REVIEW

Cutaneous Lupus Erythematosus: Current and Future Pathogenesis-Directed Therapies

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Cutaneous lupus erythematosus (CLE) is an autoimmune disease of the skin with significant morbidity. Current treatments are often inadequate to control disease and there are no Food and Drug Administration (FDA)-approved therapies for this potentially debilitating disease, underscoring an unmet medical need. Recent insights into disease pathogenesis have implicated innate and adaptive immune components, including type I and type III interferons in the development of CLE. Promising clinical trials based on these insights are now underway. However, the full spectrum of immune cells, cytokines, and environmental triggers contributing to disease remain to be elucidated. In this review, we will highlight the current understanding of CLE immunopathogenesis, the ongoing clinical trial landscape, and provide a framework for designing future therapeutic strategies for CLE based on new insights into disease pathogenesis.

INTRODUCTION

Cutaneous lupus erythematosus (CLE) is an autoimmune skin disease that severely impairs quality of life [1]. CLE may present as skin disease alone or may occur in the setting of systemic lupus erythematosus (SLE), a severe multiorgan autoimmune disease with a wide variety of disease manifestations. In addition, patients initially diagnosed with isolated CLE may later progress to SLE. CLE is subdivided into acute, subacute, or chronic cutaneous lupus erythematosus (ACLE, SCLE, or CCLE, respectively) based on lesion morphology and histopathology. CCLE accounts for approximately 80% of CLE [2], and discoid lupus erythematosus (DLE) comprises the majority of CCLE.

The CLE subsets not only have different morphology and histopathology, but also have different rates of association with SLE. ACLE is characterized by malar erythema (the classic "butterfly rash" of lupus) and/or widespread photodistributed erythema, and it is almost always found in association with SLE. In contrast, patients with localized DLE present with skin lesions limited to the head and neck that are characterized initially by erythema, induration, and scale, followed by the development of scarring, hypopigmentation, atrophy, and permanent alopecia. A subset of patients with DLE can develop more extensive or generalized lesions beyond the head and neck to involve the trunk and extremities.

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Patients initially diagnosed with DLE develop systemic involvement in 10-20% of cases, with some studies suggesting that patients with generalized lesions are at higher risk than those with localized DLE [3-5].

In addition to these CLE-specific skin lesions, non-specific cutaneous manifestations may occur in patients with SLE, including non-scarring hair loss, vasculitis, and Raynaud's syndrome. It is estimated that 70-80% of all patients with SLE will have skin or hair involvement at some point, and a cutaneous finding is the initial disease manifestation for 20-25% of SLE patients [6].

There are currently no FDA-approved targeted therapies available for CLE and existing treatments are often ineffective for many patients. Therapeutic trials for SLE medications often exclude CLE patients who do not meet the criteria for SLE [7], which may hinder the development of FDA approved therapies for this potentially devastating skin disease. Herein, we highlight the current understanding of CLE immunopathogenesis, the ongoing clinical trial landscape, and provide a framework for designing future therapeutic strategies for CLE based on new insights into disease pathogenesis.

PATHOGENESIS OF CLE

Both SLE and CLE are multifactorial diseases, with a complex interaction occurring between environmental exposures and genetic susceptibility that triggers and/or propagates immune dysregulation, resulting in disease in affected individuals. As has been found for SLE, it may be that much of an individual's susceptibility to CLE is due to the accumulation of various risk alleles, with disease development ultimately determined by the interaction of these genetic variations with the environment [8-10].

Genetics

Genetic studies, including those of families, of affected individuals, and of affected populations in genome-wide association studies (GWAS), have identified genetic polymorphisms, mutations and risk alleles in CLE populations. The vast majority of these identified genes are involved in pathways that affect the function of innate and adaptive immune responses, predisposing to immune dysregulation. Among others, these include apoptosis/cell death, DNA processing, the type I interferon pathway, migration of leukocytes, the complement cascade and clearance of cell debris, T-cell immune checkpoints, antigen presentation, and antibody production [11-13]. Complete coverage of the genetic associations with CLE is beyond the scope of this review, and for further detail, readers are directed to recent reviews with broader coverage of this topic [8,9,14].

Mutations in the Three Prime Repair Exonuclease 1 (TREX1) represent the only monogenic cause of cutaneous lupus identified to date, resulting in a rare form of CCLE called familial chilblain lupus [15]. These patients develop cold-induced purple-red lesions on acral surfaces, which may ulcerate. TREX1 is a cytosolic DNA exonuclease that plays an essential role in the homeostatic degradation of single stranded DNA (ssDNA), and TREX1 deficiency results in intracellular ssDNA accumulation. Recognition of these accumulated nucleic acids by innate immune receptors results in chronic hyperactivation of the type I interferon pathway [16].

Female gender has long been known as a major risk factor in the development of many autoimmune diseases, including SLE and CLE. Sex hormones are some of the most well-studied potential contributors to this sex bias [17], however recent investigation into human skin sexual dimorphism identified the putative transcription factor vestigial-like family member 3 (VGLL3) as an essential regulator of female-biased genes that may contribute to an autoimmune phenotype in women. VGLL3 influences type I interferon responses and promotes the expression of genes encoding inflammatory molecules, many of which are genetic risk variants previously identified in autoimmune diseases including SLE. Unlike in normal skin, where VGLL3 is more highly expressed in female-derived tissue, in SCLE skin, VGLL3 expression levels were similar between males and females, and skin-directed overexpression of VGLL3 in mice causes a lupus-like disease with cutaneous manifestations, suggesting that VGLL3 may play a role in the pathogenesis of CLE [18,19].

