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REVIEW ARTICLE

Cutaneous Lupus Erythematosus: An Update on Pathogenesis and Future Therapeutic Directions

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Abstract

Lupus erythematosus comprises a spectrum of autoimmune diseases that may affect various organs (systemic lupus erythematosus [SLE]) or the skin only (cutaneous lupus erythematosus [CLE]). Typical combinations of clinical, histological and serological findings define clinical subtypes of CLE, yet there is high interindividual variation. Skin lesions arise in the course of triggers such as ultraviolet (UV) light exposure, smoking or drugs; keratinocytes, cytotoxic T cells and plasmacytoid dendritic cells (pDCs) establish a self-perpetuating interplay between the innate and adaptive immune system that is pivotal for the pathogenesis of CLE. Therefore, treatment relies on avoidance of triggers and UV protection, topical therapies (glucocorticosteroids, calcineurin inhibitors) and rather unspecific immunosuppressive or immunomodulatory drugs. Yet, the advent of licensed targeted therapies for SLE might also open new perspectives in the management of CLE. The heterogeneity of CLE might be attributable to individual variables and we speculate that the prevailing inflammatory signature defined by either T cells, B cells, pDCs, a strong lesional type I interferon (IFN) response, or combinations of the above might be suitable to predict therapeutic response to targeted treatment. Therefore, pretherapeutic histological assessment of the inflammatory infiltrate could stratify patients with refractory CLE for T-cell-directed therapies (e.g. dapirolizumab pegol), B-cell-directed therapies (e.g. belimumab), pDC-directed therapies (e.g. litifilimab) or IFN-directed therapies (e.g. anifrolumab). Moreover, Janus kinase (JAK) and spleen tyrosine kinase (SYK) inhibitors might broaden the therapeutic armamentarium in the near future. A close interdisciplinary exchange with rheumatologists and nephrologists is mandatory for optimal treatment of lupus patients to define the best therapeutic strategy.

1 Introduction

Lupus erythematosus comprises a spectrum of autoimmune diseases that may affect various organs (systemic lupus erythematosus [SLE]) or the skin only (cutaneous lupus erythematosus [CLE]). The latter has traditionally been grouped from a clinical perspective with regard to the onset and course of symptoms, into acute, subacute, intermittent and chronic CLE (Table 1) [1]. Typical combinations of clinical, histological and serological findings define these subtypes (Fig. 1), yet there is high interindividual variation. Disease manifestations with more acute onset (malar rash,

Key Points

Cutaneous lupus erythematosus comprises a variety of clinical manifestations and displays interindividual heterogeneity.

Keratinocytes, cytotoxic T lymphocytes and plasmacytoid dendritic cells establish a self-perpetuating interplay between the innate and adaptive immune system in lesional skin, which is orchestrated by type I interferons (IFNs).

Lesional cutaneous B cells are emerging disease modulators with potential functions in fine-tuning autoreactive T cells and antigen-presenting cells.

Targeted therapeutic advances could be most effective if chosen based on individual inflammatory phenotypes with regard to abundance of B cells, plasmacytoid dendritic cells, a strong type I IFN signature, or combinations of the above.

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exanthematic CLE, and bullous LE) segregate from chronic cutaneous manifestations (e.g. discoid CLE), with a declining tendency for systemic disease and detectable circulating antibodies. Excluding organ involvement is important in all newly diagnosed CLE patients [2] and skin symptoms are a commonly expected finding in SLE patients. Unspecific skin findings and vasculopathic reactions such as livedo racemosa, Raynaud phenomenon, and urticarial vasculitis may accompany any type of CLE but are more frequently seen in patients with SLE [3]. Alopecia is also a common finding and discoid scarring lesions must be separated from unspecific diffuse non-scarring alopecia [4]. Overlap between CLE and other cutaneous inflammatory diseases is possible. For example, an overlap between CLE and lichen planus ('lichenoid CLE) harboring clinical and histological features of both diseases with or without serologic markers is mentioned repeatedly in the literature, which may cause diagnostic confusion [5]. Progression from CLE to SLE may occur but the reported numbers vary greatly in the literature between 5 and 25%, which largely depends on the patient characteristics and clinical risk factors in the study populations [6]. Furthermore, different clinical subtypes of CLE are accompanied with varying risk for development of systemic disease. In a Swedish association study for example, progression from initially isolated skin disease to systemic disease occurred in up to 18% of patients, most commonly in patients with subacute CLE [7]. In summary, risk for development of systemic disease is highest in patients presenting with acute CLE (ACLE), and lowest in chronic discoid LE (CDLE) [1]. Noteworthy, sociocultural factors (ethnicity, sex, social income, education level) are increasingly recognized to have a major impact on the severity of disease, which is comparable with other chronic inflammatory dermatoses such as psoriasis and hidradenitis suppurativa [8]. The overall incidence of SLE and CLE is comparable and female patients far outnumber males in both groups.

With emerging understanding of the pathophysiology of CLE and the underlying interplay between the innate and adaptive immune systems, the advent and licensing of targeted therapies for the treatment of SLE raises questions about a potential use of these drugs in patients suffering from disease limited to the skin [9]. This review provides an

Table 1 Overview of clinical subtypes of CLE and typical cutaneous findings. Unspecific skin reactions may accompany SLE and, less often, CLE of all types [1, 5]

	Clinical subtypes	Cutaneous findings
Acute CLE	Localized (Malar rash)	Erythematous rash extending in the midface, sparing the nasolabial folds
	Exanthematic/disseminated	Maculopapular rash, at times circinated
	Bullous	Detachment of rapidly evolving lesions
		Further symptoms include fatigue and pain rather than pruritus
Subacute CLE	Annular	Polycyclic plaques in sun-exposed localizations
	Papulosquamous	Hyperkeratotic plaques potentially imitating psoriasis vulgaris
	Rowell's syndrome	Target-like erythematous plaques imitating erythema exsudativum multiforme
	Neonatal	Polycyclic papulosquamous lesions in neonates driven by transplacental transfer of maternal antibodies
Intermittent CLE	LE tumidus/tumid LE	Papules and plaques in sun-exposed localizations with minimal epidermal involvement
Chronic CLE	Chronic discoid LE (including hypertrophic variants)	Hyperkeratotic, scarring plaques, alopecia in scalp lesions
	LE profundus (including lupus panniculitis)	Retracted atrophic lesions mainly over proximal extremities
	Chilblain LE	Tender erythematous humps in acral localization
	Mucocutaneous LE	Erosions and plaques predilected to the hard palate
	Melanotic LE	Hyperpigmented plaques in dark-skinned individuals
Overlap syndrome	CLE-Lichen planus overlap syndrome ('lichenoid discoid LE')	Erythematous/violaceous plaques and papules with scaling, overlapping histological features of CLE and lichen planus, with or without serological markers
Unspecific skin findings in CLE		Purpura
		Raynaud phenomenon, periungual telangiectasia
		Vasculopathy, thrombophlebitis
		Urticarial vasculitis
		Neutrophilic urticarial dermatosis
		Livedo racemosa
		Oral ulcers
		Diffuse alopecia

CLE cutaneous lupus erythematosus, *LE* lupus erythematosus, *SLE* systemic lupus erythematosus

