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Therapeutic options for cutaneous lupus erythematosus: recent advances and future prospects

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Abstract

Introduction—Treatment and prevention are of critical importance in patients with cutaneous lupus erythematosus (CLE), as the disease can have a devastating effect on patient well-being and quality of life.

Areas Covered—We conducted a selective search of the PubMed database for articles published between December 2010 and November 2015. This review encompasses both non-pharmaceutical (photoprotection, smoking cessation, drug withdrawal, and vitamin D replacement) and pharmaceutical (topicals, antimalarials, immunosuppressives, biologics, etc.) interventions used in the treatment of CLE.

Expert Commentary—Recent work has expanded our understanding of established therapies as well as introduced new treatments for consideration, though existing medications still prove inadequate for a subset of patients. Changes in trial design may help to alleviate this issue.

Keywords

cutaneous lupus erythematosus; topical calcineurin inhibitors; antimalarials; immunosuppressives; immunomodulators; biologics; Cutaneous Lupus Erythematosus Disease Area and Severity Index™ (CLASITM)

1. Introduction

Lupus erythematosus (LE) is an autoimmune disease characterized by a wide range of cutaneous (CLE) and/or systemic (SLE) symptoms. CLE can be seen with or without SLE (i.e. as part of a systemic disease or as a separate entity with primarily cutaneous manifestations), and the latter may present or develop cutaneous manifestations. As such,

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evaluating for potential systemic involvement is a critical component of initial clinical staging and subsequent monitoring of disease progression.

Current theories regarding the pathogenesis of CLE emphasize a multifactorial etiology involving genetic polymorphisms and susceptibility loci, environmental factors such as UV exposure, and induction of innate and adaptive autoimmune responses. Standard treatment of CLE involves preventative measures, such as sunscreen use and smoking cessation, coupled with topical corticosteroids or calcineurin inhibitors. For more severe cases, antimalarials are implemented as first-line systemic treatment. In patients unresponsive to or unable to tolerate antimalarial therapy, alternative options include immunosuppressive, immunomodulatory, or biologic agents. Recent work over the past five years has been successful in both reinforcing the efficacy of established treatments as well as introducing new options for consideration.

2. Methods

We conducted this review through a selective search of the PubMed database for articles published between December 2010 and November 2015 using two overlapping search strategies with the following keywords: 1) “lupus erythematosus” and “treatment” and 2) “cutaneous lupus erythematosus” and “treatment”. We selected articles based on their relevance and contribution to recent advances in the treatment of CLE and incorporated additional articles published prior to the designated time frame as needed.

3. Classification of CLE

CLE is divided into acute (ACLE), subacute (SCLE), and chronic (CCLE) subtypes, with lupus erythematosus tumidus (LET) either grouped with chronic CCLE, its own category, or in lupus nonspecific skin findings. CCLE includes discoid lupus erythematosus (DLE) and lupus erythematosus panniculitis (LEP), as well as LET depending on which of the classifications are used [1].

The 1997 American College of Rheumatology (ACR) SLE classification criteria are comprised of 11 criteria, 4 of which must be met for classification as SLE [2]. However, the first 4 criteria (malar rash, discoid rash, photosensitivity, and oral ulcers) could all be present in a patient with skin-predominant disease who is otherwise healthy, raising issues regarding the potential inaccuracy of this classification system. Another system has been developed by the Systemic Lupus International Collaborating Clinics (SLICC) and includes a total of 17 clinical and immunological criteria. The SLICC criteria do not include photosensitivity and are able to account for additional cutaneous manifestations. Classification of SLE by this system also needs a minimum of 4 criteria to be met, but with the added requirement of at least one criterion present in each category [3]. Though this therefore avoids the aforementioned issue with the ACR criteria, the requirement of at least one immunological criterion excludes all seronegative patients, even those with extensive skin disease and other significant systemic features. This may limit the number and breadth of patients included in SLE studies.

4. Evaluation of Disease Severity

Disease damage and activity can be measured with the CLE Disease Area and Severity Index™ (CLASI™), a quantitative scoring tool in which a 4-point or 20% decrease in activity score indicates a clinically significant improvement [4]. The CLASI™ can be used to follow patients in a specialty clinic, but its main role is for cohort or therapeutic studies. The CLASI™ has been validated against physician- and patient-reported outcomes, including measures of cutaneous damage [5] and quality of life [4]. The latter is especially important to consider in the assessment of these patients, as individuals with CLE have demonstrated a poorer quality of life than those with other common conditions affecting the skin [6] across multiple geographic populations [7]. Worse quality of life in CLE patients is associated with a number of factors including female gender, younger age, presence of facial lesions, and non-responsiveness to treatment [6, 8]. There are a number of other measures that have not been fully validated or utilized in international trials [9, 10].

