division and inhibits the generation of antibodies. Orally or subcutaneously, a dosage of 7.5 to 25 mg per week is advised.

Hepatotoxicity, mucosal ulceration, nausea, vomiting, stomach discomfort, and bone marrow suppression are some of the adverse effects. The usage of folic acid in the days after taking medicine might greatly lessen gastrointestinal adverse effects, as can subcutaneous injection.

In the initial few weeks of medication use, after increasing dosages, and periodically during routine follow-up, the patients should have laboratory monitoring. Patients who are alcoholics, using other hepatotoxic medications concurrently, have severe hepatic steatosis, renal failure, or underlying liver disease, especially viral hepatitis, should avoid using MTX. These factors should be looked into before beginning the medication. Outside of these circumstances, the risk of hepatotoxicity is minimal. Pneumonitis in the interstices is an uncommon and possibly dangerous side effect.

Since MTX might cause birth defects, appropriate contraception is advised.[49]

### 7.3.3 SYSTEMIC RETINOIDS

Retinoids, particularly the verrucous versions, are used well in the treatment of refractory CLE. They control and maintain proper keratinocyte differentiation and suppress the synthesis of pro-inflammatory cytokines including IL6 and IFN-. There is no discernible difference in the effectiveness of HCQ and acitretin in patients with many CLE subtypes. Small case series have also employed isotretinoin.

The dosage of isotretinoin with acitretin is 0.2 to 1 mg/kg/day. In most cases, a response comes in two to six weeks. Additionally, recurrence frequently happens soon after stopping a medication.

Patients who use retinoids should have regular blood tests to check for signs of hepatotoxicity and elevated serum triglyceride levels. Mucocutaneous xerosis and bone abnormalities such as hyperostosis are additional negative effects. The danger of increasing photosensitivity should prompt increased sunscreen usage. Women of reproductive age should be put on sufficient contraception during and after therapy (isotretinoin, up to one month, and acitretin, up to two to three years) due to the potential of teratogenicity.[50]

### 7.3.4 DAPSONE

Myeloperoxidase is a protein that is found in neutrophils and monocytes and is inhibited by the immunomodulatory and antibacterial drug dapsone. It may be utilized separately or in conjunction with AM. Dapsone is effective in treating more than 50% of CLE patients, including those with DLE, a historically more resistant variant, where the response rate is closer to 60%. In the management of bullous LE and other neutrophilic manifestations of LE, such as urticarial vasculitis, dapsone is regarded as the medicine of first choice. Dapsone typically has a poor therapeutic response in hyperkeratotic variations.

The starting dose is 50 mg per day, while the maximum daily dose is 200 mg. Before beginning therapy, patients should have their glucose-6-phosphate dehydrogenase levels checked.

Serious side effects might include methemoglobinemia, agranulocytosis, and drug rash with eosinophilia and systemic symptoms (DRESS syndrome). Up to 50% of individuals may get hemolytic anemia. During the first month of treatment and then every three months after that, it is important to evaluate hemoglobin levels. Methyl-hemoglobin levels can be checked between the eighth and fourteenth day after the medicine is started. The only second-line medication that is safe to take while pregnant and nursing is dapsone.[51]

### 7.3.5 MYCOPHENOLATE MOFETIL

The drug mycophenolate mofetil (MMF) is regarded as a third-line therapy for CLE. In addition to promoting T-lymphocyte death and decreasing B-lymphocyte activation, MMF promotes guanosine triphosphate depletion, which is necessary for lymphocyte and monocyte adherence to the endothelium throughout the inflammatory process. In 62% of CLE patients, a complete or significant response rate has been seen. The beginning dose is 500 mg/day, which may be escalated to 3 g/day, and it can be taken alone or in conjunction with AM.

Gastrointestinal issues, Cytopenias, hepatotoxicity, and viral and urinary infections are the most prevalent adverse effects. Patients should have regular laboratory evaluations. As a category X medication, it is contraindicated during pregnancy.[52]

### 7.3.6 AZATHIOPRINE

A purine analog called azathioprine inhibits T- and Blymphocyte activity and lessens antigen presentation. If the aforementioned treatments fail, it could be suggested in CLE. CLE has been successfully treated in case series, despite the lack of significant studies to back this suggestion. Pregnant SLE patients can use it, although the risk-benefit ratio needs to be considered. The dosage is 1-3 mg/kg/day, which is advised. gastrointestinal, opportunistic infections and cytopenias are side effects.[53]

### 7.3.7 THALIDOMIDE

Thalidomide is a medication with a significant risk of scarring that is used as rescue therapy in severe, refractory situations. It functions by preventing the manufacture of TNF, angiogenesis, and UVR-induced keratinocyte death, while also lowering IFN production and polymorphonuclear cell phagocytosis. Although there is a considerable risk of recurrence, of up to 70%, after stopping the medicine, especially in DLE, the response rate is higher than 90% in diverse subtypes of CLE, the highest among all therapies. Once a clinical response is seen, the beginning dose of 100 mg/day should be decreased.

Its usage may be restricted by the high frequency of side effects, which affect 24% of individuals (16% have peripheral neuropathy and 2% have thromboembolic events). Hands and feet are often affected by polyneuropathy, which is painful and symmetrical. Loss of sensory perception and the preservation of muscular strength are often present. To maintain control, an EMG should be done at the beginning and every six months. Sedation, orthostatic hypotension, a maculopapular rash, diarrhea, and dry mouth are further adverse effects.