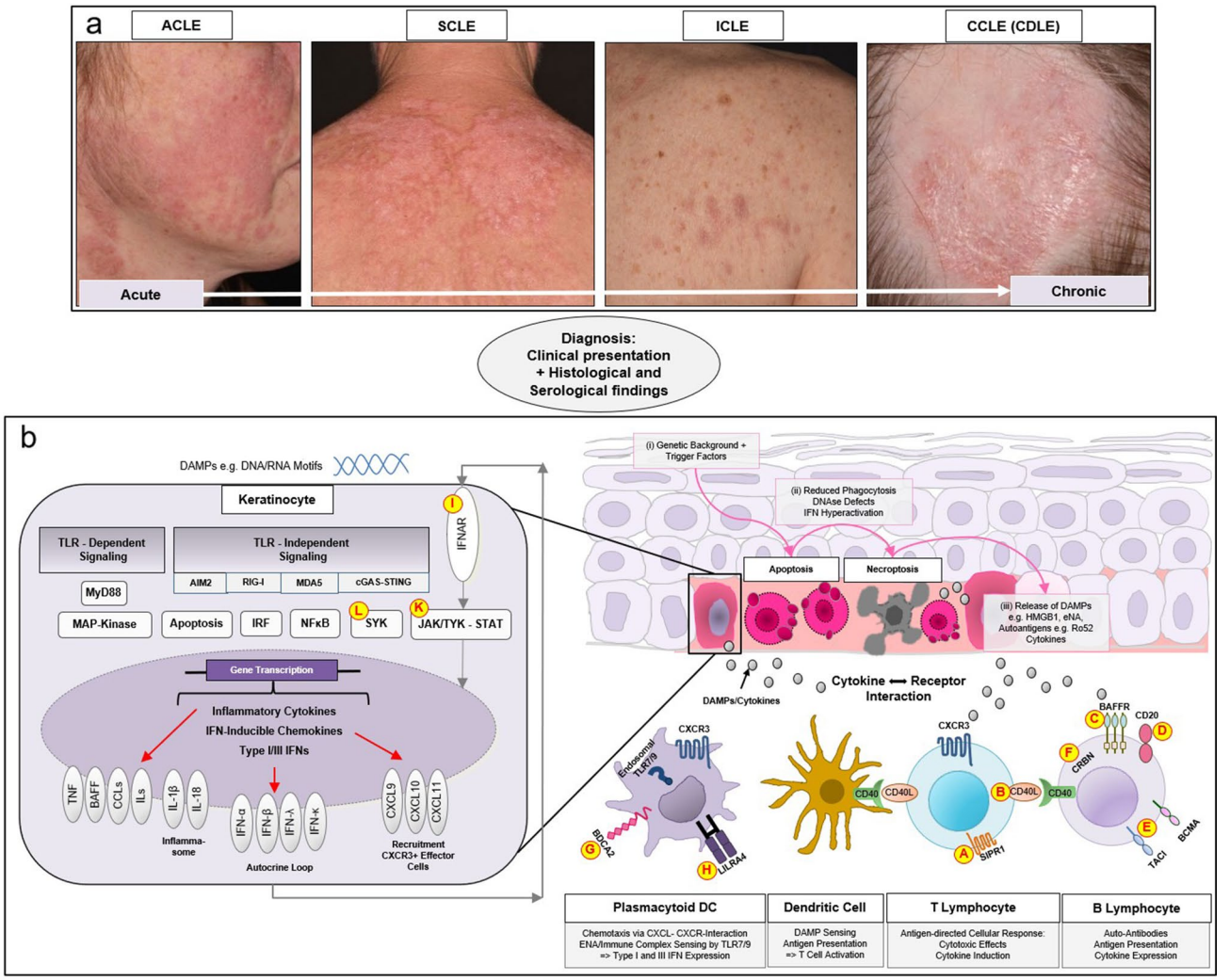

Fig. 1 Overview of cutaneous lupus erythematosus subtypes and schematic illustration of pathogenic mechanisms in CLE. (**a**) Clinical classification of CLE based on chronicity of lesions. The most common subgroups represent ACLE, SCLE, ICLE, and CCLE, of which CDLE is the most common form. (**b**) Concept of inflammatory signature-oriented, therapy-directed histological evaluation. Pathophysiologically, CLE is understood to be an IFN-driven autoimmune skin disease characterized by cytotoxic lesional inflammation with activation of primarily TLR-independent innate immune pathways as depicted. With a corresponding genetic background, trigger factors lead to cell stress and subsequently apoptosis. Due to several defective mechanisms (reduced phagocytosis, DNAse/TREX1 defects, IFN hyperactivation), necroptosis occurs, leading to an inflammatory response with release of DAMPs (e.g. endogenous nucleic acids, HMGB1), autoantigens such as Ro52, and cytokines such as CXCL chemokines, ILs, and IFNs. DCs sense potential autoantigens and present them to lymphocytes in nearby lymph nodes. This leads to lymphocytic differentiation with subsequent cytotoxic effector functions against keratinocytes, as well as production of autoantibodies. Recruited pDCs are stimulated to express type I and type III IFN after recognition of released nucleic acids, thus amplifying lesional inflammation. Histologically, different inflammatory signatures can be assessed in the lesional tissue of CLE patients, e.g. a B-cell- or pDC-rich infiltrate or a strong IFN signature. Targeted therapeutic options are directed against different inflammatory cytokines and their receptors or intracellular targets. T lymphocytes: (A) S1P receptor 1 antagonists (amiselimod); (B) CD40L antagonists (dapirolizumab pegol, frexalimab). B lymphocytes: (C) BAFF receptor antagonists such as the monoclonal antibody belimumab; (D) CD20 antibodies, e.g. rituximab; (E) fusion proteins that bind to BAFF and TACI (telitacicept); (F) the cereblon E3 ligation modulator iberdomide. pDCs: (G) BDCA2 inhibition (litifilimab); (H) anti-LILRA4 antibody daxdilimab. IFN-associated pathways: (I) IFNAR1 inhibition (anifrolumab); (K) JAK inhibition (e.g. filgotinib, tofacitinib, delgocitinib), TYK2 inhibition (deucravacitinib). Other intracellular pathways: (L) SYK inhibition (lanraplenib). *CLE* cutaneous lupus erythematosus, *ACLE* acute CLE, *SCLE* subacute CLE, *ICLE* intermittent CLE, *CCLE* chronic CLE, *CDLE* chronic discoid LE, *IFN* interferon, *TLR* toll-like receptor, *DAMPs* danger-associated molecular patterns, *ILs* interleukins, *pDCs* plasmacytoid dendritic cells, *SIP* spingosine-1-phosphate, *BAFF* B-cell-activating factor, *TACI* transmembrane activator and CAML interactor, *BDCA2* blood dendritic cell antigen 2, *LILRA4* leukocyte immunoglobulin-like receptor subfamily A member 4, *IFNAR1* interferon-α/β receptor α chain, *JAK* Janus kinase, *TYK* tyrosine kinase, *SYK* spleen tyrosine kinase, *HMGB1* high mobility group box 1, *DCs* dendritic cells, *CD40L* CD40 ligand, *pDCs* plasmacytoid dendritic cells

update on the most recent pathophysiological findings with a focus on immunology in CLE. We also address diagnostic and therapeutic challenges due to the complexity of the disease and speculate on future therapeutic directions.