In addition to genetic mutations and polymorphisms that predispose to CLE, external stimuli may interact with the genome in susceptible individuals to cause epigenetic variation, leading to dysregulated gene expression via DNA methylation, histone modification, and microRNA-mediated gene silencing. Potentially pathogenic epigenetic changes have been described in SLE and include DNA hypomethylation in T cells, which results in increased inflammatory gene expression. Several microRNAs are dysregulated in SLE, and at least four of those upregulated in T cells promote hypomethylation [20]. Histone modifications are also found in SLE patient peripheral blood mononuclear cells [10,21]. MicroRNA profiling of DLE lesional skin identified overexpression of keratinocyte-derived miR-31, which is upregulated upon ultraviolet (UV) exposure and induces keratinocyte apoptosis and inflammatory cytokine production. Leukocyte-derived miR-485-3p was also identified, which induces T cell activation and pro-inflammatory cytokine production [22]. DNA methylation patterns of naïve CD4$^+$ T cells in SLE patients reveal differentially methylated regions (DMRs)

associated with the development of malar rash or DLE. These DMRs involve genes mediating cell proliferation, apoptosis, and antigen presentation, suggesting a role in pathogenesis [23]. DNA methylation analyses in SCLE patients reveal demethylation of the perforin and CD70 promoters in CD4$^+$ T cells. Both perforin and CD70, a B-cell costimulatory molecule expressed on T cells, are overexpressed in SCLE T cells, suggesting a possible pathogenic link [24,25]. Further investigation into the role of the epigenome in CLE is needed and may yield targets for therapy to restore normal epigenetic patterns.

Environmental

Ultraviolet (UV) light exposure is a common provoking factor for CLE, and photosensitivity is one of the 11 American College of Rheumatology criteria for SLE. Between 60-80% of CLE patients report photosensitivity, and patients with ACLE are more likely to report photosensitivity than those with SCLE or CCLE [26,27]. UV irradiation directly induces chemokine production by epithelial cells, and it also causes DNA damage, resulting in keratinocyte apoptosis and necrosis. Dying keratinocytes release inflammatory cytokines and chemokines, which in turn recruit lymphocytes and plasmacytoid dendritic cells (pDCs). Keratinocyte death may also result in release of nuclear debris, which can stimulate pDCs via Toll-like receptors (TLRs) and can also serve as a reservoir of autoantigen for autoreactive T and B cells [28]. Recently, lupus-prone mouse studies have identified Langerhans cells (LC) as a source of protective epidermal growth factor receptor (EGFR) ligands that prevent UV-induced keratinocyte death and decrease the development and severity of UV-induced lupus skin lesions. Nonlesional skin from SLE patients demonstrated decreased LC numbers and epidermal EGFR phosphorylation, suggesting a possible correlate in human SLE [29]. Currently, the only treatment for photosensitivity is sunlight avoidance and broad-spectrum, high sun protective factor (SPF) sunscreen, which prevents the development of disease-specific skin lesions in CLE patients exposed to UVA/UVB [30].

Cigarette smoking is associated with CLE, and it is suggested that tobacco smoke contributes to CLE disease activity by increasing inflammatory cytokines, apoptosis, autoantibodies, and the development of free radicals. Compared with non-smokers, smokers with CLE have worse quality of life and worse skin disease, as measured by the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). There is conflicting data regarding whether smokers respond to antimalarials as well as non-smokers [31,32], but smokers exhibit more recalcitrant disease than non-smokers if both antimalarials and immunomodulators are required [32,33]. It is still unknown whether decreased treatment efficacy in smokers is due to direct interference of cigarette smoke with the treatment or to the higher disease severity in smokers [34]. It is also possible that some smokers may have lower medication adherence rates; current smokers have been found to be less adherent with recommended preventative care recommendations and medications in other clinical settings [35].