5. Assessment for Systemic Involvement

Patients with indications of systemic disease, including proteinuria, low complements, and/or high-dsDNA titer are at an increased risk for progression to systemic disease. Such patients should receive careful follow-up testing, with complete blood counts and urinalyses every two to three months. In contrast, in patients with stable, long-standing CLE, monitoring may be performed annually. Anti-Smith antibody titers may also assist with patient diagnosis and serve as a high-sensitivity, low-specificity test for SLE. In patients with a history of clots or livedo pattern, an anti-phospholipid antibody panel should be ordered. Patients with CLE or minor SLE can be treated and continually evaluated by a dermatologist, whereas those with active significant SLE should be referred to rheumatology for co-management.

6. Non-Pharmaceutical Interventions

6.1 Photoprotection

Recent studies have reaffirmed the role of UV irradiation in the development and progression of CLE lesions. In a multicenter study of 47 subjects with CLE, a standardized photoprovocation protocol caused UV-induced lesions in about half of all patients, with the highest rates observed in those with SCLE and LET [11]. An updated retrospective analysis revealed even higher rates of positive photoprovocation (61.7%) [12]. Photoprotection thus represents a key component of preventative therapy in CLE, and the consistent use of sunscreens is commonly recommended for these patients [13]. Application of a photoprotective sunscreen was shown to limit UV-induced inflammatory responses through a decrease in CD11c- and CD123-positive dendritic cells, with a corresponding decrease in MxA expression and interferon levels [14]. Another study assessing the efficacy of a broad-spectrum sunscreen reported the complete absence of lesions in sunscreen-treated portions of the skin following UV irradiation [15]. Similar results were obtained in an open-label study involving a liposomal sunscreen, with CLE lesions observed only in untreated, UV-irradiated areas of the skin [16].

Unfortunately, most patients with CLE fail to remain consistent in their use of sunscreen and other photoprotective methods [17, 18]. A cross-sectional survey of 100 CLE subjects identified only a third of the group as daily sunscreen users, with over half of the remaining individuals not using sunscreen at all. Poor levels of adherence were most often attributed to simple factors such as forgetfulness or presumed ineffectiveness [18]. A separate study also revealed that patients between 31 to 50 years of age and/or with medium to dark skin were least likely to engage in photoprotective habits [17]. Outside of traditional sun exposure, additional sources of UV irradiation exist which should also be limited whenever possible. A pilot study investigating the effect of different lighting types on patient symptoms showed that UV-emitting bulbs (compact fluorescent lamp and energy-efficient halogen) were erythema-inducing. These two light sources should be avoided in favor of light-emitting diode bulbs, which were identified as a safer, non-UV-emitting alternative [19]. Surgical lighting was also recently reported to induce flares in a photosensitive LE patient [20].

Given the exacerbative effect of UV exposure on patient symptoms, it is imperative that individuals with CLE put their best effort toward the prevention of UV-induced disease progression. Therefore, in addition to recommending and educating patients on proper and routine sunscreen use, it is equally important to monitor and assess the photoprotective habits of these patients throughout the course of treatment. Though sunscreens are not yet recognized as therapeutic drugs and therefore not covered by most health insurances worldwide, this may change with the increasing emphasis on preventative care.

6.2 Smoking cessation

Smoking cessation is also recommended in controlling CLE symptoms. A prospective cohort study of CLE patients showed greater disease severity and worse quality of life measurements in current smokers [21]; a separate, larger-scale study also identified smoking as a risk factor for increased disease severity [22], though other analyses have suggested that the association is restricted to select CLE subtypes such as LET and DLE [23]; and baseline data from a recently completed randomized trial has demonstrated significantly increased CLASI™ scores in current smokers [24]. Previously, many reports concerning smoking in CLE patients have emphasized its negative impact on antimalarial treatment efficacy [25]. In the case of hydroxychloroquine (HCQ), smoking was observed to counteract the drug's proposed inhibition of Toll-like receptor-mediated signaling [26]. However, recent studies have revealed the absence of any significant relationship between smoking and patient response to HCQ [27] and other antimalarials [24], suggesting a treatment-independent effect of smoking on disease severity.

6.3 Drug withdrawal

Drug-induced SCLE (DI-SCLE) has been observed and some cutaneous features may distinguish it from idiopathic SCLE [28]. A case-control study of SCLE patients identified terbinafine, tumor necrosis factor-alpha inhibitors, antiepileptics, and proton pump inhibitors as the most common offending agents, with DI-SCLE accounting for over a third of all SCLE cases. As DI-SCLE symptoms are reversible, discontinuation of the drug is an effective method of treatment and demonstrates the importance of active medication screening in SCLE patients [29]. Other drugs previously implicated in DI-SCLE include

calcium-channel blockers, angiotensin-converting enzyme inhibitors, and thiazide diuretics [30].