2 Pathogenesis

The pathogenesis of CLE is complex and has been widely studied [10]. Briefly summarized, in all clinical subtypes of CLE, a self-amplifying inflammatory loop is established between cells of both the innate and adaptive immune system (Fig. 1) [11]. Recruitment of these cells occurs in the course of keratinocytic cell death due to environmental triggers such as ultraviolet (UV) radiation and drugs. Several studies suggest smoking is a risk factor [12, 13]. Release of cytosolic and nuclear debris into the extracellular space typically leads to activation of danger-associated receptors, which then sparks the recruitment of specific inflammatory cells. Central key to the pathogenesis of LE is overexpression of interferons (IFNs), which leads to an inflammatory loop mimicking an antiviral response [14]. Yet, only susceptible individuals develop disease manifestations, largely depending on genetics, epigenetics and other variables such as hormones, skin, and gut microbiome [15]. Thus far, it is not clear why given patients develop a specific clinical phenotype.

Over the last years, there has been emerging evidence that apart from autoreactive T cells and plasmacytoid dendritic cells (pDCs), B cells could also play a major role in the orchestration of the inflammatory response. In this review we focus on immunology while omitting environmental pathogenetic aspects such as (passive) smoking and UV exposure, as these aspects have been extensively reviewed elsewhere [1, 16]. Of note, new onset and exacerbation of autoimmune disease, including CLE, was described in the context of coronavirus disease 2019 (COVID-19) infection and vaccination, which is still of importance in light of the ongoing pandemic [17]. Histopathology is also out of the scope of this article and detailed information can be found in another review by our group [18].

2.1 Genetics and Epigenetics

Only a small portion of lupus patients harbor a genetic variant of CLE. Namely, a monogenetic mutation in the *TREX1* gene, which encodes an enzyme responsible for cytosolic degradation of deoxyribonucleic acid (DNA) [19], may be detected in these patients. Because of DNase deficiency, high levels of cytosolic DNA accumulate and are sensed by specific receptors, which ultimately activates the type I IFN system. Typical symptoms include recurrent swelling and pernio-like nodules in acral areas. This disease manifestation is known as familial chilblain LE. Over the last years, a growing list of gene mutations capable of triggering lupus-like skin lesions was identified [19]. In particular, gene mutations in *SAMHD1* and complement factor C2 raise the individual risk to develop CLE lesions [20]. The vast majority of CLE patients bear no specific genetic mutations; however, there is an abundance of associated gene polymorphisms associated with a higher risk of CLE. The involved genes encode for proteins involved in cell death cascades (apoptosis, ubiquitination), clearance of cell debris (e.g. immune complexes), cellular adhesion and activation or regulation of the immune system (innate immune system activation, B-cell/T-cell function) [20].

2.2 Pathophysiology and Immunology

As non-inflammatory cells, keratinocytes contribute to lesional inflammation in CLE. An initial trigger, such as UV radiation, smoking or drugs causes keratinocyte apoptosis. UV radiation leads to an upregulation of autoantigens, such as Ro52, in keratinocytes, inducing and activating the proinflammatory pathways [15, 21]. Apoptotic keratinocytes present antigens, which can be recognized by autoantibodies in autoantibody-positive patients [22]. Autoantibodies against ribonucleoproteins could also have an independent pathophysiological role, as they trigger the development of lupus lesions in mice [23]. Interestingly, UV radiation or other damaging triggers initially lead to keratinocytic cell death and chemokine production in the whole epidermal layer [24], however, later in established CLE lesions, keratinocytic apoptosis and proinflammatory chemokine production is limited to the dermoepidermal junction, resulting in interface dermatitis [25]. Even keratinocytes from uninvolved (non-lesional) skin of CLE patients are more sensitive to UV radiation-induced cytotoxicity compared with keratinocytes from healthy donors, which leads to the assumption of disease predisposition [26, 27]. Following the initial keratinocyte damage, secondary necroptosis of keratinocytes further sparks lesional release of nucleic acids and danger-associated molecular patterns (DAMPs). The latter include high mobility group box 1 protein (HMGB1), a proinflammatory cytokine, which can also function as autoantibody in CLE [28]. UV radiation also leads to DNA damage, generating immune-stimulatory DNA motifs, such as 8-hydroxyguanosine [29]. Phagocytic clearance of apoptotic cells and nucleic acids can be impaired in CLE [27]. Nucleic acids are recognized via pattern recognition receptors (PRRs), including MDA5, RIG-I and cGAS–STING, expressed by keratinocytes leading to production of IFN-regulated genes [29]. The response in keratinocytes is toll-like receptor

(TLR)-independent [1]. Keratinocytes produce IFNκ and IFNλ (type I and type III IFNs), which, by autocrine secretion, further induce the keratinocytic production of IFN-regulated proinflammatory cytokines, including interleukin (IL)-6, and chemokines, including CXCL9, CXCL10 and CXCL11, which are CXCR3 ligands [29–31]. The IFN response is, among others, mediated via Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling [30]. The aforementioned chemokines interact with (autoreactive) cytotoxic T cells via CXCR3-binding, also promoting keratinocyte cell death by recruitment of cytotoxic T cells [32, 33]. Nucleic acid motifs also activate the inflammasome via melanoma 2 (AIM2) [34]. Interestingly, IFN-k is upregulated and basal phospho-STAT (pSTAT) activity is higher even in healthy-appearing skin of CLE patients compared with skin of patients with other chronic inflammatory skin disease (psoriasis) [30]. As outlined, the inflammatory interplay is complex and numerous inflammatory cells contribute to CLE pathology. Therefore, in the following sections, we outline recent findings considering specific types of cells in the orchestration of inflammation in SLE and CLE.

2.2.1 Dendritic Cells

After initial keratinocyte cell death, antigen-presenting cells (APCs) sense accumulating nucleic acids, among them dendritic cells (DCs) and pDCs. pDCs are recruited to the skin lesions via CXCL-chemokine interaction with CXCR3 [24]. PDCs sense nucleic acids mostly via TLRs, especially TLR7 and TLR9 [35]. Uptake of nucleic acids and immunecomplexes may be achieved by endocytosis via TLR9 and cluster of differentiation (CD) 32, at least in SLE [36]. Upon PRR activation, pDCs produce large amounts of type I and type III IFNs, cytokines and ILs, further orchestrating the autoimmune circle [37, 38]. The presence of type I IFN is necessary for pDC maturation and migration [39].

PDC infiltrates are observed in a great proportion of skin biopsies and can form clusters in CLE skin lesions [38, 40]; however, not all skin lesions harbor a pDC infiltrate [41]. Recently, single-cell ribonucleic acid (RNA) and spatial RNA sequencing has shown that even healthy-appearing skin of CLE patients contains a type I IFN-rich environment and that CD16+ DCs undergo IFN priming in the skin, leading to proinflammatory subtypes [42]. Because of their central role in CLE pathophysiology, pDCs are an attractive therapeutic target. One potential targeted pDC therapy is the blood DC antigen 2 (BDCA2) receptor, which is exclusively expressed on pDCs [43]. BDCA2 suppresses IFN induction [44].

