Recent Advances in Cutaneous Lupus Erythematosus

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ABSTRACT
Cutaneous Lupus Erythematosus (CLE) is an autoimmune disease that encompasses a wide range of dermatologic manifestations with varying degrees of association with systemic disease. Treatment options for CLE are limited, and no medication has been approved specifically for CLE. However, increased emphasis on the role of biological therapies for CLE has emerged in recent years due to an improved understanding of the pathogenesis of CLE. This review summarizes the recent insights into the pathogenesis of CLE and current advances in the development of CLE treatments.

Keywords: Cutaneous Lupus Erythematosus; Lupus; Systemic Lupus Erythematosus; Discoid Lupus; Autoimmune; Discoid Lupus Erythmatosus

INTRODUCTION
Lupus Erythematosus (Le) is a spectrum of autoimmune connective tissue diseases that encompasses differing symptoms and severities, ranging from limited skin manifestations to multisystemic disease [1]. Systemic lupus erythematosus (SLE) is a clinical entity that refers to inflammation and tissue damage involving multiple organ systems, whereas cutaneous lupus erythematosus (CLE) primarily affects the skin and mucosal tissue. Up to 70% of patients with SLE experience skin involvement, and certain clinical subtypes of CLE have an increased risk for progression to systemic disease. The incidence of CLE is slightly higher than the incidence of SLE, estimated to be 4.3 per 100,000, compared to 2.9 per 100,000 in SLE [2-4]. CLE exhibits a female predominance with an average age at onset of 48.5 years [2]. CLE is associated with psychological stress and severely impaired quality of life [5].

CLINICAL MANIFESTATIONS OF CLE
CLE is a photodermatosis, meaning that ultraviolet UV light can trigger disease or disease flares. CLE can be divided into three main groups based on the location and prognosis of the skin lesions [6]. These include acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE). ACLE is characterized by a transient erythematous patch, known as the malar or “butterfly” rash, over the cheeks and nose but sparing the nasolabial folds [6]. Widespread erythematous eruptions may also be present on sun-exposed areas. ACLE is almost always associated with systemic disease, particularly renal disease. In SCLE, patients develop papulosquamous and/or annular-poly cyclic lesions on sun-exposed areas [6]. The lesions are usually nonscarring and associated with scaling, depigmentation and telangiectasias. Up to 50-60% of all patients with SCLE may develop systemic involvement, however unlike ACLE; severe renal or CNS disease is uncommon [7]. CCLE can be further divided into several subsets, including tumid lupus, chilblain lupus, lupus panniculitis and discoid lupus erythematosus (DLE). DLE is the most common variant, usually presenting as localized, chronic, scarring lesions on the scalp, face, ears and other sun-exposed areas [6]. Generalized lesions affect larger areas of the body, above and below the neck, and are more frequently associated with SLE. Excutaneous symptoms in DLE are uncommon, with only 5% of patients developing SLE [8].

PATHOPHYSIOLOGY
CLE is characterized histopathologically by interface dermatitis with a mononuclear cellular infiltrate at the dermoepidermal junction. Similar to SLE, the etiology of CLE is multifactorial, involving genetic, environmental and immune factors.

GENETICS
CLE occurs in patients with a family history of lupus, particularly between twins, suggesting a genetic component to the pathogenesis of CLE. Certain major histocompatibility complex (MHC) class I and II alleles, such as HLA-DR2 and HLA-DR3 have been linked to CLE [9]. Genetic regions outside the MHC have also been shown to increase susceptibility to CLE disease by stimulating activity of innate and adaptive immune pathways. These include various cytokine genes (IL-...
activity of a DNA exonuclease, TREX1 [11]. Moreover, nodules, is associated with mutations that decrease the receptor), adhesion molecules (ICAM-1, E-selectin), antioxidant enzymes (glutathione S-transferase M1) and keratinocytes via production of reactive oxygen species, IL-10), their receptors (gamma receptor II, T cell origin [17]. High levels of IFN-λ is controversial [15]. Type III IFNs, particularly IFN-λ, is important trigger for CLE. Skin lesions in patients with CLE are often provoked or aggravated by sunlight exposure. UV light causes apoptosis of keratinocytes via production of reactive oxygen species, direct DNA damage, and activation the Fas/FasL system [13,14]. The accumulation and defective clearance of apoptotic cells causes externalization of autoantigens resulting in an inflammatory cascade and recruitment of immune cells that leads to formation of CLE skin lesions [15]. UV light directly induces production of inflammatory cytokines and chemokines, particularly type I IFNs and interferon-stimulated genes (ISGs), which recruit inflammatory cells into the skin and cause tissue inflammation [16,17]. Simultaneously, UV exposure drives Langerhans cells, a specialized dendritic cell that is thought to play a role in regulatory responses, out of the skin and into draining lymph nodes [16]. In addition to the plasmacytoid dendritic cells (pDCs), which are the most established type I IFN producers in the skin, there is evidence to suggest that UV may activate the type I IFN system in many cell types of both immune and non-immune origin [17]. High levels of IFN-α induce apoptosis of keratinocytes, and also abrogate anti-inflammatory signals resulting in an amplified inflammatory response [18].