6.4 Vitamin D replacement

Vitamin D monitoring and treatment may also represent a valid option for CLE symptom control. A recent analysis revealed a greater prevalence of vitamin D deficiency among CLE patients, especially with increasing age and disease duration. Disease severity was noted to improve in the treatment group, suggesting a therapeutic role for vitamin D replacement [31]. Oral vitamin D supplementation has also been observed to decrease T-cell production of IFN-γ and IL-17 [32], and certain polymorphisms in the vitamin D receptor gene were associated with cutaneous, arthritic, and immunological manifestations of SLE [33]. Therefore, in patients with low vitamin D levels, especially with sunscreen use, vitamin D replacement should be considered and recommended as part of the overall treatment plan.

7. Pharmaceutical Interventions

7.1 Topical corticosteroids

Topical corticosteroids serve as first-line treatments for mild or local cases of CLE. Though they have therefore been applied in all CLE subtypes, the only randomized controlled trial to date supporting their use in CLE involved 78 DLE patients. The 12-week crossover study revealed a greater response rate with 0.05% fluocinomide than with 1% hydrocortisone, suggesting that higher-potency topical corticosteroids are more effective for treatment [34]. However, the potency and duration of topical steroid use should generally be kept to a minimum due to side-effects including atrophy and telangiectasia. Treatment of facial lesions should be limited to low-potency steroids such as hydrocortisone butyrate, while high-potency steroids such as clobetasol proprionate should be reserved for lesions involving thicker areas of the skin or cases of severe disease activity [35].

7.2 Topical calcineurin inhibitors

With their greatly reduced side-effect profile, the calcineurin inhibitors tacrolimus and pimecrolimus have emerged as effective alternatives to corticosteroids in the topical treatment of CLE [36]. A study of 38 patients showed both tacrolimus and pimecrolimus to be effective in improving symptoms of erythema, desquamation, and edema, independent of disease type [37]. In a comparison between 0.1% tacrolimus and 0.05% clobetasol propionate ointments in 21 DLE patients, negative effects of tacrolimus were limited to transient pruritus and burning, whereas telangiectasia was observed in 61% of patients following clobetasol treatment. Though tacrolimus had a lower overall efficacy, both treatments led to significant decreases in disease severity [38]. In a randomized, vehicle-controlled trial, similar improvements were seen in patients treated with 0.1% tacrolimus ointment, especially in those with LET [39]. More recently, treatment with a 0.3% tacrolimus lotion was also observed to relieve symptoms in three patients with antimalarial-resistant DLE [40].

7.3 Topical vitamin D derivatives

In addition to its frequent deficiency among LE patients, vitamin D has also demonstrated immunomodulatory effects that further support its use in the treatment of autoimmune diseases [41]. Topical derivatives of vitamin D have been developed that achieve similar immunomodulatory activity while limiting subsequent risk of hypercalcemic toxicity [42, 43]. Calcipotriene, for instance, is an FDA-approved treatment for psoriasis that has also been reported to improve LE skin lesions. Topical application of the drug may therefore be considered in CLE [44–46].

7.4 Antimalarials

Antimalarials such as HCQ, quinacrine, and chloroquine continue to serve as first-line systemic treatments for more severe cases of CLE and are administered according to ideal and/or real body weight [47]. Despite recommended dosing, chloroquine is associated with a higher risk of eye toxicity [48, 49]. HCQ is typically the treatment of choice [50], though its utility as a monotherapy is limited due to variations in patient response. Factors most strongly associated with a lack of response include smoking, disease severity, and presence of SLE. In a retrospective cohort study of 200 DLE patients, 60% showed a response to HCQ in the first six months of treatment [27]. Further analysis of the same population revealed an overall decline in response rate over time, with the long-term HCQ response rate dropping to 45% [51].

In such cases, quinacrine can be added to improve the response to HCQ. In a prospective study, 67% of HCQ non-responders showed a significant improvement in disease activity following the addition of quinacrine [52]. Similarly, patients that had failed to maintain an initial response to HCQ were often observed to regain symptom control through this combination of antimalarial agents [51]. Though quinacrine remains a valid therapeutic option in the treatment of recalcitrant CLE, it has declined in use and is currently only available from compounding pharmacies, including those in the United States, United Kingdom, and Germany [35].

Rates of adherence to antimalarial treatment have been studied and reported in LE patients, though much more so in SLE. Treatment maintenance can be assessed by monitoring serum HCQ concentrations, with low levels in the blood indicative of poor adherence [53]. Among 203 patients with SLE, 7% were found to have a low mean HCQ concentration and later confirmed their non-adherence. Similarly, a prospective, multicenter study of 300 refractory CLE patients identified 10% of subjects as non-adherent, and higher HCQ concentrations were associated with partial or complete remission. In both studies, a 200 ng/ml blood HCQ concentration was proposed and applied as a minimum cutoff threshold for adherence [54, 55].