2.2.2 T cells

Lesional inflammatory infiltrates mainly consist of T cells, B cells, DCs, natural killer (NK) cells, and, infrequently, neutrophils [25, 45]. CXCR3-expressing T cells are recruited into skin lesions via CXCL10. Physiologically, T cells recognize antigens presented by APCs via T-cell receptor (TCR)/major histocompatibility complex (MHC) interaction. Upon TCR engagement, downstream signaling pathways are activated, leading to various T-cell functions. T cells have a lower threshold of activation in lupus patients [46]. Due to defective CD3 chains, the spleen tyrosine kinase (SYK) and Fc receptor γ-chain (FcRγ) association results in higher phosphorylation of signaling molecules and an enhanced calcium influx, leading to enhanced TCR downstream signaling [47]. Additionally, transcription factors lead to differential expression of numerous genes, including the CD40 ligand (CD40L) [48], a co-stimulatory molecule engaged in B-cell interaction, promoting B-cell functions such as proliferation, differentiation, antibody production, and class switching [46]. Increased CD40L does not only have an impact on B cells interacting with T cells but also on APCs. It leads to increased expression of co-stimulatory receptors on APCs, further intensifying the TCR signal [49]. Several different pathways have been described as defective (such as cyclic adenosine monophosphate-dependent phosphorylation, protein kinase C) or increased (such as phosphatidylinositol-3 kinase (PI3K) [46]. Apart from altered pathway signaling, lupus T cells display differential DNA methylation of several genes, leading to differential gene expression [46]. Furthermore, SLE patients show an IL-2 deficiency [50]. IL-2 is important for T-cell polarization, and decreased IL-2 expression enhances inflammatory T-helper 17 (Th17) cell formation [51].

Upon activation, cytotoxic T cells target keratinocytes of the basal epidermal layer, histologically resulting in interface dermatitis [52]. However, this applies for CLE subtypes with superficial involvement and plays a minor part in dermal or subcutaneous CLE subtypes such as LE profundus. Cytotoxic markers such as granzyme B expressed by CD8+ T cells are present in CLE skin lesions and are likely to be induced by IFN [53, 54]. Interestingly, granzyme B expression is higher in scarring lesions of CDLE compared with non-scarring lesions of subacute CLE, suggesting a pathophysiologic role in scarring lesions in CLE [54].

Initiation of cutaneous inflammation is likely to be triggered by Th2 cells, but fully established lesions shift to a Th1-dominated inflammation [52, 55]). Th1 cells stimulate type I IFN production of cytotoxic T cells and macrophages [52, 56]; not only cytotoxic T cells are responsible for keratinocytic apoptosis. Lesional CD4+ T cells can directly induce keratinocytic apoptosis via FAS/FAS ligand (FAS-L)

interaction [57]. T-helper cells produce IL-21, inducing the expression of granzyme B in pDCs, promoting NK cells to attack keratinocytes [58, 59]. On the other hand, type I IFNs negatively regulate granzyme B production by pDCs [58]. Th cells can react to nucleosomes released from dying cells and induce (anti-DNA-)antibody production of B cells in SLE [60–62]. Th clones in lupus produce IL-2, IFNγ, and IL-4 [63], and CD4+ T cells overexpress perforin, which is epigenetically regulated via DNA methylation [64].

The number of CD4+, CD8+ regulatory, and γδ-T cells is significantly reduced in CLE compared with other inflammatory skin diseases or healthy individuals, and impairment of regulatory immunosuppressive function contributes to the autoimmune circle [46, 65, 66]. Furthermore, emerging evidence points out that composition of the inflammatory infiltrate differs among CLE subtypes. CD4+ T cells and FOXP3+ T cells are significantly reduced in skin lesions of patients with subacute CLE compared with CDLE, as is the CD4/CD8 ratio [67].

2.2.3 B Cells and Plasma cells

B cells harbor a central role in LE pathogenesis by the production of autoantibodies against nuclear components and their complex interplay with T cells [18, 68–70]. The capacity of B cells to produce antibodies is enhanced by different IFNs, however, prolonged type I IFN exposure drives autoantibody production [71]. A new mouse model established the role of IL-21 and TLR7/9 in the context of B-cell recruitment to inflammation sites in CLE lesions and localized antibody production [72]. IL-17 recruits immune cells and augments antibody production of B cells in SLE [73]. SLE patients frequently present with antinuclear antibodies (ANAs) but only a minority of CLE patients display detectable autoantibody levels in the serum [74]. Similarly to SLE, autoantibodies against ribonucleoproteins (anti-Ro antibodies) and La are frequently found in SCLE but fewer in CDLE [75]. Different studies reported a specificity of autoantibody presence and CLE subtype [76]. The presence of antibodies are in accordance with the HLA-DR3 phenotype in SLE [74], and the presence of different antibodies (e.g. Ro or LA) are associated with disease severity in SLE [77]. IL-17 recruits immune cells and augments antibody production of B cells in SLE [73]. Besides autoantibody production, B-cell migration, receptor engagement, antigen presentation, cytokine responsiveness and production, survival, differentiation and class-switching are IFN-dependent [71].

Recently, the understanding of the pathophysiological role of B cells in LE has shifted, since strong B-cell signatures and lesional B-cell infiltrates have been described in patients with autoantibody-negative CLE [41, 78]. Beside antibody production, B cells can contribute to the autoimmune reaction by different mechanisms. For example, emerging evidence points towards an antigen-presenting, T-cell activating function of B cells [41]. Lesional B-cell infiltration varies among LE subtypes [41, 79]. B cells can form clusters and arrange in lymphoid-like structures in the skin, called tertiary lymphoid organs/structures (TLO). In different subtypes of CLE, the formation of dense B-cell clusters or TLOs has been described, e.g. in LE profundus or CDLE [41, 80]. TLOs are highly organized structures containing T and B cells, contributing to autoimmunity [81], and have been described in detail in lupus nephritis [82, 83]. B cells can harvest a regulatory function, as is described for SLE [84], and can interact with keratinocytes via B-cell-activating factor (BAFF/Blys) and its receptor in both SLE and CLE, whereby BAFF is expressed by lesional keratinocytes and the associated receptors (BAFF-receptor [BAFF-r], transmembrane activator and CAML interactor [TACI], B-cell maturation antigen [BCMA]) by B cells [41, 85–87]. BAFF is a membrane-bound or soluble factor necessary for B-cell maturation [88]. BAFF expression in keratinocytes can be induced by immunostimulatory DNA motifs, highlighting its significance in CLE [86]. B cells produce high levels of cytokines such as IL-6, which in turn is important for B-cell survival [18, 89].

During the maturation process, B cells exhibit immunoglobulin class switching and somatic hypermutation to differentiate into antibody-secreting plasma cells; those processes can occur either in germinal centers or extrafollicular locations, and both have been described in SLE [90]. Somatic hypermutation and isotype switching are dependent on CD40 and IL-21 [18]. Plasma cell differentiation is supported by Th cells [90]. After activation of naïve B cells, plasma cells are generated and persistently produce antibodies while receiving survival signals, mediated by the BAFF axis and IL-6, originating from adjacent cells [81]. Plasma cells can reside and accumulate at the site of inflammation [91]. Even in the absence of antigens, plasma cells can produce antibodies, as they receive survival signals via BAFF or IL-6 [18]. Similar to naïve B cells, plasma cells are responsive to IFN [92]. Different plasma cell subsets have been described to secrete autoantibodies against different structures in SLE [93, 94].

2.2.4 Natural Killer Cells

In SLE, peripheral NK cell levels show an inverse correlation with disease activity [76]. Lupus NK cells secrete higher IFN levels compared with healthy controls, and cytotoxic functions are impaired [95, 96]. NK cells are enriched at lesional inflammation and are able to proliferate in CLE skin lesions [97]. The definitive role of NK cells remains unclear regarding CLE pathophysiology.