Drug-induced SLE (DI-SLE) is an established adverse effect of certain medications, historically most commonly due to procainamide, hydralazine, and quinidine and less frequently due to a number of other medications, including minocycline, penicillamine, carbamazepine, methyldopa, sulfasalazine, chlorpromazine, propylthiouracil, and isoniazid. Medications highly associated with DI-SLE are thought to enhance innate immune responses, particularly of neutrophils, resulting in increased neutrophil extracellular trap (NET) formation and autoantigen exposure [36]. In addition, procainamide and hydralazine both inhibit DNA methylation, and thus may cause DI-SLE via epigenetic effects [20]. DI-SLE from procainamide rarely involves the skin, but cutaneous involvement is reported in up to one third of cases of DI-SLE due to hydralazine or quinidine [36]. Cutaneous manifestations may also be seen in up to one quarter of DI-SLE cases due to minocycline [37]. Drug-induced skin-limited SCLE and much less commonly CCLE may occur due to other medications. A systematic review of drug-induced SCLE found the most frequently reported causative medications to be antihypertensives (most commonly hydrochlorothiazide and calcium channel blockers) and terbinafine, with less frequent reports of many other medications including chemotherapeutics, antihistamines, leflunomide, interferon, antiepileptics, statins, lansoprazole, and non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen and piroxicam [38]. A subsequent population-based matched case-control study found an increased odds ratio of developing SCLE within 6 months of medication initiation for patients prescribed terbinafine, TNF-α inhibitors, proton pump inhibitors, carbamazepine, platelet inhibitors, ACE inhibitors, and NSAIDs [39]. It is hypothesized that DI-SLE or SCLE due to TNF-α inhibitors may be in part due to the immunogenicity of the medications themselves, though more recent formulations have lower immunogenicity and DI-SLE/SCLE continue to be reported to these agents. There may also be a component of "unmasking" rather than causing the SLE or SCLE, as some patients treated with TNF-α inhibitors have conditions that are associated with a higher baseline risk of SLE, such as rheumatoid arthritis [36]. In addition, TNF-α functions to inhibit both the development of pDCs and their IFN-α production. Treatment with TNF-α inhibitors results in IFN-α activation, which may thus promote the development of
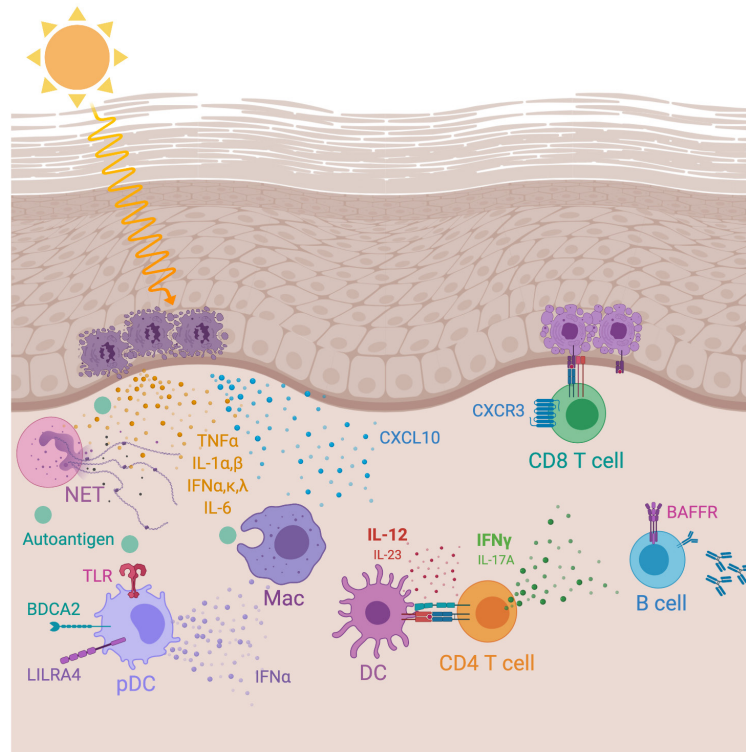
Figure 1. **Immunopathogenesis of cutaneous lupus**. Ultraviolet (UV) radiation induces keratinocyte necrosis or apoptosis, resulting in the release of proinflammatory cytokines including tumor necrosis factor α (TNFα), interleukin-1α (IL-1α) and IL-1β, IL-6 and interferon (IFN) α,κ,λ as well as chemokine CXCL10. Autoantigen release from dying keratinocytes admixed with neutrophil extracellular traps (NETs) activates pDCs to release IFNα. Dendritic cells (DC) secrete IL-12 or IL-23 to activate CD4+ T cells to secrete IFNγ or IL-17A, respectively. CD8+ T cells expressing CXCR3 are recruited to dermal-epidermal junction via CXCL10 and attack keratinocytes, resulting in keratinocyte apoptosis (vacuolar interface dermatitis). B cells expressing BAFF (B cell activating factor) receptor secrete autoantibodies. Macrophages (Mac) phagocytose autoantigens released from dying keratinocytes and help prime adaptive immune lymphocytes against keratinocytes. BDCA2, blood dendritic cell antigen 2; LILRA4, leukocyte immunoglobulin-like receptor subfamily A member 4; TYK2, tyrosine kinase 2.

interferon-driven diseases (*e.g.* CLE and SLE) [40].

Studies investigating the microbiome in SLE patients have suggested that host-microbe interactions contribute to the development of disease. Molecular mimicry is proposed to play a role in the development and propagation of autoimmunity in SLE and SCLE patients with anti-Ro (SS-A) antibodies. An evolutionarily conserved Ro60 protein ortholog was identified in a subset of human skin, oral, and gut commensal bacteria, which was found to be cross-reactive with both the SCLE/SLE patient's anti-Ro antibodies as well as their Ro60 autoreactive T cell clones [41]. The host microbiome has also been implicated in development of SLE via *Enterococcus gallinarum* bacterial translocation from the gut to the liver and other systemic tissues, promoting the development of autoantibodies and SLE-like disease in autoimmune-prone mice. *E. gallinarum*-specific DNA was also identified in liver biopsies of SLE and autoimmune hepatitis patients, suggesting that translocation of a gut

pathobiont may cause human autoimmune disease [42]. Microbiome-host interactions and their influence on host autoimmune disease is an area of active research, and their role, if any, in the development or propagation of CLE remains to be elucidated [43].

Immunopathogenesis

Insights from genetic studies and environmental triggers in lupus pathogenesis implicate both innate and adaptive immune components. Overall, CLE is a disease of dysregulated immune homeostasis, resulting in unwanted innate immune stimulation and adaptive immune activation. The autoimmune pathways involved in CLE development and pathogenesis remain incompletely understood. It must also be emphasized that the sequence of events from environmental trigger, if any, to immune activation to disease is also unknown. However, there is substantial data to suggest that CLE is a disease of type I interferon (IFN) excess and resultant cytotoxic CD8+ T

cell attack of the epidermis (Figure 1) [7,8,14,28,44-46]. Although animal models of lupus help inform potential mechanisms of disease pathogenesis, they do not always recapitulate human disease [47]. Our discussion is limited to evidence from human CLE patients.