7.5 Retinoids

In patients failing to tolerate or show improvement with other treatments, retinoids may be employed as second-line therapeutic agents. Successful off-label use of alitretinoin was reported in a case series of three patients with recalcitrant SLE, DLE, and SCLE. Alitretinoin was well tolerated and led to a complete clearance of lesions in all three patients

[56]. Similarly, in a patient receiving oral isotretinoin for SCLE, significant symptom reduction was observed within the first month with no evidence of recurrence after six months [57]. A rare case of lupus/lichen planus overlap syndrome also demonstrated improvement following treatment with acitretin [58]. As retinoids are known teratogens, women of child-bearing age are required to take contraceptives before, during, and after treatment. In such cases, isotretinoin is typically preferred for its shorter half-life [59].

Immunosuppressives—Immunosuppressives such as methotrexate and mycophenolate mofetil (MMF) can also be used as second-line treatments for CLE. Past retrospective analyses have supported the safety and efficacy of methotrexate with refractory CLE [60, 61], with successfully treated cases of SCLE [62, 63] and DLE [64] also reported in the literature. More recently, in a prospective, open-label study of 41 patients comparing low-dose methotrexate to chloroquine, both treatments were shown to be equally effective in treating cutaneous symptoms [65]. When combined with the calcineurin inhibitor cyclosporine, methotrexate was also observed to improve symptom control in two cases of recalcitrant SCLE. However, the long-term safety of this combination is in need of further study, and both drugs have been associated with nephro- and hepatotoxicity [66]. In SLE patients, methotrexate treatment has been shown to be highly effective, leading to significant reductions in SLEDAI-measured disease activity and overall steroid burden [67–69].

Like methotrexate, MMF can also be used in combination therapies targeting recalcitrant CLE. In a retrospective analysis of 24 patients with antimalarial-resistant CLE, many were able to achieve complete symptom control following the addition of MMF to the established drug regimen [70]. Similarly, a combination of MMF and HCQ was reported to induce either partial or full remission in three patients with recalcitrant CLE [71].

In pregnancy, the immunosuppressant azathioprine may be used if there are no suitable alternatives for the treatment of skin disease.

7.6 Immunomodulators

Though it is more commonly used as an antimicrobial agent, dapsone has been successfully implemented in the treatment of various subtypes of CLE, with an overall response rate of 55% across multiple case series [72]. The immunomodulatory antibiotic was also shown to be effective in treating a rare case of pediatric, corticosteroid-resistant bullous SLE [73]. Dapsone should not be given to patients with glucose-6-phosphate dehydrogenase deficiency due to an increased risk of hemolysis and methemoglobinemia [59].

Thalidomide is an anti-inflammatory agent that prevents UV-induced apoptosis of keratinocytes. A prospective study of 60 patients with recalcitrant CLE showed a 98% response rate with thalidomide, though many experienced disease recurrence following withdrawal of the drug. This relapse was especially common among DLE patients, whereas SCLE patients tended to maintain symptom control even after withdrawal [74]. Thalidomide is also known to cause multiple neuropathic side-effects in those receiving treatment, as confirmed by a recent retrospective analysis [75]. Though treatment dosage and duration are typically held to a minimum, neither of these factors has been shown to have an impact on resulting rates of thalidomide-associated neuropathy [74, 76]. As neurotoxic and teratogenic

side effects may be observed even at low doses of the drug, thalidomide use should therefore be limited to more severe cases of recalcitrant CLE [59, 76].

Lenalidomide is a thalidomide derivative that has demonstrated similar utility in the treatment of recalcitrant CLE. Of 15 such patients enrolled in a single-center pilot trial, 85% showed a complete response to lenalidomide therapy, and no neuropathic effects occurred as a result of treatment [77]. In a smaller open-label study, four out of five patients experienced meaningful improvement in their cutaneous symptoms [78]. Long-term follow-up of this same group revealed a clinically significant decline in CLASI™ score at 12 weeks for all five patients. Again, neuropathy was not observed following treatment, suggesting that lenalidomide may be preferred over thalidomide in the treatment of recalcitrant CLE [79]. In either case, it should be noted that the off-label use of thalidomide or its derivatives for CLE can be very costly, making it difficult for some patients to receive treatment with these drugs.

7.7 Biologics

Much of the recent work involving the use of biologics in LE has focused on the treatment of SLE rather than CLE. In addition, many of these studies did not closely evaluate the skin with established indices but were instead limited to general observations of skin manifestations.

Rituximab is a monoclonal antibody that acts against human CD20, leading to B cell death and depletion. A systematic review of the literature supported the short-term efficacy of rituximab in the treatment of recalcitrant SLE, though relapse was frequently observed [80]. A retrospective analysis of 17 patients showed similar results [81], and a prospective study further demonstrated a steroid-sparing effect with early treatment [82]. For CLE patients, studies suggest that rituximab may only be helpful in treating those with ACLE [83], though treatment of other subtypes has been reported in a few cases [84–87].

