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Current Pathogenesis and Treatment of Cutaneous Lupus Erythematosus

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ABSTRACT

Lupus erythematosus (LE) is a chronic autoimmune illness with a broad range of clinical symptoms. These conditions can range from systemic lupus erythematosus (SLE), which affects different organ systems in the body, to cutaneous lupus erythematosus (CLE), which affects only the skin. The precise pathophysiology of CLE is unknown, although it appears to include a complicated interaction of genetic predisposition and environmental stimuli such as UV light, medications, trauma, and hormones. The emergence of the inflammatory infiltrate seen in CLE lesions has also been documented in several studies; this information is crucial for figuring out which specific inflammatory mediators are responsible for tissue damage. Currently prescribed medications for CLE often include antimalarials, systemic corticosteroids, immunosuppressants, and immunomodulators; cytotoxic drugs are only used in the most severe instances.

Keywords

Lupus erythematosus, Cutaneous lupus erythematosus, Pathogenesis, Treatment

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INTRODUCTION

Lupus erythematosus (LE) is a chronic autoimmune illness with a broad range of clinical symptoms. Skin-specific lupus erythematosus (CLE) and systemic lupus erythematosus (SLE), which affect many organ systems, are two examples of these disorders. The prevalence of CLE, which can occur alone or in conjunction with SLE and is 2-3 times more common than SLE, is greater than that of SLE.[1] Incidence of LE is higher in women than in men across all age groups and races, peaking in maturity, but in affected males early onset may occur later.[2]

Gilliam's categorization distinguishes between LE-specific CLE subtypes such as acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE). CCLE is classified into four types: discoid lupus erythematosus (DLE), lupus erythematosus profundus (also known as lupus panniculitis), lupus erythematosus tumidus, and lupus chilblain.[1]

The hallmarks of ACLE, which is almost always linked to SLE, include extensive erythema and/or malar erythema (the well-known "butterfly rash" of lupusThose who have localized DLE, however, have small skin lesions on their head and neck that initially show erythema, induration, and scaling before progressing to hypopigmentation, permanent scarring, atrophy, and baldness. A subgroup of DLE patients may develop lesions that affect the trunk and extremities in addition to the head and neck. In 10–20% of patients with DLE who are initially identified, systemic involvement occurs. According to several studies, individuals with broad DLE are more vulnerable than those with localized DLE.[3]

Along with these CLE-specific skin lesions, SLE patients may also experience non-specific skin symptoms such as hair loss without scarring, vasculitis, and Raynaud's disease. Skin or hair involvement is

thought to affect 70–80% of SLE patients at some time, and for 20–25% of SLE patients, skin abnormalities are the first signs of the disease.[3]

Significant impairment and a decline in quality of life are possible effects of CLE. Women and patients with widespread CLE lesions or severe illness have a much lower quality of life in CLE. The CLE Disease Area and Severity Index (CLASI), which measures the activity of CLE skin diseases, shows a correlation between rising skin-specific quality of life and increasing disease activity.[4]

Pathogenesis of Cutaneous Lupus Erythematosus (CLE)

SLE and CLE are both multifactorial diseases that are brought on by a complex interaction between genetic predisposition and environmental exposures that starts or spreads immune dysregulation and result in disease in vulnerable individuals. The aggregation of many risk alleles, as was observed in SLE, contributes significantly to an individual's susceptibility to CLE. The environment and these genetic variations eventually influence how the disease appears. [3]

1. Genetic

Three mutations in the Prime Repair Exonuclease 1 (TREX1), which results in a rare variant of CCLE known as familial chilblain lupus, are the only monogenic cause of cutaneous lupus that has been identified thus far. The type I interferon pathway is persistently hyperactivated as a result of ssDNA accumulation through innate immune receptors, whereas intracellular DNA accumulation is brought on by TREX1 deficiency.[3]

Females have long been recognized as having a significant risk for several autoimmune diseases, including SLE and CLE. In recent studies on human skin sexual dimorphism, the transcription factor vestigial-like family member 3 (VGLL3) was identified as a key female bias regulator that may assist to explain the female autoimmune phenotype. In addition to influencing type I interferon response, VGLL3 also promotes the expression of genes that code for inflammatory chemicals, many of which have genetic risk variations that have been previously linked to autoimmune disorders, including SLE. In contrast to normal skin, where VGLL3 expression levels were higher in female-derived tissues, VGLL3 expression levels in SCLE skin were comparable in males and females. Furthermore, VGLL3 overexpression was found to cause a lupus-like disease with skin manifestations in mice, suggesting that VGLL3 may be involved in the pathogenesis of CLE.[3,5]

Furthermore, the X chromosome contains more harmful genes, and Klinefelter's syndrome is related to a higher incidence of SLE, given that female cells express immunity-related genes such as CD40LG and CXCR3 in a biallelic fashion, X inactivation, and reactivation may have a role.[6-9] SLE T cells contain altered heterochromatin and X-inactivated-specific transport RNAs, which explains why the epigenetic alteration of the X chromosome is disturbed. One of the important immunity-related genes is TLR7, which binds single-stranded RNA and appears to avoid X inactivation. This results in biallelic expression in B and myeloid cells. SLE has polymorphisms in this X chromosome gene, whereas DLE does not.[10]