2.2.5 Neutrophil Granulocytes

Neutrophil granulocytes are early responders in the course of tissue damage. Neutrophils produce antimicrobial peptides (AMPs; e.g. LL-37) and reactive oxygen species (ROS) [98], and establish neutrophil extracellular traps (NETS), which are nets consisting of chromatin, histones and other intracellular content [99, 100]. The process of NET formation, 'NETosis', can be a source of immunogenic materials, and along with release of AMPs, has been linked to autoimmunity. A recent study showed a high molecular heterogeneity in pathogenic neutrophil subsets in SLE (so-called low-density granulocytes [LGS]) with, among others, differences in NET formation and response to type I IFNs, displaying a high number of IFN-induced genes [101]. LGS have been associated with increased vascular inflammation and arterial dysfunction in SLE [102]. Not only are neutrophils prone to NETosis, but also impaired degradation of NETs due to enzymatic blockade or antibody formation can promote SLE activity [103].

Upon NET formation and by release of other immune cells, complexes formed by double-stranded DNA (dsDNA) and LL-37 are taken up by pDCs via endocytosis and are recognized via TLR9, leading to activation and type I IFN production in SLE [104]. LL-37/dsDNA complexes can serve as autoantigens [98]. Higher levels of LL-37 and other AMPs have also been observed in CLE skin lesions, as well as skin lesions from SLE patients compared with healthy controls [105, 106]. Furthermore, NETs are present in several CLE subtypes (panniculitis, ACLE, DLE) [107]; however, it has yet to be elucidated if, and to what extent, those subsets of neutrophils and AMPs play a pathophysiologic role in CLE.

2.2.6 Macrophages

Monocytes and macrophages hold different biological functions, such as phagocytosis or cytokine production [108]. Monocytes exert antigen-presenting properties in SLE [109]. Contrary results have been published on whether differing monocyte and macrophage numbers in lupus patients versus healthy controls are found. Several studies describe an impairment in uptake of apoptotic material and prolonged phagocytosis, leading to accumulation of potential autoantigens and further immune stimulation lupus [110, 111]. One study reported an impaired phagocytosis capacity of macrophages from SLE patients only in the presence of patients' serum [111]. Macrophages from SLE patients have an impaired adhesion capacity [110]. Furthermore, macrophages can be classified into M1 macrophages, which harbor inflammatory and destructive properties and are induced by IFN, while M2 macrophages, which harbor regulatory properties, are involved in tissue repair and are induced by IL-4 or IL-13 [112]. In SLE, polarization tends towards M1 macrophages, as M1 genes (e.g. *STAT1* and *SOCS3*) were among differentially expressed genes in monocytes from SLE patients [113, 114]. In a mouse model, adoptive M2 macrophage transfer led to decreased SLE severity [115].

One study found FAS-L-expressing macrophages enriched around hair follicles in CLE patients, potentially being responsible for lupus-associated scarring alopecia via a direct FAS/FAS-L interaction with keratinocytes of hair follicles [57]. More detail about the potential functions of macrophages in SLE is outlined elsewhere [116]. Of note, a recent study suggested a pathophysiologic, inflammatory role for the microRNA (miRNA) miR-4512 in monocytes and macrophages in SLE via the TLR4-CXCL2 axis [117].

3 Treatment and Future Directions

Based on the aforementioned pathophysiology of CLE, treatment mainly relies on the avoidance of typical triggers and dampening of the effects of key immunologic reactions. We briefly recapitulate commonly used substances and reflect on developments that are more recent.

3.1 Conventional Treatments

A variety of immunosuppressive and immunomodulatory drugs are in use for CLE (see Table 2 for an overview). There is a striking lack of licensed drugs both in Europe and the United States (US). Being a chronic-relapsing inflammatory skin disease, long-term remissions are rare in CLE and many patients require continued treatment. In a longitudinal cohort study, factors associated with a lower chance of long-term remission were smoking and discoid CLE [118].

3.1.1 Topical Treatment

Optimal broad-spectrum sunscreen is mandatory for all patients. Topical corticosteroids (TCS), especially more potent agents such as fluocinonide, are the first-line options for circumscribed CLE [119]. Intralesional application with triamcinolone suspension may also be suitable in specific localizations such as the scalp. However, use is limited by typical adverse effects (skin atrophy) and lack of efficiency in widespread disease. Topical calcineurin inhibitors (TCI; pimecrolimus, tacrolimus) may be used (off-label) for sustaining remissions, especially in facial lesions, but they often fail to control flares of the disease. The response varies among clinical subtypes. Some authors argue for off-label use of topical retinoids (tazarotene, tretinoin) in hypertrophic lesions [119]. Topical treatment is also a mainstay as adjunct to systemic treatments [120].

Table 2 Overview of conventional systemic therapeutic approaches and their value in national guidelines [119, 123, 124, 126, 182]

Mode of action	Drug	Mode of action and application	Setting	FDA approval	EMA approval	Recommendation for CLE
Glucocorticoids	Prednisolone Dexamethasone	Immunosuppressive; oral/intravenous	SLE/CLE	Yes	Yes	First-line (GER, UK) for flares
Antimalarials	HCQ	Immunomodulatory: suppression of TLRs, enhancement of Tregs; oral	SLE/CLE	Yes	Yes	First-line (GER, UK)
	Chloroquine			–	Yes (SLE)	First-line (GER), second/third-line (UK)
	Mepacrine	Immunomodulatory; oral	CLE	–	–	First-line as an alternative to HCQ or as an adjunctive (GER, UK)
Antibiotics	Dapsone	Immunomodulatory; oral	CLE	–	–	Second-line (GER, UK)
	Clofazimine	Immunomodulatory; oral	CLE	–	–	Third-line (UK)
dMARDs	Methotrexate	Immunosuppressive/immunomodulatory; oral/subcutaneous	SLE/CLE	–	–	Second-line (GER, UK)
	Azathioprine	Immunosuppressive; oral	SLE	–	Yes (SLE)	Not recommended (GER, UK)
	Ciclosporin	Immunosuppressive; oral	SLE	–	–	Not recommended (GER, UK)
	Cyclophosphamide	Immunosuppressive; oral/intravenous	SLE	–	Yes (severe SLE with nephritis)	Not recommended (GER, UK)
	Mycophenolate mofetil/mycophenolic acid	Immunosuppressive; oral	SLE/CLE	–	–	Second-line (UK), third-line (GER)
	Lenalidomide	Immunomodulatory; oral	CLE	–	–	Third-line (UK), selected cases (GER)
	Thalidomide	Immunomodulatory; oral	CLE	–	–	Third-line (UK), selected cases (GER)
Retinoids	Acitretin	Modulation of keratinocytic differentiation; oral	CLE	–	–	Second-line (GER, UK) for hypertrophic types of CLE

dMARDs disease-modifying antirheumatic drugs, *TLR* toll-like receptor, *Tregs* regulatory T cells, *SLE* systemic lupus erythematosus, *CLE* cutaneous lupus erythematosus, *FDA* US Food and Drug Administration, *EMA* European Medicines Agency, *GER* Germany, *UK* United Kingdom, *HCQ* hydroxychloroquine