CLE as an Interferonopathy

Inherited autoinflammatory disorders with excessive type I IFN signaling are referred to as type I interferonopathies. Some of these disorders develop CLE-like phenotypes, such as Aicardi-Goutières syndrome and familial chilblain lupus [48]. Although CLE encompasses several types of skin and molecular phenotypes, type I IFNs appear to be central to disease development [49]. There are 17 type I IFN family members that share a common receptor, the interferon-α/β receptor (IFNAR) [50]. Another member of type I IFN family, IFNκ, is of considerable interest given it is produced by keratinocytes in response to stress along with IFNα [51]. Multiple gene expression studies have demonstrated upregulation of type I IFNs and IFN-stimulated genes in CLE [52-55]. Importantly, type I IFN genes are associated with disease activity in CLE [54]. The consequences of type I IFN are broad and include activation of innate immune cells and promotion of adaptive immunity. A potential initial source of type I IFNs are keratinocytes in response to UV irradiation [51,56]. Type I IFN release activates multiple innate immune cells including neutrophils, macrophages, and plasmacytoid dendritic cells (pDCs). The most likely source of continuing type I IFN production, and thereby promotion and maintenance of disease progression, are pDCs. Upon UV stimulation of skin, pDCs accumulate and are found in abundant numbers in CLE tissues [57,58]. Type I IFNs also help to promote release of IFNγ and its subsequent induction of chemokines, including CXCL10, that attract cytotoxic CD8+ T cells expressing CXCR3 to the dermal-epidermal junction of CLE [59-64]. Thus, pDCs may be one of the most critical immune cells contributing to disease pathogenesis given the secretion of type I IFNs, which in turn leads to IFNγ release. On the other hand, T cells are the most abundant cell type within CLE [52], and cytotoxic CD8+ T cells are the driver of keratinocyte death and disruption of the dermal-epidermal junction [52,64]. Both cells appear to be absolutely critical to pathogenesis, and emerging therapies are designed to target these cells. In addition to type I and type II IFNs, there is also evidence that type III IFNs (IFNλ) produced by keratinocytes contribute to CLE disease [65]. Type III IFNs are considered critical immunomodulatory cytokines that play important roles in host defense at barrier tissues such as the skin [50]. Taken together, all three families of IFNs appear to contribute to CLE disease pathogenesis and appear to be the most critical immune pathway involved, implicating CLE as an acquired interferonopathy.

Keratinocytes as Innate Immune Cells in CLE

Keratinocytes are the essential cell type that comprises the epidermal barrier of skin. Therefore, keratinocytes are key players in barrier immunity where they perform specialized functions in response to environmental insults, skin microbiome, and pathogen invasion. Furthermore, keratinocytes interact with host immunity and often serve as innate immune cells by releasing "alarmins" and danger signals that activate neighboring immune sentinels and recruit adaptive immune lymphocytes to areas of stress or damage [66,67]. Thus, the release of alarmins such as keratins, S100 proteins, and HMGB1 upon keratinocyte death can help initiate and amplify an immune response [68,69]. In CLE, UV light can trigger necrosis or apoptosis of keratinocytes, resulting in release of proinflammatory cytokines interleukin-1α (IL-1α), IL-1β, IL-6, TNFα, IFNα, IFNκ, IFNλ, and chemoattractants such as CXCL10 [45,51,56,63,65,70-72]. Nuclear debris such as RNA and DNA may activate pDCs through toll-like receptors (TLRs), resulting in type I IFN release. Together, keratinocytes and IFNs appear to initiate and sustain disease activity.

Other Cytokines Involved in CLE

Multiple other cytokines have been detected in CLE tissue [63,73]. However, the importance of each detected cytokine is unclear. Given the complex interplay of keratinocytes, IFNs, and innate and adaptive immune cells, it is no surprise that multiple inflammatory pathways are active in CLE. It is reasonable to assume that the major drivers of disease are also the most abundant and consistent pathways activated, such as IFNs in CLE. However, the true test to determine the major pathogenic inflammatory pathway is through clinical trials investigating targeted therapy in patients with CLE. Since these trials are in the earlier phases of development, it is unclear which pathway will be the most effective to target. Some studies have demonstrated the presence of IL-17A in CLE [74,75]. However, another study comparing DLE with psoriasis, which displays a pathogenic Th17 pathway (IL-17), found that DLE showed an IFNγ and Th1 predominant expression pattern [76]. Secukinumab, a monoclonal (mAb) targeting IL-17A is currently under investigation for CLE (NCT03866317). IL-18 may also be contributing to CLE pathogenesis by inducing the secretion of TNFα from keratinocytes [77], however no targeting strategy to block IL-18 is in clinical trials for CLE. In contrast, blockade of IL-12/IL-23 cytokines with ustekinumab is in clinical trials and has shown efficacy in CLE [78]. Gene expression studies have demonstrated elevated IL-12 in lesional CLE skin as compared to non-

lesional skin [73].