2. Environtment

UV exposure directly increases TNF- and other interleukins and interferons. These cytokines play a key role in the progression of CLE. These cytokines are responsible for tissue damage, inflammation, and immune cell malfunction in CLE. UV light triggers keratinocyte death, which increases cytokine and autoantigen release. Keratinocyte necrosis and UV radiation effects on keratinocytes cause nucleoproteins to migrate from within the cell to the cell surface. Antibodies bind to these nucleoproteins, causing tissue damage and inflammation to worsen.[11]

UV radiation causes classic CLE lesions and photosensitivity while playing a significant role in cytokine generation in CLE. New CLE lesions can be caused by UV light, particularly UVB (290–320 nm), and pre-existing CLE illness can become worse. After being exposed to UV radiation, 76% of LE tumors, 63% of SCLE, 60% of SLE, and 45% of DLE individuals acquired skin lesions. 34% of lesions and 42% of lesions

were brought on by UVA alone. 53% of individuals who received UVA and UVB radiation had skin lesions.[11]

CLE lesions can develop from UV radiation in several ways. UV radiation causes keratinocytes to express autoantigens, perish, produce cytokines and chemokines, and be recruited by immune cells that are activated and have enhanced antibody binding to keratinocytes (Table 1). Through these processes, UV radiation can aggravate the systemic symptoms of SLE and produce CLE lesions. [11]

Table 1. The role of UV light in the pathogenesis of CLE.[11]

Potential CLE pathogenic factors	Primary source(s)	Primary function	Primary role(s) in the pathogenesis of CLE
UV light	Sun Artificial lights	Proinflammatory	• Increases production of inflammatory cytokines and chemokines such as IFN, TNFα, IL and CCL27, wich recruit activated immune cells and cause tissue inflamation • Triggers keratinocyte apoptosis and necrosis • Increases expression of autoantigens on keratinocytes and antibody binding keratinocytes

CCL27 = Chemokine (C-C motif) ligand 27. CLE= Cutaneous lupus erythematosus. IFN= Interferon. IL= Interleukin. TNFα=Tumor necrosis factor. UV=Ultraviolet

3. Life Style

It has been established that smoking increases the generation of inflammatory cytokines, autoantibodies, apoptosis, and free radicals, all of which contribute to the activity of CLE illness. Smoking has also been associated with CLE. The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) found that smokers with CLE had worse quality of life and skin disease than nonsmokers.[3]

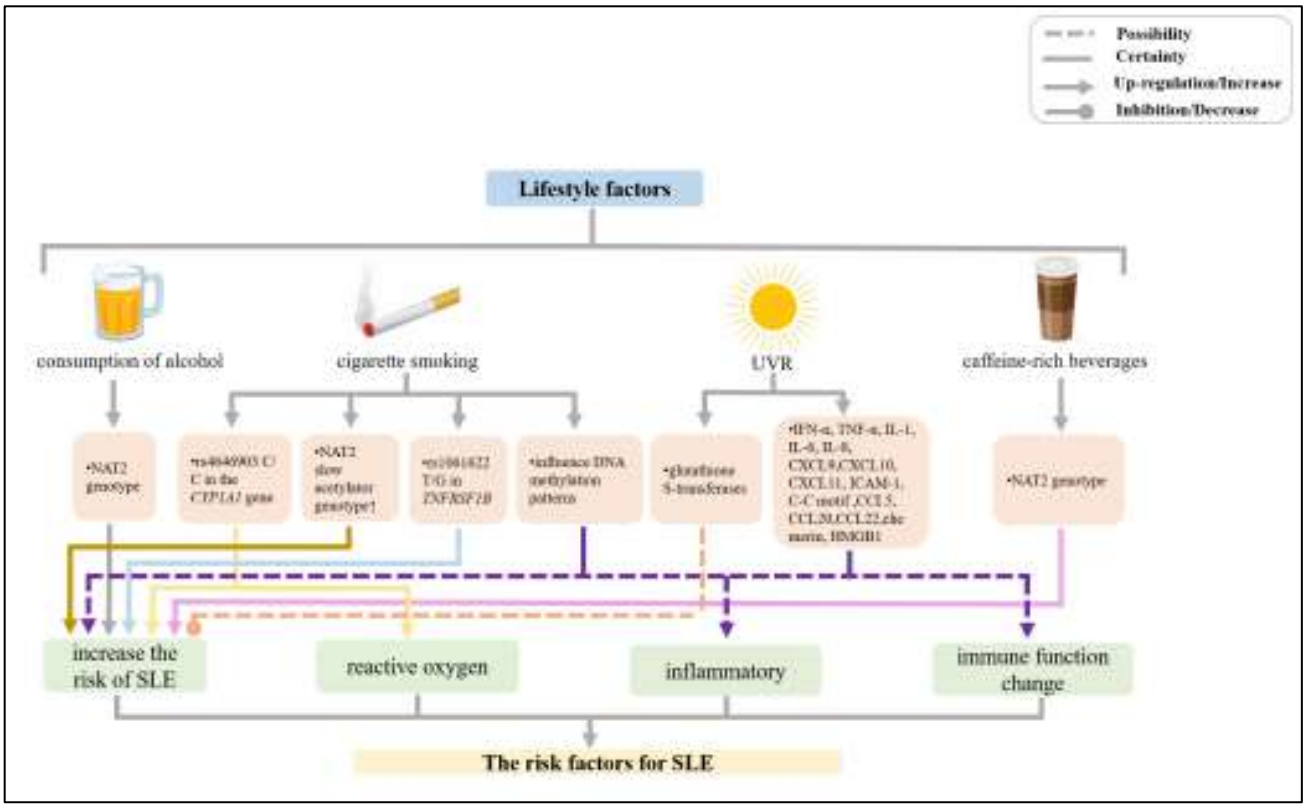

Figure 1. The processes of lifestyle factors.[l]