Belimumab, a monoclonal antibody specific to B lymphocyte stimulator, has consistently shown positive results in clinical trials involving SLE patients and was the first biologic to be approved for SLE treatment [88]. Its safety and efficacy in CLE patients have yet to be studied, though it was successfully implemented in a case of refractory SCLE [89]. In the BLISS-52 and -76 randomized controlled trials, belimumab doses of 1 and 10 mg/kg were evaluated and compared to placebo plus standard therapy in SLE patients, with both trials demonstrating the safety and therapeutic efficacy of the drug [90, 91]. Subsequent analyses revealed significant musculoskeletal and mucocutaneous improvement [92] as well as increased health-related quality of life [93] in those receiving treatment, and a long-term continuation study of a separate trial showed effective disease control over a seven year treatment period [94]. Data from the two BLISS trials was also used to show that factors such as increased disease activity, low complement levels, anti-dsDNA positivity, and corticosteroid use were associated with an increased benefit from treatment. These characteristics may therefore be helpful in the decision-making process and, when identified in patients, support the use of belimumab therapy [95].

Other biologic agents have also been reported to improve outcomes in patients with drug-resistant LE. Ustekinumab is a monoclonal antibody that binds and sequesters IL-12 and IL-23, thereby inhibiting pathways of Th1 and Th17 differentiation. 45 mg injections of the drug successfully treated a case of recalcitrant SCLE, with sustained remission through seven months of follow-up [96]. Similar results were seen in a separate patient with DLE [97]. Ustekinumab was also used to treat a rare case of coexistent psoriasis and DLE. Slight reductions in DLE symptoms were observed following a series of 45 mg injections, with significant improvement upon switching to a 90 mg dose [98].

Sirukumab and tocilizumab are monoclonal antibodies that act as inhibitors of the IL-6 pathway. Sirukumab was well tolerated in a phase I trial of 46 LE patients and led to dose-dependent decreases in white blood cell counts and acute phase reactant levels [99]. Tocilizumab was successfully implemented in the treatment of an LET patient with elevated IL-6 levels [100]. Positive results were also initially observed in two other SLE patients, though subsequent flares required treatment with belimumab for long-term symptom control [101].

Anifrolumab and sifalimumab are another pair of biologics that target human interferon-alpha and interferon-alpha receptor, respectively. 300 and 1000 mg doses of anifrolumab were shown to lead to equally dramatic reductions in disease activity and severity in a phase II randomized controlled trial of 385 patients with drug-resistant SLE [102]. Sifalimumab was well-tolerated by patients and showed an acceptable safety profile in two phase I trials [103, 104], and a recent phase II trial of 431 SLE patients demonstrated significant improvements in disease activity following treatment with the drug [105].

The anti-T cell therapies abatacept (CTLA4-Ig) and AMG 811 (anti-IFN- γ) have also been evaluated in randomized controlled trials, though their results did not demonstrate efficacy. In both studies, participants failed to demonstrate an adequate response to treatment. However, these outcomes may be attributed to issues in endpoint determination or overall trial design [106, 107].

7.8 Laser therapy

Pulsed dye laser (PDL) therapy may be used in cases of refractory CLE. Though PDL therapy has not yet been reported to induce skin lesions, lasers should still be employed with caution in LE patients, and spot testing is recommended prior to treatment. In a prospective study of nine CLE patients, clinical and histological improvements were observed four weeks after 595-nm PDL treatment [108]. PDL therapy has also been reported to successfully treat individual cases of refractory LET [109] and DLE [110, 111].

8. Conclusion

Studies concerning the treatment and prevention of lupus erythematosus have led to significant advances in the field over the past five years. Topical steroids and oral antimalarials continue to serve as first-line treatments with methotrexate and systemic steroids as second-line options. In cases of recalcitrant disease, other agents such as dapsone, retinoids, immunosuppressives, and targeted biologic therapies may be also be

implemented. As research continues to unveil the underlying mechanisms of LE pathogenesis, novel therapeutic options will surely follow, and it will be interesting to observe the role that pharmacoepigenetics and genetic analysis play in the development of future treatments.

9. Expert commentary

As the list of available treatments for CLE continues to grow, implications for clinical practice and decision-making abound. Though treatment of patients tends to follow a basic pattern, individual options should still be considered in the context of disease subtype and severity, as many of the aforementioned studies have demonstrated the impact of these factors on treatment response. Maintenance of treatment should be regularly assessed and closely monitored to avoid unnecessary escalation or alteration of treatment in cases of non-adherence. Finally, a holistic approach to the evaluation and treatment of these patients is key, as patient well-being and quality of life are especially impacted by CLE.

