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Review Article

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-polycyclic 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. Extracutaneous 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-

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1, IL-10), their receptors (gamma receptor II, T cell receptor), adhesion molecules (ICAM-1, E-selectin), antioxidant enzymes (glutathione S-transferase M1) and apoptosis genes (Fas) [10]. Genetic variations in genes involving the type I interferon pathway are implicated in CLE pathogenesis. Specifically, mutations in the IFN regulatory factor 5 (IRF5), tyrosine kinase 2 (TYK2), and three prime repair exonuclease 1 (TREX1) genes, increase type I IFN production in some patients with CLE. Familial chilblain lupus, a rare form of CLE characterized by ulcerating acral nodules, is associated with mutations that decrease the activity of a DNA exonuclease, TREX1 [11]. Moreover, deficiencies in genes encoding complement components (C1q, C1r, C1s, C2 and C4) have also been reported to contribute to the pathogenesis of CLE, due to defective complement clearance of apoptotic debris [12].

ENVIRONMENT

UV exposure

It is well known that ultraviolet (UV) irradiation is an important trigger for CLE. Skin lesions in patients with CLE are often provoked or aggravated by sunlight exposure. UV light contributes to CLE lesions through several pathways. Exposure of the skin to 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, with IFN as a 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 IFNα 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 IFNα, 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 stimulate 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 cytotoxic 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 TNFα in their serum, however the role of TNFα 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 IFNα 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 IFNγ (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 17-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 simulator (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 treatment of LE skin lesions. Baricitinib and Ruxolitinib (JAK1/2 inhibitaors) 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.

Table 1: Ongoing clinical trials for CLE treatments.

	Trial	Clinical trials.gov identifier (NCT number)	Phase	Therapeutic intervention	Population	Measured end points
Immunotherapies	Study of M5049 in Cutaneous Lupus Erythematosus (CLE) and Systemic Lupus Erythematosus (SLE) Participants	NCT04647708	Ib	M5049 (TLR7/8 inhibitor)	SLE and CLE	Safety
	A Study to Assess the Safety and Drug Levels of BMS986256 in Participants With Active Cutaneous Lupus Erythematosus	NCT04493541	Ib	BMS-986256 (TLR7/8 inhibitor)	SLE and CLE	Safety
	Open-label Study of Tofacitinib for Moderate to Severe Skin Involvement in Young Adults With Lupus	NCT03288324	I/II	Tofacitinib (JAK inhibitor)	SLE and CLE	Safety, CLASI, SLEDAI, Skindex, BILAG index
	A Study to Assess the Safety and Efficacy of Secukinumab in Alleviating Symptoms of Discoid Lupus Erythematosus	NCT03866317	II	Secukinumab (anti-IL-17A antibody)	DLE	CLASI
	Study to Evaluate Safety and Efficacy of Filgotinib and Lanraplenib in Females With Moderately-to-Severely Active Cutaneous Lupus Erythematosus (CLE)	NCT03134222	II	Filgotinib (JAK inhibitor) & Lanraplenib (SYK inhibitor)	CLE	CLASI
	Oral Tofacitinib in Adult Subjects With Discoid Lupus Erythematosus (DLE) and Systemic Lupus Erythematosus (SLE)	NCT03159936	I	Tofacitinib (JAK inhibitor)	DLE and SLE	CLASI
Device Therapies	Low-dose UVA1 Radiation in Cutaneous Lupus Patients	NCT01776190	NA	UVA1 radiation treatment	CLE	CLASI

Abbreviations: CLE=Cutaneous Lupus Erythematosus; SLE=Systemic Lupus Erythematosus; DLE: Discoid Lupus Erythematosus; CLASI: The Cutaneous Lupus Erythematosus Disease Area and Severity Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; BILAG: British Isles Lupus Assessment Group

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

JMR is an inventor on use patents for targeting CXCR3 (0#15/851,651) and IL15 (# 62489191) for the treatment of vitiligo.

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