The processes behind the preventive effects of alcohol use and the worsening effects of SLE may entail interactions between genes and the environment. According to a study from the Korean Lupus Network (KORNET), drinking alcohol may affect how quickly skin damage develops in SLE patients. According to research by Kiyohara et al., the NAT2 genotype significantly altered the correlation between the risk of SLE and alcohol and black tea intake. However, the link between alcohol use and the prevalence of SLE is still debatable and calls for additional study.[12]

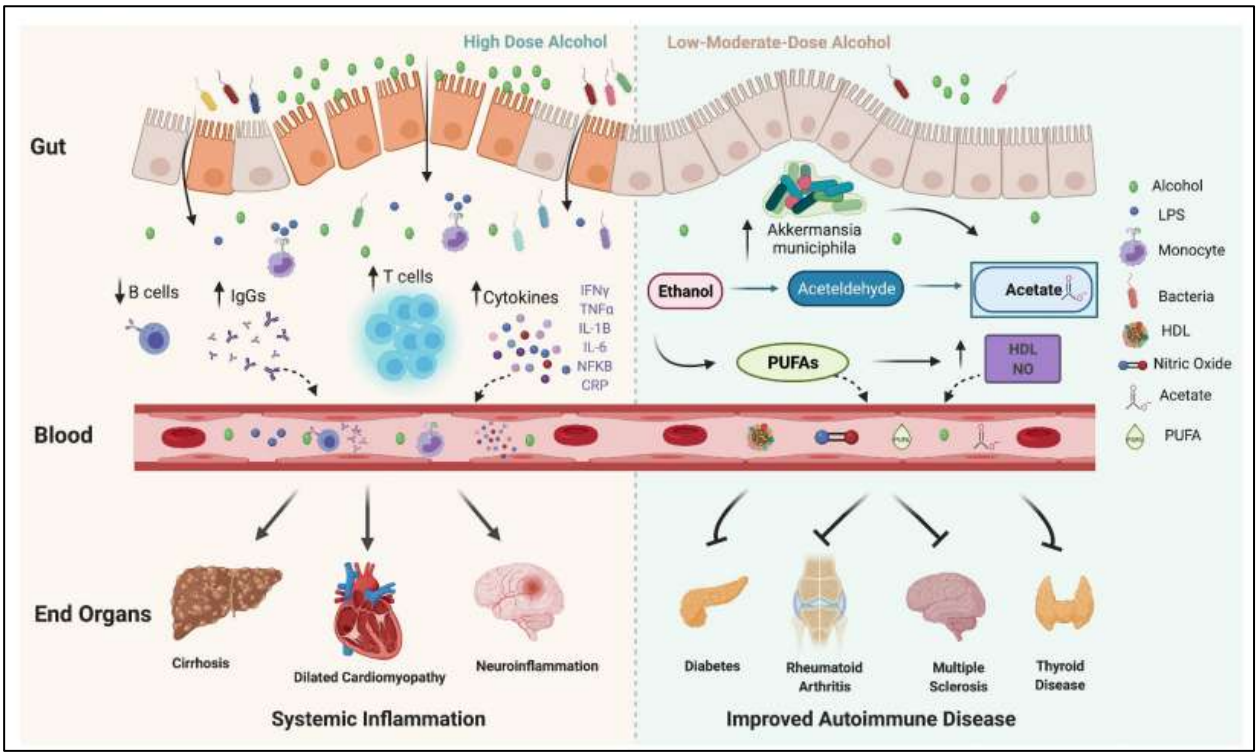

Figure 2. Alcohol affects the body in a variety of ways. When ingested in high quantities, alcohol can harm the intestinal barrier. This can result in dysbiosis, a rise in bacterial wall products, and liposaccharides (LPS), which can activate TLRs in immune cells and increase the amounts of monocytes, T cells, cytokines, and immunoglobulin (IgG) while lowering B cells. can assist in preventing organ damage. Alcohol has been found to raise the risk and progression of autoimmune illnesses at low to moderate dosages. Low to moderate alcohol use may reduce inflammation by boosting ackermansia muciniphila and other anti-inflammatory gut flora, as well as raising levels of acetate, polyunsaturated fatty acids (PUFA), HDL, and NO, though the precise mechanisms are still unclear.[13]

4. Microorganisms

Host-microbe interactions may have a role in the development of the disease, according to studies looking at the microbiome in SLE patients. In SLE and SCLE patients with anti-Ro (SS-A) antibodies, molecular mimicry appears to be connected to the development and dissemination of autoimmunity. Human skin, oral, and intestinal commensal bacteria were found to contain evolutionarily conserved Ro60 protein orthologs that were observed to interact with anti-Ro antibodies and Ro60 autoreactive T-cell clones from SCLE/SLE patients as well as a subset of these bacteria's species.[3,14]