Still, the need for novel therapeutic options remains evident. Older drugs such as quinacrine and chloroquine are becoming increasingly difficult to obtain, and existing regimens are often inadequate for patients who present with recalcitrant CLE or are unable to tolerate otherwise-effective medications. Unfortunately, not a single drug has yet been approved for the treatment of CLE (if defined as separate entity), and belimumab remains the only medication approved for SLE in the past 50 years. This disparity between the increasing need for new medications and the near-complete lack of formal drug approval can in part be attributed to challenges in trial design, as studies of LE patients often involve background treatments that lead to inflated placebo response rates. This then decreases the accuracy of results and may prevent identification of a clinically significant response in the treatment arm, especially when evaluating medications with a smaller therapeutic effect. In order to alleviate these issues, it may therefore be helpful to identify individuals who are less responsive to background therapies and assess treatment efficacy separately in that subset of patients.

10. Five-year view

In spite of certain challenges, significant progress has already been made in the treatment of CLE, and we anticipate the identification and development of additional therapeutic options in the near future. Recent treatments that have been reported but are in need of further study include lenalidomide, a thalidomide derivative [77–79]; octreotide, a peptide analog of somatostatin [112]; mizoribine, an immunosuppressive [113]; and blisibimod, a biologic BAFF inhibitor [114], among others. Likewise, treatments such as intravenous immunoglobulin therapy [115], mesenchymal stem cell transplantation [116], and regulatory T cell therapy [117] that have shown success in other diseases are now being applied to CLE in exploratory studies. Table 2 provides a summary of ongoing clinical trials [117–144].

As our understanding of CLE pathogenesis matures, novel therapeutic targets may be identified that lead to the development of new treatments. For instance, in the STING-interferon-beta pathway, signaling begins with the binding of dsDNA by cyclic GMP-AMP

synthase (cGAS) and ultimately results in the upregulation of interferon response genes [145]. Antimalarials were recently observed to prevent the initial cGAS-dsDNA binding interaction, suggesting that other inhibitors of this pathway could be designed as alternative treatments for CLE [146]. Antimalarial inhibition of endosomal TLRs, which was recently demonstrated to occur through nucleic acid binding, may provide a similar opportunity for treatment development [147]. Proteins involved in apoptotic signaling such as TWEAK [148, 149], TRAIL [150], and Fas/FasL [151, 152] have also been implicated in the pathogenesis of CLE. Similarly, elevated levels of corticotropin-releasing hormone [153], anti-C1q antibodies [154], and serum cytokine CXCL16 [155] have been detected in CLE patients and suggest the wide array of molecules that could eventually serve as potential biomarkers for disease.

Pharmacoepigenetics may also be involved in future treatment development. Aberrant demethylation of B and T cell DNA has been suggested to play a role in SLE pathogenesis, and DNA methyltransferase inhibitors currently being implemented in the treatment of cancer may soon be applied to LE as well [156, 157]. In addition, CLE susceptibility loci in multiple antigen presentation, apoptosis, RNA processing, and interferon response genes have been identified by genome-wide analysis. Identification of these CLE-associated SNPs in patients would then have a significant impact on counseling and preventative treatment practices [158].

In addition, there are likely different pathways activated, leading to similar phenotypes. Dissecting these pathways and individualizing approaches to treatment are likely to be fruitful approaches in the future.

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Reference annotations

* Of interest

** Of considerable interest

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Key Issues

- Increased CLASI™-measured disease severity is associated with worse quality of life in CLE.
- Preventative practices such as photoprotection and smoking cessation should always be recommended. Drug withdrawal or vitamin D replacement can also be helpful in patients with drug-induced lesions or vitamin D deficiency.
- Depending on the severity of disease, first-line treatment of CLE lesions may involve topical corticosteroids or oral antimalarials.
- Alternative treatment options include methotrexate, mycophenolate mofetil, dapsone, and retinoids.
- Biologics have emerged as a major class of drugs in the treatment of recalcitrant CLE.
- There is not yet an FDA-approved drug for CLE. Belimumab has been approved for use in patients with SLE.
- Continued research on CLE pathogenesis has identified multiple potential therapeutic targets and may contribute to the development of novel treatments in the coming years.
- Certain genetic polymorphisms and epigenetic modifications have been suggested to contribute to LE susceptibility and disease. Pharmacoepigenetics may play an important role in future treatment development.