One of the most dreaded adverse effects of thalidomide usage is teratogenicity. Its use in women who are of childbearing age must be an exception, and then only after all other therapies have failed. In these situations, the adoption of two contraceptive methods—one very effective and the other a barrier method—is advised. 24 hours before beginning therapy, once per week for the first month, and then every two to four weeks following that, a pregnancy test should be done on individuals with significant cardiovascular risk or the presence of antiphospholipid antibodies, acetylsalicylic acid, at modest dosages, can be taken with thalidomide.

Though there is less information in the literature on the usage of lenalidomide, a thalidomide derivative, in CLE patients, it has a superior safety profile in terms of the risk of neuropathy. Due to the possibility of causing SLE, several publications advise against using it in CLE.[54]

### 7.3.8 SYSTEMIC CORTICOSTERIODS

When treating severe and disseminated types of CLE, systemic corticosteroids might be utilized as a temporary measure until other drugs take effect. They ought to be cut back on and stopped as soon as feasible.

Due to their connection to SLE, they have a greater reaction rate in ACLE. Prednisone should be lowered from the standard dose of 0.5 to 1 mg/kg/day as soon as feasible to achieve daily doses of less than 7.5 mg. Systemic corticosteroid medication should not be continued long-term in CLE.[55]

## 8. OTHER TREATMENTS

The antibacterial, anti-inflammatory, and immunosuppressive effects of clofazimine. The dosage ranges from 100 to 200 mg per day and is suitable as a complementary therapy.

Brownish-gray hyperpigmentation, cutaneous xerosis, nausea, and vomiting are the primary adverse effects. Although fumaric acid esters have been utilized successfully in DLE, the literature is still lacking in data.

Patients with livedo racemosa, malignant atrophic papulosis-like lesions (Degos disease), ulceration, thrombophlebitis, and anetoderma are advised to utilize antiplatelet medications. Pulsed dye-laser therapy is referred to as a form of scar treatment. Its usage is not

advised in the presence of active skin lesions due to the danger of photosensitivity, though.

Without systemic involvement, cyclosporine, cyclophosphamide, and intravenous immunoglobulin are not recommended. This route is critical for IFN upregulation. The initial generation of inhibitors, baricitinib, and ruxolitinib, demonstrated efficacy in a small number of individuals with perniotic LE. Clinical studies are now underway for second-generation inhibitors, or the treatment of CLE.[56]

## 9. TARGET THERAPIES

A new area of study for a new class of medications, the so-called immunobiological, has been made possible by advancements in our understanding of pathogenesis, particularly of the activation pathways of the innate and adaptive immune systems.

The primary treatment targets include pro-inflammatory cytokines, their receptors, and intracellular signaling pathways, such as IL-6, IL-12, IL-23, IFN, and JAK/STAT, as well as the activation pathways of B cells, T cells, and PDC.

**9.1 B CELL TARGETING:** An FDA-approved monoclonal antibody against B-cell activating factor (BlyS) called belimumab is used to treat SLE. Though subsequent evaluations have revealed an improvement in the skin condition, the first investigations did not specifically analyze the results of skin lesions. In phase III research, its effectiveness in CLE is being examined.

Rituximab, an anti-CD20 monoclonal antibody, was used in three observational trials to treat LE's mucocutaneous symptoms, with response rates ranging from 35% to 76%. ACLE showed a more positive response, but there was no proof that the subacute or chronic subtypes of CLE benefited.[57]

**9.2 INTERFERON PATHWAY TARGETING:** Clinical experiments of attempts to specifically inhibit IFN have not produced adequate outcomes, most likely as a result of the significant redundancy between different kinds of IFN. A more encouraging possibility is the IFN receptor blocking. In a phase IIb clinical study, anifrolumab, a monoclonal antibody targeting type I IFN receptor, decreased the skin lesion activity ratings in individuals with SLE.[58]

**9.3 JAK/STAT PATHWAY TARGETING:** This route is critical for IFN upregulation. The initial generation of inhibitors, baricitinib, and ruxolitinib, demonstrated efficacy in a small number of individuals with perniotic LE. Clinical studies are now underway for second-generation inhibitors.[59]

## CONCLUSION

So, we conclude that cutaneous lupus is a heterogeneous and autoimmune disease. The interplay of environmental, genetic, and immunological variables results in a variety of dermatological symptoms. The identification of the clinical subtype is critical for the diagnostic approach, treatment choice, and prognosis, both in cutaneous illness and in the setting of SL. Diagnostic criteria for distinct subtypes of CLE are currently in the works. More forceful criteria are envisaged, which may be implemented into clinical practice and therapeutic trials in the future, assisting in the assessment of LE cutaneous symptoms. The first lines of therapy for CLE are still photoprotection, topical corticosteroids, and antimalarials. Alternative systemic treatments include methotrexate, oral retinoids, dapsone, and thalidomide, among others. With breakthroughs in disease pathogenesis understanding, new therapeutic techniques have been created, targeting the many immune activation pathways that have been identified.

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## CONFLICT ON INTEREST

None.

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