The migration of the Enterococcus gallinarum bacteria from the gut to the liver and other systemic tissues, which encourages the production of autoantibodies and SLE-like disease in autoimmune-prone mice, has also been linked to the host microbiome and the development of SLE. Additionally, specific E. gallinarum DNA was found in liver biopsies from individuals who had SLE and autoimmune hepatitis, indicating that gut pathogen translocation can cause autoimmune illness in humans.[3]

The significance of infectious agents, particularly viruses, in the development of SLE and CLE, has been the subject of extensive speculation. Nearly all SLE patients develop seroconversion to Epstein-Barr virus (EBV), and recent studies indicate that these patients have trouble controlling latent EBV infection, which may be related to altered T-cell responses to EBV.[15]

Table 2 General pathways of virus-induced autoimmunity.[16]

Mechanism	Description
Molecular Mimicry	The presentation of viral antigens that resemble self-antigens structurally can activate autoreactive T cells.
Epitope Spread	It's possible to find viral antigens that resemble self-antigens structurally. Autoantibodies that are directed against several epitopes of the same antigen or even different antigens develop over time as a result of persistent viral infection, expanding the scope of the immune response and activating autoreactive T cells.
Superantigen production	Low antigenic specificity Superantigens that attach to the TCR and MHC class II activate T cells.
Bystander activation	Antigen-presenting cells (APC) or virus-specific T lymphocytes release cytokines, which activate adjacent pre-configured autoreactive T lymphocytes.
Apoptotic changes and disposal deficits	If there is a discharge deficiency, viral infection may accelerate cell death, resulting in Th17 activation and the release of undigested nuclear material, which may promote the survival of autoreactive B lymphocytes.
Epigenetic Factors	The three main epigenetic processes by which viruses can control the expression of immune response-related genes are DNA methylation, histone modification, and RNA-based mechanisms.
Persistent or recurrent viral infection	Infection with lymphotropic viruses on a regular basis can encourage the formation of polyclonal lymphocytes, which creates autoantibodies. Repeated infections have been related to "facilitator autobodies" that induce autoimmunity by increasing inflammation and antigen exposure in subsequent infectious episodes.
Innate immunity activation	When viral DNA/RNA attaches to a different PRR, the mechanism leading to a type I IFN response is triggered.
Direct cytotoxicity	Viruses have the ability to infect and kill target cells directly, leading to AIDs.

5. Drugs

Drug-induced SLE is a well-known adverse effect of many medications and includes the production of skin lesions like CLE. Procainamide, hydralazine, quinidine, and omeprazole are a few medications that have historically been linked to drug-induced SLE. These medications have been shown to either directly or indirectly activate the innate immune system by preventing autoantigen clearance. TNF-blocking medications can also cause adverse effects similar to SLE, such as the development of CLE-like lesions. This is because they prevent TNF from controlling the interferon system, which causes pro-inflammatory factors to be upregulated by interferons. The direct pathophysiological role of type I interferon in CLE is supported by the ability of recombinant type I interferon to cause skin lesions at injection sites that resemble CLE. Additionally included to the list of medications that have the potential to cause SLE are immune stimulators such checkpoint inhibitors.[17]

6. Immunopathogenesis

The inflammatory reaction in the skin generated by type I interferon activation has been associated to CLE, a painful and disabling disorder. Nucleic acids become more prevalent as a result of deficiencies in clearance in the extra- and intracellular spaces, which the innate immune system interprets as a danger signal. The DNA and RNA sensors, which originally developed to provide virus defense, can be stimulated by nucleic acids themselves. Localized skin cells, macrophages, and dendritic cells may respond to their activation with a type I interferon-dominant response that leads to enhanced adaptive immunity. This pathogenic idea was discovered through the genetic investigation of uncommon disorders caused by monogenic type I interferon. Due to their genetic predisposition, people with lupus are more vulnerable to environmental triggers like UV radiation, which can cause inflammation, localized tissue damage, and ultimately systemic disease.[18]

Both innate and adaptive immunological mechanisms are investigated in the pathogenesis of lupus in relation to hereditary factors and environmental stimuli. Overall, CLE is an immunological homeostasis problem that causes unintentional adaptive immune system activation and stimulation of the innate immune

system. It is currently unclear how the autoimmune pathways contribute to the pathophysiology and progression of CLE. It should be underlined as well that it is unknown how environmental factors lead to immune activation against disease. Data, however, suggest that CLE is a condition characterized by an excess of type I interferon (IFN) and an attack by cytotoxic CD8+ T lymphocytes made in the epidermis (Figure 3).[3]