JAK-STAT Pathway in CLE

After cytokines engage with their respective receptors, intracellular signaling pathways transmit those signals to induce cellular functions through gene transcription, protein translation, and protein trafficking. The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways are critical for a diverse array of downstream cytokine receptor signaling [79]. Approximately 60 cytokines, including the interferons, transmit molecular instructions through the JAK-STAT pathway [80]. Type I IFNs use JAK1, TYK2, STAT1, and STAT2 to induce the expression of hundreds of interferon-stimulated genes (ISGs) frequently found upregulated in CLE tissues [52-55]. In contrast, type II IFNγ uses JAK1, JAK2, and STAT1. In fact, many of the cytokines implicated in CLE pathogenesis utilize the JAK-STAT pathway including IL-6, IL-12, IL-23, and the interferons. Therefore, it is not surprising that lesions of CLE express elevated levels of STAT and JAK proteins [73]. Given that multiple cytokine receptors utilize the JAK-STAT signaling cascade, drugs targeting JAKs have shown recent efficacy in the treatment of numerous autoimmune diseases of the skin including psoriasis, atopic dermatitis, dermatomyositis, vitiligo, and alopecia areata [81]. Current clinical trials using JAK inhibitors in CLE are ongoing (Table 1).

Autoantigens and Autoantibodies in CLE

During keratinocyte cell death, nuclear material and cellular debris are released, including potential autoantigens. In combination with alarmins, innate immune cells become poised to uptake and process keratinocyte autoantigens, which may amplify and sustain ongoing autoimmunity. Priming of the adaptive immune response with autoantigens results in T cell activation against cells harboring those antigens as well as the production of autoantibodies by B cells. Although the specific autoantigens in CLE remain elusive, the detection of autoantibodies such as Ro suggest that they may be playing a role in disease progression [26]. However, not all patients with CLE have detectable autoantibodies, which is in contrast to SLE which nearly always has autoantibodies present. In those CLE patients that do have autoantibodies, disease activity positively correlates with autoantibody concentrations in the serum [82]. In SLE, B cells are thought to be critical players in the development of disease through autoantibody production. Targeting a cytokine critical for B cells (B cell activation factor, BAFF) with belimumab led to the first new FDA-approved drug for SLE in 50 years [83]. B cells and associated BAFF and BAFF receptors are found in CLE [84] and the effect of belimumab in CLE is currently under investigation.

In SLE, neutrophils are thought to be important for presentation of autoantigens through the generation of neutrophils extracellular traps (NETs) [85]. Recently, NETs were detected in CLE skin [86]. However, it is unknown if NETs in CLE are presenting autoantigens to the multiple myeloid subsets found in CLE such as conventional DCs, CD163^{+} macrophages or CD68^{+} macrophages [87,88]. Finally, defects in apoptosis or clearance of apoptotic cells have been hypothesized to play a role in lupus pathogenesis by increasing autoantigen exposure and proinflammatory cytokine release [89]. On the other hand, type I IFNα induces keratinocyte apoptosis [55]. Thus, the role of apoptosis and apoptotic signaling in CLE need further investigation.

TREATMENT OF CLE

Current Therapy for CLE

Although there are no FDA-approved medications for CLE, established therapies for CLE are effective for many, but not all, patients with CLE [7,14]. In this review, we will focus on new emerging therapies for CLE and only briefly discuss current established therapies [7,14]. Most of these established therapies involve general immunosuppressants or therapies borrowed from SLE. Nevertheless, dermatologists and rheumatologists successfully treat CLE patients with ultrapotent topical and intralesional corticosteroids and anti-malarial therapies such as hydroxychloroquine, which are recommended as first-line treatments [90]. Although the mechanism of anti-malarial drugs is incompletely understood, there is evidence that they inhibit antigen processing and presentation by DCs as well as masking stimulatory DNA epitopes, preventing their recognition by endosomal TLR9 in pDCs, thereby reducing type I IFN production [91]. Thus, hydroxychloroquine may more selectively impair the type I IFN response than other broad immunosuppressants. Nevertheless, in difficult to treat cases other broad immunosuppressants such as systemic corticosteroids, methotrexate, mycophenolate mofetil, azathioprine and cyclosporine are also used with varying degrees of success [92]. Thalidomide is another treatment option for patients with recalcitrant CCLE that has been demonstrated to be very effective [93-96]. In addition, a thalidomide analogue, lenalidomide, has also shown efficacy in cutaneous lupus [97]. Thalidomide and lenalidomide [94] are likely effective due to their immunomodulatory effects, including a reduction of proinflammatory cytokine TNF-α [98]. Despite success with these medications, some patients still have recalcitrant disease or treatment-related toxicity, underscoring the need for improved therapies. Recent
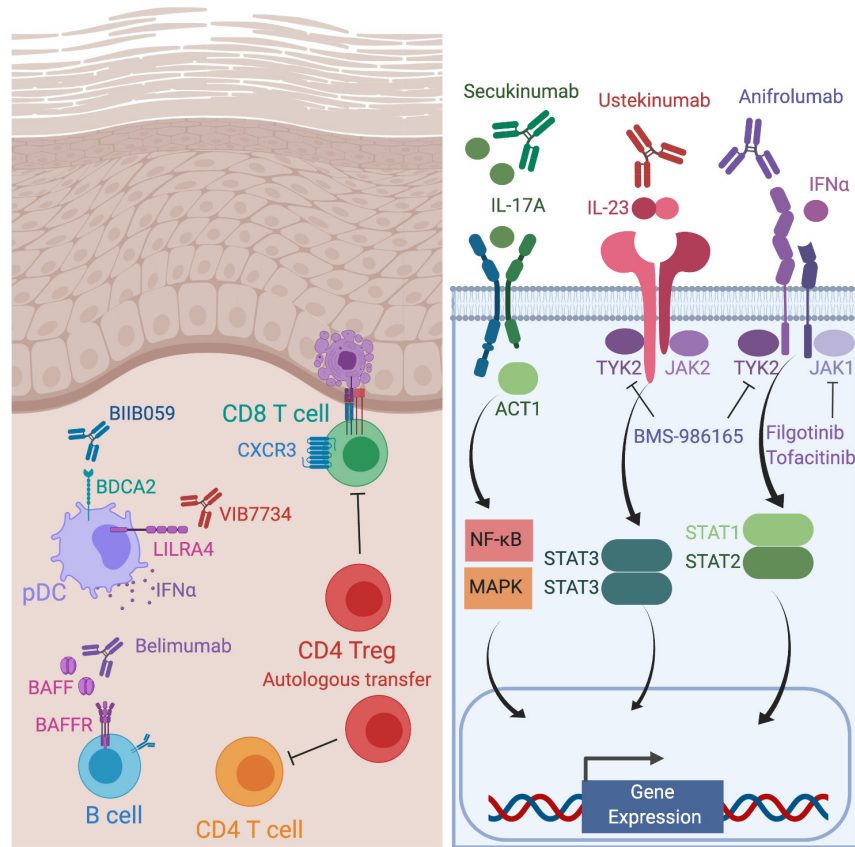
Figure 2. **Emerging therapeutic strategies for cutaneous lupus**. Cellular targets including belimumab against BAFF, BIIB059 against BDCA2 on plasmacytoid dendritic cells (pDCs), V1B7734 against LILRA4 on pDCS and autologous transfer of Tregs (left). Secukinumab binds to IL-17A, ustekinumab binds to the IL12p40 subunit shared by IL-12 and IL-23, and anifrolumab binds IFNAR1 subunit (right). Intracellular targeted therapies include BMS-986165 which inhibits TYK2, and filgotinib and tofacitinib which block JAK1 (right). 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; LILRA4, leukocyte immunoglobulin-like receptor subfamily A member 4; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase 2.