3.1.2 Systemic Treatment

In widespread CLE or circumscribed CLE irresponsive to topical treatment, a variety of systemic agents are in use, mostly with a low level of evidence. Recommended first-line treatments for active or widespread lesions are systemic glucocorticosteroids (e.g. prednisolone, dexamethasone) that typically exert a broad immunosuppressive effect, and antimalarials with an immunomodulatory effect. Both groups of drugs have been available for decades and are licensed for this indication. Among the antimalarials, hydroxychloroquine (HCQ) is generally favored above chloroquine (CQ) due to a more favorable adverse effect profile. Mepacrine may be used if HCQ and CQ are not well tolerated or if monotherapy fails to achieve disease control. The exact mode of action of antimalarials in CLE is still not exactly defined, yet dampening of TLRs and inhibition of the production of type I IFNs have been described [1]. A recent study found variability in the therapeutic response to antimalarials defined by alternating immune profiles of responders and non-responders [121]. Predictive biomarkers for therapeutic response are missing. To prevent osteoporosis in the course of sun protection and glucocorticosteroid use, vitamin D supplementation should be incorporated in the treatment plan [122]. Second- and third-line treatments according to the German [119, 123] and British [124] national guidelines are summarized in Table 2. Drugs most commonly used include methotrexate (MTX), dapsone, and mycophenolate mofetil (MMF) [125], whereas immunosuppressive agents in use for SLE [126], such as azathioprine (AZA), are not recommended for the management of CLE. In a recent retrospective analysis of CLE patients irresponsive to antimalarials, MTX and MMF showed similar therapeutic efficiency in different clinical subgroups [127]. Dermatologic peculiarities include the use of acitretin for hypertrophic CLE lesions and the use of

thalidomide and lenalidomide for severe or refractory cases. Acitretin was found to be an effective treatment option in a recent prospective, open-label, uncontrolled study with an acceptable safety profile [128]. The use of lenalidomide is supported by retrospective observational studies [129] and case series [130]; however, strict contraceptive measures must be taken into account, and neurotoxicity limits its use. All of the aforementioned immunosuppressive or immunomodulatory drugs have various effects on the pathophysiology of CLE but none of them act in a targeted manner. The current state of CLE treatment is concisely summarized in previous works that deserve mentioning [131, 132].

3.2 T-Cell-Directed Treatments

As stated previously, the inflammatory reaction in CLE may be skewed towards a prevailing of different inflammatory cell types. We discuss targeted treatments based on our aforementioned approach, with a focus on T cells, B cells, pDCs, or IFN preponderance. A more general review about recent developments in targeted therapy of autoimmune skin diseases has been reported elsewhere [133]. We therefore omitted some targeted approaches using cytokine blockade that is well-established in psoriasis (e.g. IL-12/23 blockade, ustekinumab) [134].

Various drugs are in development either to reduce the effects of cytotoxic T cells or to promote the anti-inflammatory properties of regulatory T cells (Table 3). Amiselimod (MT-1303) is a functional antagonist of sphingosine 1-phosphate (S1P) receptor 1 that showed good tolerability in a multicenter, open-label, phase Ib clinical trial for SLE patients [135]. S1P is involved in the egress of T cells from secondary lymphoid organs to sites of inflammation. A reduction of skin symptoms was described in patients finishing the 24-week trial period according to the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), without mentioning further details. Another potential target is the CD40 ligand; antagonistic drugs may interfere with antigen presentation to T cells. Use of dapirolizumab pegol was assessed in a randomized, placebo-controlled, phase II study in patients with moderate to severe active SLE. Improvements in various clinical measures, including in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), compared with placebo, were observed although the primary objective was not met [136]. Another CD40 ligand antagonist is frexalimab (SAR441344). Recruiting clinical trials in the indications of SLE and primary Sjögren's syndrome are currently ongoing, however no results are available yet. Another T-cell-directed approach is the selective expansion of regulatory T cells, and an agent of interest is efavaleukin alfa (AMG 592). Results from a phase Ib study in 35 subjects with SLE are available and demonstrated a favorable safety profile [137]. Clinical efficacy will be investigated in phase II studies.

3.3 B-Cell-Directed Treatments

Modulation of B-cell activity has been within the scope of therapeutic research in SLE and CLE for a while. Similar to antimalarials, the individual therapeutic response is hard to predict, which may be attributable to the variety of functions of B cells in fine tuning the inflammatory response as outlined earlier. However, a B-cell-directed therapy was the first to achieve US FDA and European Medicines Agency (EMA) approval for SLE in decades, which highlights the potential of B-cell modulation.

3.3.1 B-Cell-Activating Factor Receptor Inhibition

BAFF is a cytokine crucial for the development, survival and differentiation of B cells, and is also known as a B-lymphocyte stimulator (BLyS). A closely related protein with similar functions is A PRoliferation-Inducing Ligand (APRIL), also known as CD256. Both proteins may bind to three receptors, i.e. BAFF-r, BCMA, and TACI. Monoclonal antibodies and fusion proteins capable of interfering with the ligand–receptor interaction are potential candidates for the treatment of CLE. Notably, belimumab, a monoclonal antibody binding to BAFF, was licensed for the treatment of refractory SLE in 2011 [138], although the pivotal study did not precisely assess clinical outcome regarding skin lesions. A first case series regarding successful use of belimumab in five patients with CLE was published 2017 [139], followed by case reports [140] and a monocentric case series with seven patients [141]. In 2020, a multicenter, retrospective, observational trial was published that included 16 CLE patients [142]. After 6 months of treatment, half of the patients showed at least a 50% reduction in CLASI scores. Finally, in 2021, a prospective, observational study with five patients with CLE was published and showed favorable results [143]. Currently, the efficacy of belimumab for therapy-resistant skin manifestations in LE patients is being investigated in a phase III, multicenter, randomized, double-blind, placebo-controlled, 24-week trial (BELI-SKIN, EUDRA-CT: 2017-003051-35) and the results are eagerly anticipated. Another monoclonal antibody binding to BAFF (tabalumab) did not meet key clinical endpoints in a phase III study in SLE and there is limited information on the efficacy on cutaneous lesions [144]. Fusion proteins binding to BAFF and TACI represent a similar mode of action. Atacicept showed the capacity to reduce flares in patients with SLE in a phase IIb clinical trial, but data on CLE are limited [145]. Telitacicept is currently under investigation for SLE and received fast-track designation status by the FDA in light of positive results. The Chinese National Medical Products

Table 3 Overview of targeted therapy approaches that could be most useful depending on the dominant inflammatory cell/cytokine subsets (modified from Braegelmann et al. [133]) last updated November 2022

Mode of action	Drug	Mode of action and application	Setting	FDA approval	EMA approval	Phase of development/identifier
T-cell-directed therapies	Amiselimod (MT-1303)	Sphingosine 1-phosphate receptor 1 functional antagonist; oral	SLE	–	–	Phase I: NCT02307643 (completed)
	Dapirolizumab pegol	CD40-ligand antagonist; intravenous	SLE	–	–	Phase III: NCT04976322 (recruiting by invitation); Phase III: NCT04294667 (recruiting)
	Frexalimab (SAR441344)	CD40-ligand antagonist; intravenous/subcutaneous	SLE	–	–	Phase II: NCT05039840 (recruiting)
	Efavaleukin alfa (AMG 592)	IL-2 mutein Fc fusion protein; subcutaneous	SLE	–	–	Phase I: NCT03451422 (completed)
B-cell-directed therapies	Belimumab	BAFF/BLyS inhibition; intravenous/subcutaneous	CLE/SLE	SLE: March 2011	SLE: July 2011	Phase III: EudraCT: 2017-003051-35 (ongoing)
	Telitacicept	TACI inhibition (fusion protein); subcutaneous	SLE	SLE: Fast track status April 2020	–	Phase I: NCT05247203 (recruiting); Phase II: NCT04905212 (recruiting)
	Rituximab	Anti-CD20-antibody; intravenous	SLE	–	–	Phase I/II: NCT00036491 (completed); Phase II/III: NCT00137969 (completed)
	Obinutuzumab	Anti-CD20-antibody; intravenous	SLE	Breakthrough designation for lupus nephritis: September 2019	–	Phase III: NCT04963296 (recruiting)
	Iberdomide (CC-220)	Cereblon E3 ligase modulator; oral	SLE	–	–	Phase II: NCT03161483 (completed)
Plasma-cell-directed therapies	Bortezomib	Proteasome inhibitor; intravenous	SLE	–	–	Phase II: NCT02102594 (terminated)
	Ixazomib	Proteasome inhibitor; oral	SLE	–	–	Phase I: NCT02176486 (terminated)
pDC-directed therapies	Litifilimab (BIIB059)	BDCA2 inhibition; subcutaneous	CLE/SLE	–	–	Phase II: NCT02847598 (completed); Phase III: NCT05352919 (recruiting)
	Daxdilimab (HZN-7734, VIB7734)	Anti-LILRA4 antibody; subcutaneous	CLE	–	–	Phase I: NCT03817424 (completed); Phase II: NCT05591222 (ongoing)