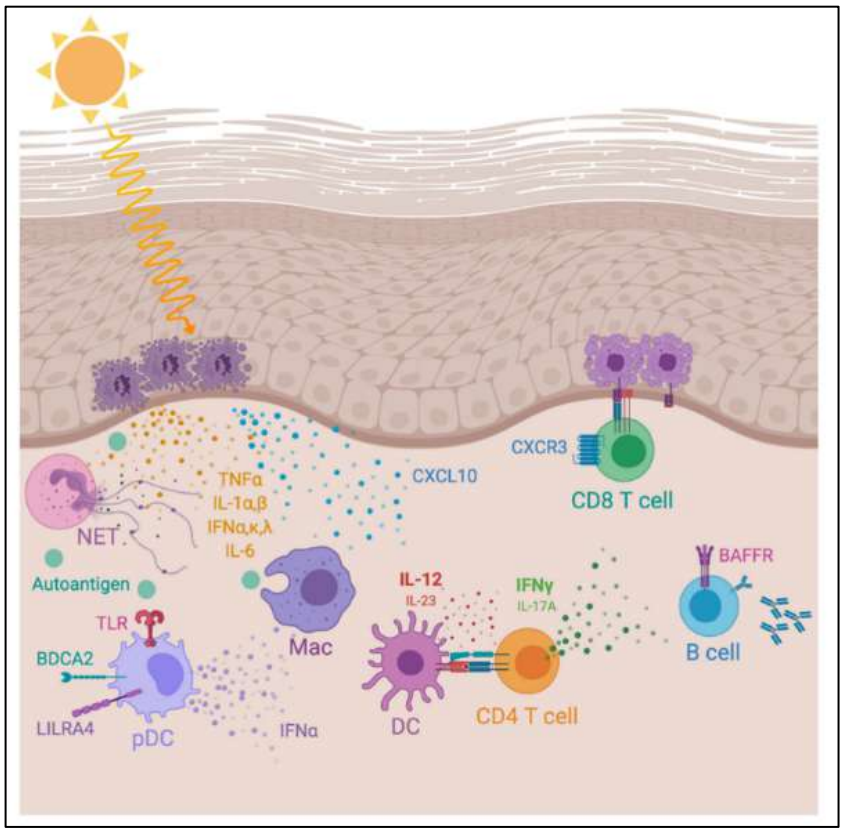

Figure 3 Lupus immunopathogenesis in the skin. Tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-1, IL-6, interferon (IFN), and CXCL10 chemokines are produced as a result of keratinocyte necrosis or death caused by UV radiation. Autoantigen produced from dying keratinocytes mixed with neutrophil extracellular traps (NETs) stimulate pDCs to release IFN. Dendritic cells (DC) release IL-12 or IL-23 in order to activate CD4+ T cells to secrete IFN or IL-17A. Keratinocyte invasion by CXCR3-expressing CD8+ T cells results in keratinocyte death (vacuolar interface dermatitis), which is aided by CXCL10 recruitment at the dermal-epidermal junction. B cells that express BAFF receptors (B cell activating factor) produce autoantibodies. By phagocytosing autoantigens produced by dead keratinocytes, macrophages (Macs) aid primary adaptive immune cells in their fight against keratinocytes. (TYK2, leukocyte immunoglobulin-like receptor subfamily A member 4, and BDCA2, blood dendritic cell antigen 2).[3]

Latest Therapies Based on The Pathogenesis of CLE

The insight gained regarding CLE's pathogenesis has created the ability to design pathogenesis-directed treatments.The immune system is currently being aggressively studied through a number of various modulation techniques to help treat this illness (Figure 4). CLE and CLASI disease activity, which are increasingly utilized as primary or secondary endpoints in clinical studies, are among the significant advancements in assessing response to medication.[3]

According to recent studies on the pathogenesis of CLE, environmental factors, including ultraviolet (UV) light, with stimulation of the innate immune response and adaptive immunological responses, play a role in the development of CLE skin lesions. Numerous cytokines and chemokines that are controlled by interferon (IFN) regulate this process. CLE is presently being used to evaluate new biologic medicines that specifically target immune cells (B cells, T cells, and plasmacytoid dendritic cells) or proinflammatory mediators like type I IFN. A number of recent trials have also focused on CLE therapy.[19,20]