insights into pathogenesis provide promise for new pathogenesis-directed therapeutics for CLE.

EMERGING PATHOGENESIS-DIRECTED THERAPY FOR CLE

Critical insights gained into the pathogenesis of CLE in addition to explosive immunomodulatory drug development with more precise mechanisms of action have resulted in unprecedented opportunity to develop pathogenesis-directed therapies for CLE. Multiple distinct strategies to modulate the immune system are now under active investigation to ameliorate disease (Figure 2) (Table 1). One key advance in monitoring response to therapy is the cutaneous lupus erythematosus disease activity and severity index (CLASI) [99], which is now being used as a primary or secondary endpoint in clinical trials.

Cellular Targets

A wide variety of adaptive and innate immune cells have been investigated for a potential role in CLE pathogenesis, including T-cells, B-cells, dendritic cells (particularly pDCs), macrophages, and neutrophils [28]. Although clinical trials enrolling patients with CLE are limited [7], trials employing targeted therapies against pDCs and B cell signaling have shown promise. The humanized monoclonal antibody BIIB059 targets blood DC antigen 2 (BDCA2), a receptor specifically expressed on pDCs that, when bound by BIIB059, is rapidly internalized, resulting in decreased pDC production of type I interferons, cytokines, and chemokines. A phase 1B randomized, double-blind, placebo-controlled trial of BIIB059 in patients with SLE and active cutaneous disease showed a reduction in CLASI-A score in treated patients vs placebo controls, and this clinical improvement correlated with normalization of the type

Table 1. Current clinical trials for CLE.

Drug name	Target	Phase
Belimumab	BAFF (BLyS)	3
Ustekinumab	IL-12/IL-23	3
Secukinumab	IL-17A	2
Anifrolumab	IFNAR1	3
Filgotinib	JAK1	2 (in combination with lanraplenib)
Lanraplenib	SYK	2 (in combination with filgotinib)
Tofacitinib	JAK 1 and JAK3	2
BMS-986165	TYK2	2
BIIB059	BDCA2 (CD303)	2
VIB7734	LILRA4 (ILT7)	1

BAFF, B cell-activating factor; BLyS, B lymphocyte stimulator; BDCA2, blood dendritic cell antigen 2; IFNAR1, interferon alpha receptor subunit 1; IL, interleukin; ILT7, immunoglobulin-like transcript 7; JAK, Janus kinase; LILRA4, leukocyte immunoglobulin-like receptor subfamily A member 4; SYK, spleen tyrosine kinase; TYK2, tyrosine kinase 2.

I interferon response in the skin [100]. A phase 2 clinical trial of BIIB059 in CLE patients with or without systemic manifestations is currently underway (NCT02847598). An additional phase 1 clinical trial targeting pDCs in systemic and cutaneous lupus is underway, employing VIB7734, a monoclonal antibody against the pDC-specific cell-surface molecule leukocyte immunoglobulin-like receptor subfamily A member 4 (LILRA4, also known as ILT7) (NCT03817424).