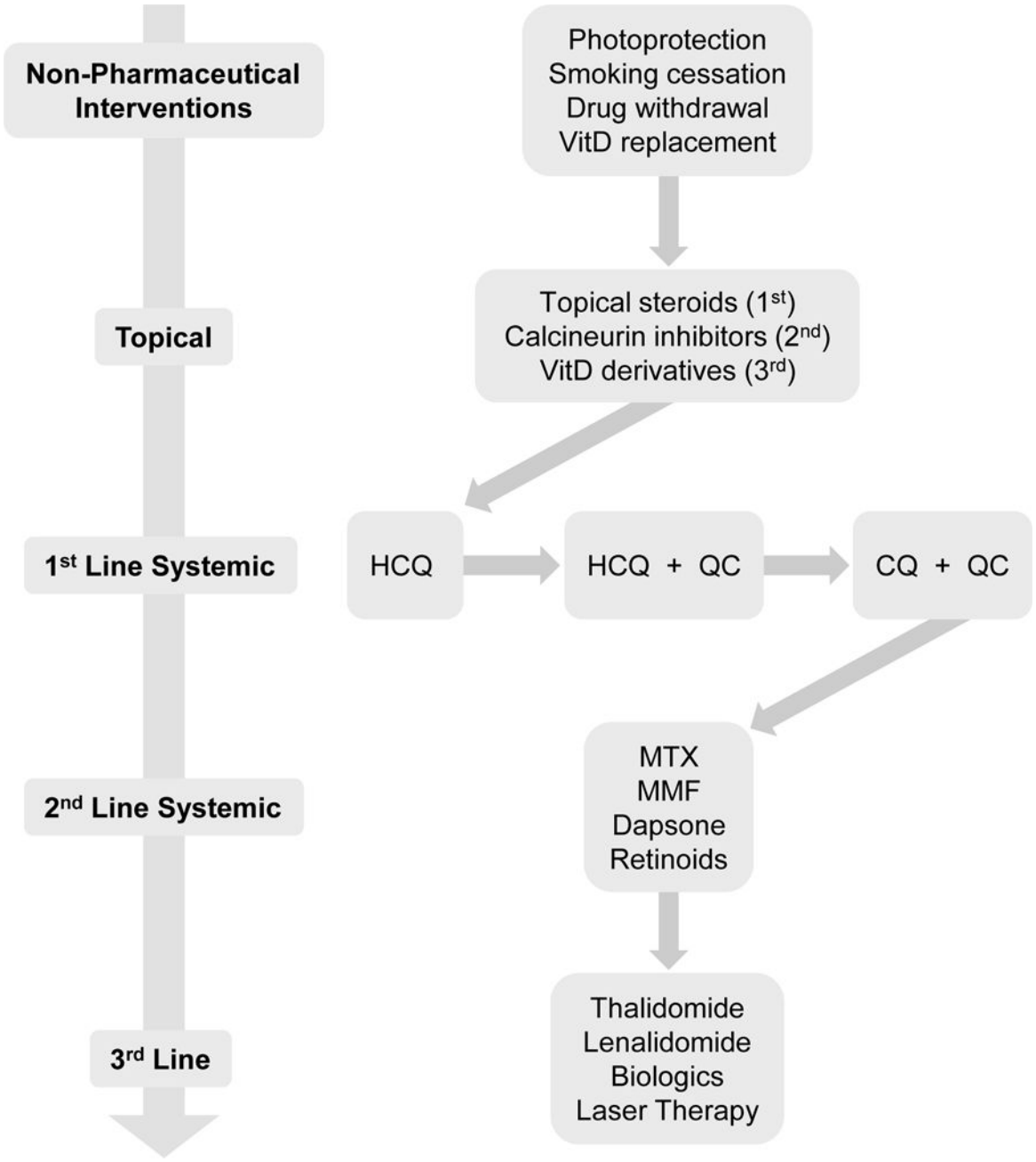

Figure 1.

Cutaneous lupus erythematosus treatment algorithm. Treatment of mild or local disease begins with topical therapies, whereas treatment of severe or widespread disease begins with systemic therapies. If the response to therapy is inadequate, arrows indicate the direction of treatment progression. In many cases, combining therapies from multiple classes (e.g. first- and second-line systemic treatments) may be necessary.

HCQ = hydroxychloroquine; QC = quinacrine; CQ = chloroquine; MTX = methotrexate; MMF = mycophenolate mofetil

Table 1

Level and subtype-specific distribution of evidence for cutaneous lupus erythematosus treatments. Evidence level: +/− = weak or controversial support; + = support limited to case reports or similar; ++ = support limited to non-randomized studies or similar; +++ = support limited to randomized trials or similar. Evidence distribution: check mark = corresponding literature explicitly demonstrates favorable response to the treatment in this subtype; question mark = corresponding literature only provides weak or controversial support for treatment in this subtype; x mark = corresponding literature explicitly demonstrates little or no response to the treatment in this subtype; blank = majority of literature does not explicitly address effects of the treatment in this subtype.