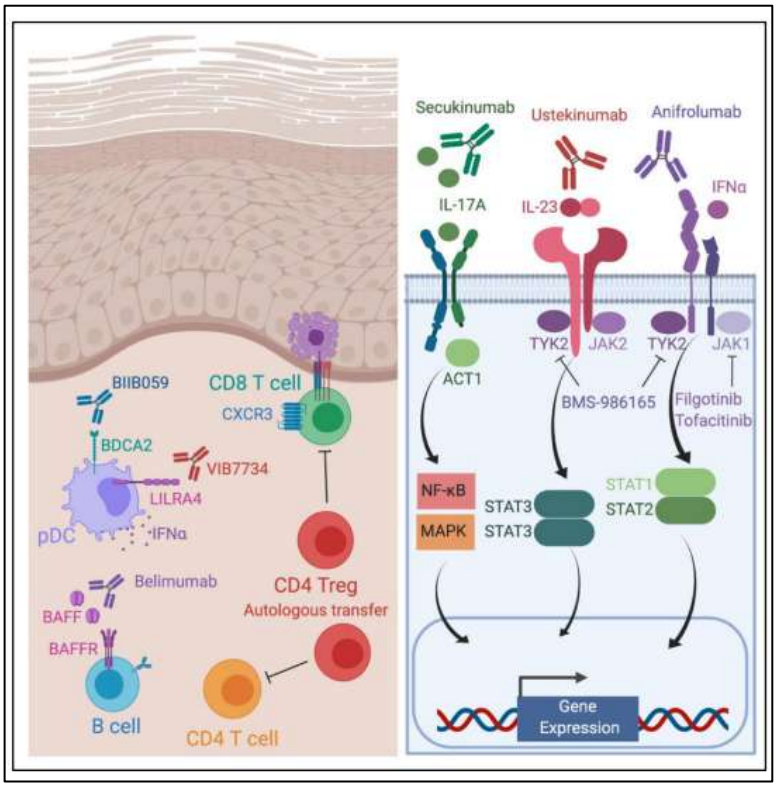

Figure 4 Recent approaches to CLE therapy. Among the cellular targets are autologous Treg transfer (left), belimumab against BAFF, BIIB059 against BDCA2 in plasmacytoid dendritic cells (pDC), and V1B7734 against LILRA4 in pDCS. Secukinumab binds to IL-17A, whereas Ustekinumab and Anifrolumab bind to the IL12p40 component (right), as well as the IFNAR1 subunit. BMS-986165, which inhibits TYK2, and filgotinib and tofacitinib, which inhibit JAK1 (right), are examples of intracellular targeted medications. (BAFF, B cell-activating factor; BAFFR, BAFF receptor; BDCA2, blood dendritic cell antigen 2; IFNAR1, interferon alpha receptor subunit 1; IL, interleukin; ILT7, immunoglobulin-like transcript 7; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase 2).[3]

Cell B Target

Rituximab

Rituximab is a monoclonal antibody (mAb) that targets the CD20 protein. A systematic review of the efficacy and safety of rituximab in non-renal SLE patients found that partial or full response rates ranged from 33% to 71% for the disease's mucocutaneous manifestations (4 cohorts with general mucocutaneous manifestations of SLE and 3 cohorts with specific manifestations such as urticarial vasculitis, small vessel vasculitis, or rash). Additionally, according to this study, rituximab might be advantageous for ACLE patients. Increased British Isles Lupus Assessment Group Index (BILAG) scores were observed in 42.9% and 50%, respectively, of patients with ACLE and SCLE in a retrospective study of 26 SLE patients with active mucocutaneous symptoms who were treated with rituximab. CCLE was noticed.[21]

Belimumab

B cell activation factor (BAFF, also called BlyS) is the target of the humanized monoclonal antibody known as belimumab. When monocytes and macrophages are stimulated, BLyS is generated by these cells. B cells are the only cells with certain receptors, and BLyS binds to these receptors, causing B cells to develop into plasma cells that secrete antibodies. Belimumab (Benlysta), a human monoclonal antibody, prevents BLyS from performing its biological function. The FDA has currently approved belimumab for the treatment of SLE. Remission of cutaneous conditions happened concurrently with remission of systemic diseases in the belimumab clinical trial for SLE. There are presently few studies evaluating belimumab's effectiveness in treating particular cutaneous LE/isolated CLE.[1,15]

Iaccarino et al. conducted a retrospective analysis on 188 active SLE patients treated with belimumab from 11 Italian cohorts. Of these patients, 62 developed skin lesions, including 48 who had persistent and noticeable skin lesions. CLASI scores for the CLE disease area and severity index (mean 4 at baseline) were modest, but they increased at 6, 12, and 18 months of follow-up. Belimumab may therefore be effective in treating active SLE patients with acute mucocutaneous lesions.[21,22]

Cell T Target

Targeted T-cell treatment has not been effective or thoroughly researched for CLE to date. T-cell activation is prevented by abatacept, a fusion protein made up of the extracellular domain of CTLA-4 and the Fc region of IgG1 immunoglobulin. The findings of three studies two retrospectives and one case series indicate that this medication may have some effect on CLE lesions that are nonspecific (such as oral ulceration and facial erythema and alopecia), but it had no effect on CCLE, and its effectiveness in treating ACLE and SCLE was not examined.[21]

Targets of plasmacytoid dendritic cells and interferon signaling

BIIB059 is a humanized IgG1 mAb that binds to the pDC-specific blood DC antigen 2 (BDCA2) and inhibits the generation of type I interferons (IFNs) and other inflammatory mediators. In a recent phase I, randomized, placebo-controlled clinical trial, 8 CLE patients (4 ACLE, 1 SCLE, and 3 DLE) received a single dose of BIIB059; 5/6 patients showed a decrease in CLASI-A score at week 4 and maintained it at week 12; 3 of 4 placebo patients showed no improvement. Additionally, there was a correlation between a decline in the CLASI-A score and a decline in the blood IFN level and immune infiltration in skin lesions. A phase 2 clinical trial (NCT02847598) is now being conducted to treat SLE and CLE.[23]

Anifrolumab is a monoclonal IgG1 completely humanized antibody that binds to IFN-/-/-receptors (IFNAR) and blocks all type I IFN signaling. In a post hoc analysis of phase IIb, the grouping with high IFN gene demonstrated improvement in skin involvement when IV anifrolumab was compared to placebo in rash and arthritis.[15] A higher decrease in the CLASI activity score was seen in the anifrolumab group in a different phase II study looking at the effectiveness of subcutaneous anifrolumab in SLE with high type I IFN and active skin disease. According to these findings, anifrolumab is a viable treatment for CLE.[21]

JAK-STAT pathway target

Type I IFN, IL-21, and IL-6 signaling are all blocked by the JAK1 and JAK2 inhibitor baricitinib. Baricitinib reached the "endpoint" in a phase 2 trial for SLE, however, no differences in CLASI scores were seen. The performance of baricitinib for CLE is disputed because the trial's enrollment CLASI score was low overall. individuals with familial chilblain lupus and TREX1 mutations saw a considerable improvement in their skin lesions after taking baricitinib, and individuals with SLE completely recovered from a refractory papulosquamous rash. Case studies and numerous ongoing phase I and II clinical trials suggest the efficacy of tofacitinib for CLE in addition to baricitinib.[21,24-26]