Smoking
Smoking is another important environmental factor of CLE, particularly DLE. One mechanistic explanation is that cigarette smoke can cause neutrophils to undergo neutrophil extracellular trap (NET) formation, thereby initiating pDC maturation and activation [19]. Moreover, smoking results in a decreased response to anti-malarial drugs [20]. A recent meta-analysis demonstrated that smoking is associated with a twofold decrease in the proportion of patients with CLE achieving cutaneous improvement with antimalarials [21]. One suggested explanation is that tobacco is known to induce cytochrome p450 system, and antimalarial drugs are partly metabolized via this pathway. However, the mechanism by which tobacco smoke may interfere with antimalarials remains unclear [21].

Pharmacologic triggers
Many drugs have been associated with drug induced (DI) CLE development, with lesions presenting similarly to SCLE. These drugs include but are not limited to, antihypertensives, statins, antifungals, NSAIDs, antiepileptics, diuretics and proton pump inhibitors [22]. The etiology is not fully understood, and is likely multifaceted. Possible mechanistic explanations include molecular mimicry, disruption of central immune tolerance, direct cytotoxicity caused by certain reactive drug metabolites, and hypomethylation of DNA resulting in altered T-cell expression [23].

IMMUNE FACTORS
Dysregulation of cellular and humoral immune responses through cytokine cascades are also implicated in the pathogenesis of CLE, as IFN α as the key player in the autoimmune response. Indeed, several studies have reported increased type I IFN expression in the serum and lesional skin of lupus patients, particularly IFNo and IFNκ [24,25]. Increased type I IFN score has been shown to correlate with increased CLE Disease Area and Severity Index (CLASI) activity score, a measure of CLE skin disease severity [26]. Moreover, the patients’ systemic symptoms, including fever, fatigue, rash, arthralgia, and myalgia are associated with type I IFNs. In CLE, pDCs produce type I IFN, mainly IFNκ, in response to nuclear antigens and to immune complexes. IFNκ plays a key homeostatic role in regulating basal type I IFN responses in the skin, and has been recently implicated in the pathogenesis of CLE [25]. Increased constitutive expression of IFNκ by lupus keratinocytes drives the activation of dendritic cells, resulting in the amplification of type I IFN signaling and thus photosensitivity. IFNs activate the JAK/STAT pathway to stimuli production of CXCL9, CXCL10 and CXCL11, which recruit CXCR3+ immune cells to the skin [27]. Inflammatory cells in CLE are comprised mainly of T lymphocytes, with higher levels of Th1 and Th17 cells. Other infiltrating cells include NK cells, B cells/plasma cells, and in some subtypes, neutrophils. pDCs also express CXCR3 ligands, allowing pDC-produced IFN to recruit additional pDCs into the skin and further enhance the production of IFN. In addition to CXCL9, CXCL10, CXCL11, which are the most highly, expressed chemokines in CLE, the chemokine CCL27 has been recently identified in recruiting memory T cells into the skin [27]. Type I IFN also increases the level of cytoxic molecules perforin and granzyme B, as well as mediators of apoptosis CD59 receptor and TRAIL, the TNF-related apoptosis-inducing ligand [17].

Like type I IFN, type II and III IFN also play a role in the pathogenesis of CLE [17]. Type II IFN is involved in increasing tumor necrosis factor- (TNF) levels which serves to activate B cells antibody production. Type II IFN appears to be most associated with DLE [28]. CLE patients exhibit high levels of TFNα in their serum, however the role of TFNα in CLE is controversial [15]. Type III IFNs, particularly IFNλ, are produced by keratinocytes and induce the expression of several proinflammatory cytokines, including CXCL9, which drive the recruitment of immune cells and are associated with the formation of CLE skin lesions [29].
THERAPEUTIC OPTIONS FOR CLE

Current treatment options

To date, there are no drugs that have been approved specifically for the treatment of CLE by the Food and Drug Administration (FDA) as therapeutic trials for SLE medications often exclude CLE patients [30,31]. Most of the current treatment strategies for CLE are borrowed from SLE, and are based on severity and types of cutaneous lupus. Prevention measures, including photoprotection, smoking cessation and avoiding drugs that can trigger symptoms, are essential in CLE treatment. Pharmacologic treatments include topical corticosteroids, topical calcineurin inhibitors, and antimalarials. Antimalarial drugs, including hydroxychloroquine, quinacrine, and chloroquine, are first-line medications for CLE, and are indicated when skin lesions are widespread or refractory to topical agents [32]. They exert their effect via immunomodulatory properties. In patients with recalcitrant CLE, the addition of immunosuppressives, such as methotrexate (MTX), mycophenolate mofetil (MMF), or azathioprine, may be helpful. Other treatment options include oral retinoids, dapsone, intravenous immunoglobulin (IVIG), pulsed dye laser therapy, thalidomide and lenalidomide [31].