Treatment	Evidence Level	Evidence Distribution					
		ACLE	SCLE	DLE	LEP	LET	Bullous LE
Topicals							
Topical corticosteroids	+++	✓	✓	✓	✓	✓	
Calcineurin inhibitors	+++	✓	✓	✓	✓	✓	
Vitamin D derivatives	+	✓	✓	✓	✓	✓	
Antimalarials							
Hydroxychloroquine	+++	✓	✓	✓	✓	✓	
Chloroquine	+++	✓	✓	✓	✓	✓	
Quinacrine	++	✓	✓	✓	✓	✓	
Retinoids							
Acitretin	+++	✓	✓	✓			
Isotretinoin	++	✓	✓	✓			
Alitretinoin	+	✓	✓	✓			
Immunosuppressives							
Methotrexate	++	✓	✓	✓	✓		
Mycophenolate mofetil	++	✓	✓	✓	✓	✓	
Azathioprine *	+/−	?	?	?	?	?	
Immunomodulators							
Dapsone	++	✓	✓	✓	✓	✓	✓

Treatment	Evidence Level	Evidence Distribution					
		ACLE	SCLE	DLE	LEP	LET	Bullous LE
Thalidomide	++	✓	✓	✓	✓	?	
Lenalidomide	++	✓	✓	✓			
Biologics							
Rituximab	++	✓	✗	✗	✗		✓
Belimumab	+		✓				
Ustekinumab	+			✓	✓		
Tocilizumab	+					✓	
Laser Therapy							
Pulsed dye laser	++	✓	✓	✓	✓	✓	

*Though evidence supporting its use in CLE is weak, azathioprine may be used in pregnancy if no alternatives are available.

ACLE = acute cutaneous lupus erythematosus; SCLE = subacute cutaneous lupus erythematosus; DLE = discoid lupus erythematosus; LEP = lupus erythematosus panniculitis; LET = lupus erythematosus tumidus

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Table 2

Current clinical trials for lupus erythematosus treatment.

Treatment	Condition(s)	Phase	Enrollment	Start	Completion
Biologics					
ALX-0061 (anti-IL-6R)	SLE	2	300	Jul ’15	Mar ’18
Anifrolumab (anti-IFNAR1)	SLE	3	360	Jul ’15	Oct ’18
BIIB059 (anti-BDCA-2)	SLE	1	108	Apr ’14	Jun ’16
Brentuximab vedotin (anti-CD30)	SLE	2	40	Jul ’15	Apr ’17
BT063 (anti-IL-10)	SLE	2	36	Aug ’15	Aug ’17
Lulizumab pegol (anti-CD28)	SLE	2	350	Nov ’14	Mar ’17
Milatuzumab (anti-CD74)	CLE, DLE, SLE	1–2	30	Jan ’15	Jan ’17
Omalizumab (anti-IgE)	SLE	1	30	Oct ’12	Jul ’20
SAR113244 (anti-CCR5)	SLE	1	24	Jul ’15	Sep ’16
Ustekinumab (anti-IL-12, -23)	SLE	2	100	Oct ’15	Dec ’17
Fusion Proteins					
Atacicept (TACI:Fc5)	SLE	2	306	Dec ’13	Mar ’16
Etanercept (TNFR:Fc)	CCLE, CLE, DLE	2	25	Feb ’16	Aug ’17
RSLV-132 (RNase:Fc)	SLE	2	50	Jan ’16	Jun ’17
Immunomodulators					
AMG 570	SLE	1	40	Mar ’16	Apr ’17
CC-220	SLE	2	140	Sep ’14	Aug ’16
Cenerimod	SLE	1–2	64	Jun ’15	Jan ’17
Other					
Allogeneic mesenchymal stem cells	SLE	2	81	Jul ’16	Jun ’21
Amiselimod (immunosuppressant)	SLE	1	18	Feb ’15	Jan ’17
Autologous EBV-specific cytotoxic T cells	SLE	1–2	10	Jan ’16	Jan ’19
Autologous polyclonal Tregs	CLE, DLE, SLE	1	18	Jul ’15	Dec ’17
Bortezomib (proteosome inhibitor)	SLE	2	18	Oct ’14	Dec ’16

Treatment	Condition(s)	Phase	Enrollment	Start	Completion
Dipyridamole	SLE	Unavailable	50	Feb ’13	Feb ’16
IL-2	SLE	2	132	Jan ’14	Jan ’16
MSC2364447C (Btk inhibitor)	SLE	1	24	Nov ’15	Sep ’16
Nelfinavir	SLE	2	43	Sep ’14	Dec ’16
Rigerimod (T cell inhibitor)	SLE	3	200	Dec ’15	Jun ’17
Tofacitinib (JAK inhibitor)	SLE	1	38	Aug ’15	May ’20
UVA1 radiation	CLE	Unavailable	15	Sep ’12	Sep ’17

SLE = systemic lupus erythematosus; CLE = cutaneous lupus erythematosus; DLE = discoid lupus erythematosus; CCLE = chronic cutaneous lupus erythematosus