Other cytokine and receptor-targeting treatments

High CLASI score SLE patients with stekinumab, a monoclonal antibody against IL-12/23, showed a decrease in the activity of skin disease. At week 28, 67.7% of patients in the ustekinumab group had CLASI activity scores that had increased by at least 50%; this percentage remained constant through week 48 (68.6%). There are still Phase III trials going on.[21,27]

When compared to healthy controls, it was discovered that IL-17 levels were higher in the sera of CLE patients. Additionally, it was discovered that IL-17A levels were elevated in CLE tissue, suggesting that individuals with CLE might benefit from IL-17A targeted therapy. Phase 2 clinical trials are actively examining the therapeutic effects of secukinumab in CLE, even tough the role of the cytokine IL-17 in the pathophysiology of the condition is still unclear.[3]

Immunosuppressive or Cytotoxic Agents

In individuals with severe CLE, the administration of immunosuppressive medications such Azatioprine (Imuran) (1.5 mg to 2 mg/kg per day orally) may have a glucocorticoid-sparing effect. A purine analog like azathioprine, mycophenolate mofetil (CellCept) (2.5 g to 3 g divided into 2 doses orally) inhibits de novo lymphocyte pathways more specifically than azathioprine does. Numerous investigations have revealed that this trait confers better and less harmful efficacy when treating resistant severe CLE. For severe refractory CLE, methotrexate (7.5 mg to 25 mg orally once per week) is beneficial. In SLE patients, a double-blind, randomized, placebo-controlled experiment found that moderate doses of methotrexate (15–20 mg per week) are helpful to reducing cutaneous and joint activity and may allow prednisone dosages to be lowered. Cytarabine (cytosine arabinoside), as well as cyclosporine, are other immunosuppressive medications that may be administered. High-dose IV gammaglobulin immunotherapy has also been applied.[15,28]

Table 4. Theurapeutic options for CLE.[15]

	Drug	Dose
First Line	• Topical glucocorticoids, topical calcineurin inhibitor • Intralesionel triamcinolone acetonide	• Class 1 topical steroid daily to twice daily for 2 weeks alternating with pimecrolimus 1% or tacrolimus 0,1% twice daily for 2 weeks • 2,5-am mg/cc
Second line	• Hydroxychioroquine • Chloroquide • Quinacrine • If monotherapy fails, add quinacrine to either hydroxychloroquine or chloroquine	• 6,5 mg/kg/day based on ideal body weight • 3-3,5 mg/kg/day based on ideal body weight • 100 mg/day
Short course only (2-16 weeks)	• Prednisone • Thalidomine	• 5-60 mg/day • 50-200mg/day; taper to 50mg every other day on response
Third line (saver immunosupresive)	• Azathioprine • Mycophenolate mofetil • Methotrexate	• 1.5-2.5 mg/kg/day • 1-1.5 g/dose, twice daily • 7.5-25 mg by mouth or subcutaneously, once weekly
Worth considering	• Dapsone • Accutane • Acitretin • Gold	• 50-200 mg/day • 0.5-2 mg/kg/day • 10-50 mg/day • Titrate to 50 mg intramuscularly weekly, taper after 1 g
Investigational (some currently available for other indication)	• Leunomide • Anti–tumor necrosis factor biologics • Rituximab Belimumab • Abatacept • Janus kinase (JAK) inhibitors (tofacitinib, ruxolitinib) • Antiinterferon antibodies • CXCR3 receptor inhibitors	

CONCLUSION

Lupus erythematosus (LE) is a chronic autoimmune illness with a broad range of clinical symptoms which affect many organ systems, are two examples of these disorders. SLE and CLE are both multifactorial diseases that are brought on by a complex interaction between genetic predisposition and environmental exposures that starts or spreads immune dysregulation and result in disease in vulnerable individuals. According to recent studies on the pathogenesis of CLE, environmental factors, including ultraviolet (UV) light, with stimulation of the innate immune response and adaptive immunological responses, play a role in the development of CLE

skin lesions. Numerous cytokines and chemokines that are controlled by interferon (IFN) regulate this process. CLE is presently being used to evaluate new biologic medicines that specifically target immune cells (B cells, T cells, and plasmacytoid dendritic cells) or proinflammatory mediators like type I IFN. A number of recent trials have also focused on CLE therapy.