Emerging therapies

Improved insights into the immunopathogenesis of CLE has led to the development of therapies that specifically target critical pathways in CLE. Given the key pathogenic role of the type 1 IFN pathway, multiple newly developed IFN-directed therapies are emerging. Rontalizumab and Sifalimumab are humanized monoclonal antibodies specifically targeting IFNα. While the latter did show a reduction in CLASI, both have failed to show clinical benefit in SLE, and Sifalimumab was ultimately discontinued to pursue more encouraging results from Anifrolumab [33,34]. Anifrolumab, a human monoclonal antibody to type I IFN receptor subunit 1, has shown to improve CLASI scores in SLE patients with cutaneous involvement during phase 2 and 3 clinical trials [35]. These results suggest that type I IFN is a promising target for the treatment of CLE, and that targeting the receptor may prove to be a more effective strategy owing to the fact that it will prevent signaling from all ligands.

In addition, therapies targeting IFN-producing pDCs have also emerged. BIIB059 is a humanized IgG1 monoclonal antibody that targets pDCs, downregulating type I IFN production. A phase 2 clinical trial was recently completed with BIIB059 demonstrating significant improvement in CLE and SLE endpoints [36]. Toll-like receptors (TLRs) are also involved in inducing IFNo production, and thus antagonists targeting TLRs are currently in Phase 1 trials for CLE treatment (NCT04647708 and NCT03159936) [37]. Although type II IFN is implicated in CLE, an antibody targeting IFNy (AMG811) failed to show clinical improvement in patients with CLE [38]. Moreover, studies investigating IL-6 blockade via monoclonal antibody Sirukumab, did not show any clinically significant changes for skin manifestations in SLE patients [39].

In recent years, several monoclonal antibodies targeting type I7-mediated inflammation have shown success in multiple autoimmune diseases such as psoriasis and rheumatoid arthritis [40,41]. Studies have shown that IL-17A may play a major role in the pathogenesis of DLE, and thus the efficacy and safety of an anti-IL-17A monoclonal antibody, Secukinumab, is currently under investigation (NCT03866317). In a study assessing the safety and tolerability of Ustekinumab, an IL-12/23 monoclonal antibody, there was a statistically significant improvement in skin disease compared with placebo [42]. However, Ustekinumab has also been paradoxically reported to induce CLE, thus the roles of IL-12 and IL-23 remain unclear [43]. Similarly, conflicting results exist for therapies targeting TNF [30].

B-cell targeted therapeutic approaches have also been developed for lupus. Belimumab is a monoclonal antibody against B-lymphocyte stimulator (BLyS), a B-cell survival factor, which has been approved for use in SLE. While Belimumab improves cutaneous disease in CLE patients, larger randomized controlled studies are needed to fully elucidate its role in CLE [44]. Mixed results have been observed for the efficacy of B-cell depleting monoclonal antibody Rituximab in SLE patients with mucocutaneous manifestations [45,46].

Other potential therapeutic targets for CLE include intracellular signaling molecules [30]. Janus kinases (JAKs) are critical tyrosine kinases that act as mediators and amplifiers of pro-inflammatory signals. JAK inhibitors have been approved for use in adults with rheumatoid arthritis and psoriatic arthritis and might be a promising approach for the paradoxical benefit of LE skin lesions. Baricitinib and Ruxolitinib (JAK1/2 inhibitors) showed efficacy for patients with chilblain lupus erythematosus [47]. However, Baricitinib failed to show improvement in skin disease during a phase II clinical trial for SLE [48]. Additional trials are currently investigating the role of other JAK inhibitors, namely Tofacitinib (NCT03288324 and NCT03159936). Moreover, JAK inhibitors in combination with spleen tyrosine kinase (SYK) inhibitors are also under investigation for treatment of CLE (NCT03134222).

Inhibitors of C-Jun N-terminal kinase (JNK) and Mitogen-activated protein kinase (MAPK) have also been developed. A phase II clinical trial with a small-molecule inhibitor of JNK, tanzisertib, was conducted in CLE, however these trials were terminated due to inappropriate benefit/risk profiles (NCT01466725). Moreover, while inhibitors of the MAPK pathway have shown encouraging results in pre-clinical models of lupus, human clinical trials targeting the MAPK pathway for CLE have not yet been conducted [49,50].

Finally, pharmacologic agents that are structurally similar to lenalidomide are under development. In a phase II clinical trial, use of a lenalidomide derivative, CC-220, has been shown to correlate with improvement in CLASI score and pDC reduction [51]. Ongoing clinical trials are highlighted in Table 1.
CONCLUSION

CLE is a multifactorial condition involving genetic predisposition, environmental factors and innate and adaptive immune responses. While lupus drug trials are often focused on SLE, multiple clinical trials for CLE treatment are currently in progress. Advances in the treatment of CLE are attributed to better understanding of the pathogenesis as well as the development of CLASI, which provides a quantifiable endpoint for CLE trials. Further clinical trials for CLE should be encouraged to provide CLE-specific data and to ensure improved health outcomes.

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CONFLICT OF INTEREST

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REFERENCES