Table 3 (continued)

Mode of action	Drug	Mode of action and application	Setting	FDA approval	EMA approval	Phase of development/identifier
Interferon pathway-directed therapies	Anifrolumab	IFNAR1 inhibition; intravenous/subcutaneous	SLE	SLE: July 2021	SLE: February 2022	Phase III: NCT02446912 (completed)
	Filgotinib	JAK1 inhibition, oral	CLE	–	–	Phase II: NCT03134222 (completed)
	Tofacitinib	JAK1/3 inhibition, oral	CLE	–	–	Phase II: NCT03288324 (recruiting)
	Lanraplenib	SYK inhibition, oral	CLE	–	–	Phase II: NCT03134222 (completed)
	Deucravacitinib	TYK2 inhibition, oral	CLE	–	–	Phase II: NCT04857034 (recruiting); Phase III: NCT05617677 and NCT05620407 (not yet recruiting)
	GSK2646264	SYK inhibition, topical	CLE	–	–	Phase I: NCT02927457 (completed)
	R333 (R932333)	JAK3 and SYK inhibition; topical	CLE	–	–	Phase II: NCT01597050 (completed)
	Delgocitinib	Pan-JAK inhibition; topical	CLE	–	–	Phase II: NCT03958955 (terminated due to recruitment challenges)

SLE systemic lupus erythematosus, *CLE* cutaneous lupus erythematosus, *IL* interleukin, *FDA* US Food and Drug Administration, *EMA* European Medicines Agency, *NCT* National Clinical Trial number, *BLyS* B-lymphocyte stimulator, *BAFF* B-cell-activating factor, *TACI* transmembrane activator and CAML interactor, *BDCA2* blood dendritic cell antigen 2, *LILRA4* leukocyte immunoglobulin-like receptor subfamily A member 4, *IFNAR1* interferon-α/β receptor α chain, *pDC* plasmacytoid dendritic cell, *JAK* Janus kinase, *TYK* tyrosine kinase, *SYK* spleen tyrosine kinase

Administration (NMPA) granted telitacicept conditional marketing approval for the treatment of adult patients with active, autoantibody-positive SLE [146]. Thus far, there is no detailed information regarding the effects of cutaneous manifestations.

3.3.2 B-Cell-Depleting Therapies

CD20-based depletion of B cells was a milestone in the therapy of hematologic malignancies and numerous autoimmune diseases. To date, rituximab, a first-in-class CD20 monoclonal antibody, failed to achieve licensing in SLE [147]. In a prospective study with 82 SLE patients, 32 had severe mucocutaneous involvement before or after treatment. Only patients with ACLE showed a favorable response to rituximab, while chronic CLE patients failed to show improvement [148]. In a single-center, retrospective cohort study in Great Britain, 38 of 50 (76%) CLE patients receiving rituximab improved regarding mucocutaneous symptoms, with somewhat lower numbers for patients with subacute CLE and chronic CLE [149]. Notably, some authors describe ongoing complete remissions following only two infusions of rituximab in CLE [150]. Other B-cell-depleting agents are under clinical investigation for SLE, including obinutuzumab [151], obexelimab [152], and ocrelizumab [153], and might show alternating efficacy on mucocutaneous lesions in LE patients when compared with rituximab. Thus far, there are very limited clinical data on CLE with these agents.

3.3.3 Inhibition of Differentiation of B Cells to Plasma Cells

Iberdomide, a cereblon E3 ligase modulator that promotes degradation of transcription factors involved in autoimmunity, is under investigation for SLE. The results of a multicenter, phase II study including 288 patients were recently published. The outcome after 24 weeks was favorable in the iberdomide group when compared with placebo [154]. The reduction of CLASI was analyzed as a secondary endpoint. Sixty-four patients had a CLASI-A score of at least 10 at baseline, and the differences between the iberdomide and placebo groups with respect to a CLASI reduction of 50% ranged between 5.3% and 24.0% in different dosing groups. In light of this therapeutic range, patient selection seems to be crucial, which should be determined in further studies.

3.3.4 Plasma-Cell-Directed Therapies

In order to reduce circulating autoantibodies, one therapeutic strategy is the reduction of plasma-cell activity. Use of daratumumab to deplete long-lived plasma cells was described to be successful in SLE, as published in a small case series [155]. Proteasome inhibitors are in use for myeloma therapy and are under investigation for certain autoimmune diseases; however, clinical trials investigating the use of bortezomib and ixazomib for SLE were terminated. At this point, the use of these agents in CLE appears unlikely in the near future, although in certain combinatorial settings, proteasome inhibitors might be of use for severe cases of SLE [156].

3.4 Plasmacytoid Dendritic Cell-Directed Treatments

pDCs are major stakeholders of the innate immune system and are actively involved in the early inflammatory response. Their role in CLE is well-established as they are producers of large amounts of lesional type I IFNs, which then amplifies inflammatory loops. BDCA2 is an important surface antigen exclusively expressed on the cell membrane of pDCs and was identified as a therapeutic target [157]. A humanized monoclonal antibody binding to BDCA2 (litifilimab) is under clinical investigation for CLE with or without systemic disease. The results of a phase II trial with dosing between 50 and 450 mg subcutaneously biweekly over the course of 16 weeks are available [158]. One hundred and thirty-two patients were enrolled in the trial, with the difference from baseline CLASI in the treatment arms ranging between 24.3 and 33.4%, which was statistically significant compared with the placebo arm. Tolerability was acceptable and the authors concluded that larger and longer trials are needed to determine the effects of litifilimab in CLE [158].

Another mode of pDC inhibition is the use of a monoclonal antibody directed at leukocyte immunoglobulin-like receptor subfamily A member 4 (LILRA4) [daxdilimab]. An open-label extension study (phase II) is ongoing and the estimated enrollment is 156 patients with SLE. The primary outcome measure is safety, however no results are available as yet. It will be very interesting to follow this therapeutic approach and to determine which CLE patients could benefit the most.