Trials targeting B cells have shown mixed results. The humanized anti-CD20 monoclonal antibody rituximab depletes mature B cells, sparing early B-cell precursors and plasma cells. Case reports and open-label retrospective studies initially suggested that B-cell depletion with rituximab was effective for CLE [101], but later studies of SLE patients with CLE revealed that clinical improvement was limited to ACLE and bullous lupus, with no response in CCLE patients [102]. In addition, a subset of SLE patients who initially lacked skin disease or had baseline ACLE developed new SCLE or DLE lesions after rituximab therapy [101]. A non-depleting B-cell targeted therapy under investigation for CLE is belimumab, a monoclonal antibody against B-cell activating factor (BAFF, also known as BLyS), a cytokine that promotes B-cell differentiation and survival. Belimumab was FDA-approved for SLE in 2011, making it the first new FDA-approved SLE treatment in 50 years and the only biological therapy approved for the treatment of SLE [103]. Post-hoc analyses of the phase 3 trials of belimumab plus standard therapy in SLE patients showed improvement in mucocutaneous findings [104], and subsequent case series and observational studies have suggested that belimumab is effective in CLE [103,105,106]. Compared with normal skin, DLE and SCLE lesional keratinocytes exhibit significantly

higher BAFF expression, and treatment of cultured keratinocytes with immunostimulatory DNA induces BAFF expression [107]. In addition, the DLE and SCLE lymphocytic infiltrate expresses high levels of BAFF receptor, suggesting potentially pathogenic cross-talk between keratinocytes and skin-infiltrating lymphocytes [84,107]. Belimumab is currently undergoing a Phase 3 clinical trial for efficacy in therapy-resistant CLE (EudraCT 2017-003051-35).

Other cell types have been targeted in previous clinical trials with less success. Treatment of SCLE and DLE patients with a monoclonal antibody against macrophage colony stimulating factor (M-CSF), a growth factor that supports the differentiation and proliferation of macrophages and monocytes, resulted in a reduction of a subset of circulating monocytes but failed to improve CLASI or affect tissue macrophages [108]. A trial in DLE patients using efalizumab, a monoclonal antibody against integrin alpha L (ITGAL, also known as CD11a or lymphocyte function-associated antigen 1) that inhibits T-cell activation and migration, was terminated due to inadequate enrollment (NCT00308204); efalizumab was subsequently voluntarily withdrawn from the market due to risk of the potentially fatal disorder progressive multifocal leukoencephalopathy [109]. Agents targeting sphingosine-1 phosphate receptor 1 (S1PR1) inhibit lymphocyte migration by preventing egress from the secondary lymphoid organs and thymus, and the S1PR functional antagonist fingolimod (also known as FTY720) is approved for treatment of multiple sclerosis [110]. Pre-clinical studies in murine models of lupus suggest a role for targeting S1PR1 in SLE [111-113], and a phase II clinical trial of the S1PR1/ S1PR4-selective functional antagonist KRP203 was performed in SCLE patients (NCT01294774). However, this trial was completed in

2012 without published results, and no additional trials targeting S1PR are in process for cutaneous lupus.

Multiple additional cell-targeted therapeutics are in clinical trials for SLE, including molecules targeting B-cells, T-cells, plasma cells, and the T and B-cell costimulatory molecules essential for B-cell activation and antibody production [114,115]. Their role in the treatment of CLE, if any, remains to be determined.

Cytokine Blockade

Perhaps the most successful therapeutic strategy for cutaneous autoimmune diseases has been blockade of cytokines implicated in disease pathogenesis. This approach has revolutionized treatment for psoriasis and atopic dermatitis. Advances in cytokine and transcriptional profiling have unveiled a complex array of immune pathways upregulated in CLE tissue as compared to control skin [53]. Most notable is the type I IFN system.

The type I IFN pathway is considered a hallmark of SLE and CLE disease pathogenesis. All 17 members of the type I IFN family share a common receptor (IFNAR), including IFNκ which is produced by keratinocytes in response to stress in CLE. Antibodies targeting IFNα (sifalimumab and rontalizumab) failed to show clinical benefit in SLE [116,117]. Sifalimumab did show a reduction in CLASI, but the drug was discontinued to pursue more promising results from anifrolumab [116]. Targeting the receptor subunit IFNAR1 with anti-IFNAR1 mAb anifrolumab successfully reduced skin disease in patients with SLE during phase 2b and phase 3 clinical studies [118,119]. Targeting the receptor may be more efficacious since it will block all 17 members of the type I IFN family, including IFNκ. Although there is a type II IFN (IFNγ) signature in CLE, an antibody targeting IFNγ (AMG811) failed to show benefit in patients with CLE [120]. New insights into CLE pathogenesis have implicated type III IFN family members including, IFNλ [65]. No anti-IFNλ therapies for CLE are currently under investigation.

Other cytokines targeted such as IL-6 (PF-04236921 and sirukumab) [121,122] and the IL-6 receptor (MRA003US (NCT00046774) and vobrilizumab (NCT02437890)) have failed to show benefit in patients with CLE. Conflicting results exist for therapies targeting TNFα and IL-12/23 pathways. For example, earlier studies suggested that TNFα inhibitors infliximab and etanercept reduced CLE disease activity, but subsequent reports indicate that CLE-like disease can be induced by TNF inhibitors [123]. Similarly, ustekinumab (IL-12/23 inhibitor) has been reported to both effectively treat CLE and paradoxically induce CLE [78,124,125]. The phenomenon of paradoxical induction of disease is often associated with psoriasiform dermatitis in patients treated with TNFα inhibitors. Nevertheless, TNFα inhibitors remain highly effective for the treatment of psoriasis. Therefore, it is unclear whether CLE can be effectively targeted by TNFα inhibitors or IL-12/23 blockers. Ongoing clinical trials involving etanercept (intralesional) (NCT02656082) and ustekinumab (NCT03517722) hope to resolve this issue.

The IL-17 cytokine family is implicated in numerous autoimmune diseases including psoriasis, psoriatic arthritis, and ankylosing spondylitis [126]. There is evidence that IL-17 family members IL-17A and IL-17F are elevated in the serum of patients with CLE as compared to healthy controls [75]. Additionally, IL-17A is upregulated in CLE tissue, suggesting that targeting the pathway may provide some benefit for patients with CLE [74,75] Although the role of IL-17 cytokines remains unknown in the pathogenesis of CLE, a current phase 2 clinical trial is investigating the therapeutic effect of anti-IL17A mAb secukinumb (NCT03866317).