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REFERENCE
1. Guo LN, Nambudiri VE. Cutaneous lupus erythematosus and cardiovascular disease: current knowledge and insights into pathogenesis. Clin Rheumatol. 2021;40(2):491–9.
2. Rees F, Doherty M, Grainge M, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: A systematic review of epidemiological studies. Rheumatology 2017b;56(11):1945–61.
3. Little AJ, Vesely MD. Cutaneous lupus erythematosus: Current and future pathogenesis-directed therapies. Yale J Biol Med. 2020;93(1):81–95.
4. Chang AY, Ghazi E, Okawa J, Werth VP. Quality of life differences between responders and nonresponders in the treatment of cutaneous lupus erythematosus. JAMA Dermatol 2013;149(1):104–6.
5. Billi AC, Gharaee-Kermani M, Fullmer J, Tsoi LC, Hill BD, Gruszka D, et al. The female-biased factor VGLL3 drives cutaneous and systemic autoimmunity. JCI Insight. 2019;4(8).
6. Scofield RH, Bruner GR, Namjou B, Kimberly RP, RamseyGoldman R, Petri M, et al. Klinefelter's syndrome (47, XXY) in male systemic lupus erythematosus patients: support for the notion of a gene-dose effect from the X chromosome. Arthritis Rheum. 2008;58:2511–7
7. Cooney CM, Bruner GR, Aberle T, Namjou-Khales B, Myers LK, Feo L, et al. 46,X,del(X)(q13) Turner's syndrome women with systemic lupus erythematosus in a pedigree multiplex for SLE. Genes Immun. 2009;10:478–81
8. Wang J, Syrett CM, Kramer MC, Basu A, Atchison ML, Anguera MC. Unusual maintenance of X chromosome inactivation predisposes female lymphocytes for increased expression from the inactive X. Proc Natl Acad Sci U S A. 2016;113:E2029–38.
9. Syrett CM, Paneru B, Sandoval-Heglund D, et al. Altered X-chromosome inactivation in T cells may promote sex-biased autoimmune diseases. JCI Insight. 2019;4
10. Souyris M, Cenac C, Azar P, et al. TLR7 escapes X chromosome inactivation in immune cells. Sci Immunol. 2018;3:Eaap8855.

11. E.S Robinson, V.P. Werth. The Role of Cytokines in the Pathogenesis of Cutaneous Lupus Erythematosus. Elsevier. 2015; p 1-7
12. Jiaxuan C, Shuzhen L, Wanxian P, Fengbiao G, et al,. Life Factors Acting on Systemic Lupus Erythematosus. Frontiers in Immunology. 2022:1-10.
13. Blaine C, Kailey M, Shreya T, Esther M. Alcohol as a friend or foe in autoimmune diseases: a role for gut mictobiome. Taylor & Francis Group. 2021; 13(1): 1-15.
14. Wenzel J. Cutaneous lupus erythematosus: new insights into pathogenesis and therapeutic strategies. Nat Rev Rheumatol. 2019;15(9):519–32.
15. Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K. Fitzpatrick's Dermatology in General Medicine. Ninth. New York: McGraw Hill; 2019.
16. Marco Q, Guido M, Marco DA, Cinzia B, Vincenzo C. Viral Infections and Systemic Lupus Erythematosus: New Players in a Old Story. MDPI. 2021; 13: 1-29
17. Wenzel J. Cutaneous lupus erythematosus: new insights into pathogenesis and therapeutic strategies. Nat Rev Rheumatol. 2019;15(9):519–32.
18. Günther C. Nucleic acid immunity in the pathogenesis of cutaneous lupus erythematosus. Front Immunol. 2019;10(JULY):1–9.
19. Kathryn C, Eric FM. Systemic Lupus Erythematosus: A Clinical Update. Internal Medicine Journal. 2021;51:1219-1228
20. Wenzel J. Cutaneous lupus erythematosus: new insights into pathogenesis and therapeutic strategies. Nat Rev Rheumatol. 2019;15(9):519–32.
21. Shi H, Gudjonsson JE, Kahlenberg JM. Treatment of cutaneous lupus erythematosus: Current approaches and future strategies. Curr Opin Rheumatol. 2020;32(3):208–14.
22. Iaccarino L, Andreoli L, Bocci EB, Bortoluzzi A, Ceccarelli F, Conti F, et al. Clinical predictors of response and discontinuation of belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study. J Autoimmun. 2018;86:1–8.
23. Furie R, Werth VP, Merola JF, Stevenson L, Reynolds TL, Naik H, et al. Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus. J Clin Invest. 2019 Feb 18;129(3):1359–71.
24. Zimmermann N, Wolf C, Schwenke R, Lüth A, Schmidt F, Engel K, et al. Assessment of Clinical Response to Janus Kinase Inhibition in Patients with Familial Chilblain Lupus and TREX1 Mutation. JAMA Dermatology. 2019;155(3):342–6.
25. Fornaro M, Coladonato L, Venerito V, Cacciapaglia F, Lopalco G, Iannone F. Efficacy of baricitinib on refractory skin papulosquamous rash in a patient with systemic lupus erythematosus. Rheumatol (United Kingdom). 2020;59(5):1188.
26. You H, Zhang G, Wang Q, Zhang S, Zhao J, Tian X, et al. Successful treatment of arthritis and rash with tofacitinib in systemic lupus erythematosus: The experience from a single centre. Ann Rheum Dis. 2019;78(10):1441–3.
27. Van Vollenhoven RF, Hahn BH, Tsokos GC, Lipsky P, Fei K, Gordon RM, et al. Maintenance of Efficacy and Safety of Ustekinumab Through One Year in a Phase II Multicenter, Prospective, Randomized, Double-Blind, PlaceboControlled Crossover Trial of Patients With Active Systemic Lupus Erythematosus. Arthritis Rheumatol. 2020;72(5):761–8.
28. Lu Q, Long H, Chow S, Hidayat S, Danarti R, Listiawan Y, et al. Guideline for the diagnosis, treatment and long-term management of cutaneous lupus erythematosus. J Autoimmun. 2021;123(8):102707.