3.5 Interferon-I-Directed Therapies

When considering the major role of type 1 IFNs in CLE, it is self-evident to evaluate therapeutic interventions regarding these cytokines. Disappointing results of therapeutic trials with monoclonal antibodies directed at IFNs led to shifting the focus on the corresponding receptor (IFNAR1), which turned out to be more effective. Indeed, only recently, an IFN-targeted treatment was licensed for SLE, which might point towards therapeutic potential for (subgroups) of CLE patients. Downstream signaling of IFNAR1 mainly relies on JAK1–3 and tyrosine kinase 2 (TYK2), which is another promising approach for both topical and systemic treatment modalities.

3.5.1 Interferon Receptor Inhibition

The concept of IFNAR inhibition was found to be well tolerated and effective across multiple clinical endpoints in a phase IIb trial including 305 patients with moderate to severe SLE [159], which led to the initiation of further development of the drug. In a placebo-controlled, phase III study (TULIP-2), 362 patients with active SLE were randomized to receive 300 mg of intravenous anifrolumab or placebo every 4 weeks over a course of 48 weeks [160]. The primary outcome measure of the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) reduction was statistically higher in the verum group. Interestingly, in this trial, skin symptoms were assessed as a secondary endpoint defined by improvement of CLASI by at least 50% (CLASI50). Of the patients with a baseline CLASI of >10, within the anifrolumab group twice as many patients reached CLASI50 compared with the placebo group. A post hoc analysis of the twin phase III studies TULIP-1 and TULIP-2 established comparable findings for cutaneous disease manifestation [161]. Adverse effects most commonly observed included upper respiratory infections, zoster, and influenza, which might be attributable to interference with the antiviral cellular immune response. A recently published placebo-controlled, phase III extension trial underlined the favorable safety profile of anifrolumab, even in light of the ongoing COVID-19 pandemic [162]. A pooled safety analysis of the phase II and III trials also underlined the good tolerability [163]. The possibility of reducing the daily dose of glucocorticoids might even be favorable considering the risk of infection in subjects with LE. In light of these interesting results in SLE patients, first reports regarding the use of anifrolumab in CLE patients are available. Only recently, successful use in a case series of three patients was published by an American group [164]. Interestingly, the patients reported were pretreated heavily with second- and third-line treatments, even belimumab. Similarly, another case report described a reduction in CLASI from 17 to 7 within 8 weeks of treatment initiation in an SLE patient with predominant skin involvement [165]. After all, IFNAR1 inhibition might be a breakthrough innovation for the therapy of certain CLE patients, however more data are necessary for treatment allocation considering the high cost of the drug at this point in time.

3.5.2 Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) Pathway

Given their substantial role in signal transduction of various proinflammatory cytokines, including IFN signaling, a multitude of JAK inhibitors, SYK inhibitors, and TYK2 inhibitors are under clinical development for different inflammatory skin diseases, including CLE. As they are small molecules, administration may be oral or even topical, potentially limiting adverse effects, which are dose-dependent. Treatment approaches include selective inhibition of singular JAKs (potentially more appropriate for systemic treatment) or more broad inhibition of various JAKs (potentially more appropriate for topical treatment), depending on the specificity of the drugs.

In vitro data support the role of JAK1 and SYK in the pathophysiology of CLE [166, 167]. Use of orally available filgotinib (a JAK1 inhibitor) or lanraplenib (an SYK inhibitor) was assessed in a phase IIb study in 47 subjects with moderate to severe CLE [168]. The drugs were generally well tolerated, however the primary endpoint of CLASI50 at week 12 was not met. Efficacy was somewhat higher in the filgotinib group compared with the lanraplenib group. In 2022, French authors reported an impressive clinical response in a heavily pretreated patient with an absolute CLASI of 58 upon therapeutic challenge with oral upadacitinib 15 mg, a selective JAK1 inhibitor [169]. HCQ was continued during therapy and the patient showed a reduction in CLASI50 within 3 months. Similar reports are available for oral administration of baricitinib, a JAK1 and JAK2 inhibitor, following the encouraging results of a phase IIb trial for SLE [170, 171]. The results from two randomized phase III studies in subjects with SLE were recently posted and showed somewhat disencouraging results [172]. Tofacitinib, a JAK1 and JAK3 inhibitor, is currently under clinical investigation in an actively recruiting, open-label, phase II study for young subjects with CLE and SLE. A case series reported improvement of at least 50% skin involvement in two of three heavily pretreated CLE patients receiving tofacitinib 5 mg twice daily [173]. However, it is noteworthy that JAK inhibitors might be associated with an increased risk of major cardiovascular events. Furthermore, thromboembolic events as a safety signal were observed for tofacitinib in a surveillance study in patients with rheumatoid arthritis [174]. SLE and CLE patients are at increased risk for these events, therefore further study is needed to evaluate safety in this cohort of patients.

Selective TYK2 inhibition might be less prone to off-target adverse effects, including disruption of hematopoiesis and cardiovascular adverse effects. Results from a phase IIb trial of deucravacitinib, an allosteric selective TYK2 inhibitor, in subjects with active SLE are encouraging [175]. Three hundred and sixty-three patients were randomized to receive either placebo or 3 mg/6 mg deucravacitinib twice daily, or 12 mg once daily, and while the adverse effects were comparable between the groups, a statistically significant larger number of patients achieved CLASI50 reduction in the 3 mg group at week 48 compared with placebo. In light of these results, larger studies are planned to evaluate the potential therapeutic use in SLE and CLE patients.

Even though the aforementioned clinical trial with systemic SYK inhibition did not reach its primary endpoint, topical SYK inhibition might be of value as overexpression of SYK is frequently found in cutaneous LE lesions. A phase Ib study established a favorable safety profile for GSK2646264, however clinical efficacy did not statistically differ from placebo [176]. Another candidate that was in clinical development was R932333, a dual JAK3 and SYK inhibitor. A phase IIb study enrolled 54 patients to receive 6% verum twice daily versus placebo (vehicle). There were no serious adverse events but efficacy was not superior compared with placebo. The topical pan-JAK inhibitor delgocitinib is already available in Japan. A case report of successful treatment of facial lesions of subacute CLE with delgocitinib 0.5% ointment was recently published [177]. In light of the advent of licensing of topical ruxolitinib for atopic dermatitis and vitiligo in the US, first reports about use in CLE patients are now available [178]. More study is needed regarding this topical approach, yet potent topical JAK inhibitors might expand the therapeutic armamentarium for CLE patients, especially for specific sites such as the face and the scalp.

Apart from our focused approach in this review, even more drugs are under investigation for CLE or SLE. For further reading, we refer to other reviews dealing with emerging therapies in CLE or other connective tissue diseases [179–181].

4 Summary and Outlook

CLE is a complex disease with many facets, which might be reflected partly by a varying dominance of specific immune cell subsets and cytokine profiles. Still, a given clinical or histological pattern fails to reliably predict cytokine or gene expression. A better comprehension of molecular pathways and individual disease-perpetuating factors will render the way forward to personalized treatment options. The advent of targeted treatment options licensed for SLE might also pave the way to more precise therapeutic interventions in CLE. Entering an era of precision medicine in CLE will be of benefit for both patients and treating physicians, and upcoming data of active clinical trials and real-world data will help to further delineate the underlying multidimensional interrelations. A close interdisciplinary exchange with rheumatologists and nephrologists is mandatory for optimal treatment of lupus patients to define the best therapeutic strategy.

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Author's contributions JW conceived the idea for the article, and all authors performed the literature search and discussed the outline of the article. DN and LdV performed the data analysis, and TF drafted the graphic illustration. The first draft of the manuscript was written by DN and LdV. All authors commented on previous versions of the manuscript, and read and approved the final manuscript.

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