Intracellular Signaling Targets

A class of small molecule inhibitors targeting the Janus kinase (JAK) family members have provided new hope in treating poorly understood cutaneous autoimmunity, including CLE. JAKs are critical intracellular signaling molecules downstream of cytokine receptors, that together with STAT proteins, perform a myriad of immune functions [80]. First-generation JAK inhibitors (JAKi) are FDA-approved for several rheumatologic conditions including rheumatoid and psoriatic arthritis and have also shown promise in treating cutaneous autoimmune conditions such as alopecia areata, vitiligo, and dermatomyositis among others [81]. The first generation of JAKi, baricitinib (JAK 1/2 blockade) and ruxolitinib (JAK 1/2 blockade), showed benefit in a small number of patients with chilblain lupus erythematosus [127,128]. Although baricitinib improved patients with familial chilblain lupus [128], it failed to show improvement in skin disease during a phase II clinical trial for SLE [129]. Currently, tofacitinib (JAK1/3 blockade) is undergoing clinical trials for the treatment of CLE and SLE and results are pending (NCT03288324). Next generation JAKi with greater specificity have been developed and are also being tested in clinical trials for CLE. For example, filgotinib is a JAK1 inhibitor currently in a phase II clinical study in patients with CLE (NCT03134222). Another JAK family member, tyrosine kinase 2 (TYK2), is being targeted by BMS-986165 for the treatment of CLE, SLE, and lupus nephritis (NCT03920267). Recently, inhibition of TYK2 by BMS-986165 was shown to be effective for treatment of psoriasis [130], indicating its potent ability to modulate cutaneous inflammation.

In addition to JAKs, other intracellular signaling

molecules being targeted for the treatment of CLE include spleen tyrosine kinase (SYK), c-Jun N-terminal kinase (JNK), and mitogen-activated protein kinase (MAPK). Activation of SYK has been detected within CLE tissue and inhibition of SYK reduces proinflammatory cytokines and chemokines implicated in CLE pathogenesis *in vitro* [131]. Lanraplenib is an oral small molecule inhibitor of SYK currently under investigation for CLE therapy in combination with JAK1 inhibitor filgotinib (NCT03134222). The family of JNKs integrate into signaling pathways of the MAPK family of proteins that control critical cellular processes during inflammation, including but not limited to cellular proliferation, apoptosis, and cytokine production. Although JNKs are critical for the induction and maintenance of inflammation, a phase II clinical trial investigating JNK inhibitor tanzisertib (CC-930) in CLE was terminated due to unfavorable benefit/risk profile (NCT01466725). Therefore, it is unclear whether future development of JNK inhibitors will be of clinical utility for CLE treatment. Two inhibitors of the MAPK pathway (SB203580 and FR167653) have shown benefit in lupus disease activity in pre-clinical models of lupus [132,133], but no human clinical trials specifically targeting the MAPK pathway for CLE have been initiated.

Phosphodiesterase-4 (PDE-4) is a member of the superfamily of enzymes responsible for degrading the intracellular second messenger cyclic adenosine monophosphate (cAMP). PDE-4 is most predominately expressed in immune cells and helps transmit and amplify proinflammatory signals. Over the past decade PDE-4 inhibitors have emerged as a novel approach to combating autoimmunity. PDE-4 inhibitor apremilast showed some benefit in an open-label phase 1/2 study [134], but no subsequent studies with apremilast in CLE were initiated.

Adoptive Cell Transfer

One exciting and innovative approach for the treatment of CLE is the use of adoptive cell transfer (ACT) with regulatory T cells (Tregs) to induce immune tolerance. This approach is in its infancy for the treatment of autoimmunity, but the use of ACT of effector T cells has successfully been used to treat cancer for decades [135]. One compelling phase 1 study with a single SLE patient with cutaneous disease used expanded autologous polyclonal Tregs [136]. Infused Tregs infiltrated the inflamed skin, associated with phenotypic switch away from the IFNγ pathway and towards an IL-17 pathway [136]. The implications of this shift in immunity are unknown, but this study will hopefully inspire future cellular therapy with Tregs with an expanded cohort to validate these results. A future therapeutic approach could involve the development of chimeric antigen receptor (CAR) Tregs which have been used in preclinical models of autoimmunity [137,138]. In a distinct cutaneous autoimmune disease, pemphigus vulgaris, the development of an autoantigen-specific chimeric autoantibody receptor (CAAR) T cells is a powerful novel strategy [139]. This technological approach will have to wait until a definitive autoantigen for CLE is delineated.

FUTURE CONSIDERATIONS

Current clinical trials targeting the underlying pathogenic mechanisms in CLE hold great promise for patients afflicted with CLE. However, there are critical gaps in our understanding of CLE immunopathogenesis. Furthermore, CLE is a heterogeneous group of related diseases that has unique molecular mechanisms that may require unique targeting for treatment. Whether these therapies can be extended to treat coexistent SLE also remains unknown. Specific clinical trials on CLE using CLASI as a primary endpoint as opposed to combination trials with SLE are needed to specifically evaluate response to CLE. Taken together, there is a great need to further dissect the pathogenesis of CLE to facilitate the development of future immunotherapeutic strategies. Basic science investigators, translational scientists, clinical scholars, and pharmaceutical companies need to work together to usher in the next generation of therapeutics for our patients with this devastating disease.

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