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Treatment of Cutaneous Lupus

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Abstract

Cutaneous lupus erythematosus (CLE) is an autoimmune, inflammatory skin disease seen in patients with or without systemic lupus erythematosus (SLE). The management of CLE includes treatment and prevention of lesions, as well as routine assessment for systemic disease. Treatment options include both topical and systemic therapies. Topical therapies include corticosteroids and calcineurin inhibitors. Systemic therapies generally fall under one of three categories: antimalarials, immunomodulators, such as dapsone and thalidomide, and immunosuppressives, such as methotrexate and mycophenolate. Evidence for the treatment of CLE is limited by few prospective studies, as well as lack of a validated outcome measure up until recently. There is good evidence to support the use of topical steroids and calcineurin inhibitors, though most of these trials have not used placebo or vehicle controls. There have been no randomized placebo-controlled trials evaluating systemic therapies for the treatment of CLE.

Keywords

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

Introduction

Cutaneous lupus erythematosus (CLE) is an autoimmune, inflammatory skin disease that encompasses lupus specific skin lesions seen in patients with or without systemic lupus erythematosus (SLE). CLE has three major subtypes: chronic CLE (CCLE), subacute CLE (SCLE), and acute CLE (ACLE) [1].

CCLE is further sub-categorized into localized discoid lupus erythematosus (DLE), generalized DLE, hypertrophic LE, lupus panniculitis, lupus erythematosus tumidus, and chilblain lupus. DLE, which presents as erythematous, indurated plaques and papules, may resolve with significant scarring, dyspigmentation, and alopecia [2]. DLE is the most common form of CCLE and, when confined to the head and neck, is rarely associated with SLE [3]. SCLE, which presents as photodistributed papulosquamous or annular-polycyclic plaques, tends to heal without scarring and is commonly associated with photosensitivity and anti-SSA antibodies [4]. ACLE, which usually presents as malar erythema but can be generalized, is a very specific marker for systemic disease, as virtually 100% of patients with ACLE have SLE [3].

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The goals of treatment are to reduce activity (erythema, scale) and to minimize damage (dyspigmentation, scarring, atrophy). Treatment options are generally the same across the different CLE subtypes. Evidence for the treatment of CLE is comprised mostly of case reports, case series, and retrospective studies. Prospective studies and randomized controlled trials are few. Seven randomized controlled trials have been conducted. Five trials have been for topical therapies, and two had placebo or vehicle controls. Two trials evaluated systemic therapies, neither of which was placebo-controlled. Several recent review articles have detailed the current treatments options, as well as the evidence for their use [4,5].

Assessment for Systemic Disease

Although patients with CLE do not all have SLE, it is important to routinely assess CLE patients for systemic disease. Twenty percent of patients with generalized DLE and five percent of patients with localized DLE progress to SLE [3]. About half of patients with SCLE meet American College Rheumatology criteria for SLE, and approximately 10% are felt to be at risk for serious systemic involvement [6]. In a population-based study of CLE patients, 12.2% (19/156) of patients, including both CCLE and SCLE subtypes, progressed to SLE over a mean of eight years [7]. As such, patients are evaluated for systemic signs and symptoms (e.g. fatigue, fevers, arthritis, oral ulcers, nonscarring alopecia) at each visit. An anti-nuclear antibody test, complete blood count, and urinalysis are performed at least once a year.

Prevention

It is essential to emphasize the importance of avoiding sunlight and artificial sources of ultraviolet (UV) radiation, as well as to advocate the daily use of broad-spectrum sunscreen. The induction of CLE lesions by UVA and UVB radiation has been demonstrated [5]. Patients should be counseled to avoid the sun during peak hours, minimize travel to equatorial regions of the world, and avoid tanning salons. Furthermore, UVA can permeate window glass and induce lesions, but the likelihood of this occurring depends on the degree of protective coating and duration of exposure [5]. Recently, the risk of worsening disease in photosensitive conditions due to cumulative low-dose UV exposure from indoor fluorescent light bulbs has been described [8]. It is thus recommended that patients with CLE use compact bulbs with the lowest UV irradiance, in an effort to minimize the damage from chronic UV exposure [8].

Broad-spectrum sunscreen is essential in preventing new lesions. A small double-blinded, intra-individual open-label study of three commercially available sunscreens demonstrated that sunscreen is effective in preventing formation of CLE lesions, though there was varying efficacy amongst those tested [9]. One of these sunscreens, which provided coverage for the UVA/UVB and visible light spectrum, was efficacious in 100% (11/11) of patients. Sunscreen with at least sun protection factor (SPF) 50 and UVA/UVB coverage, such as Neutrogena with Helioplex (Neutrogena, Los Angeles, CA) or Anthelios with Mexoryl (La Roche-Posay, France) are typically recommended.

Photoprotective clothing is an option for patients who require or desire additional photoprotection. Studies from radiation laboratories in Australia and the United Kingdom have demonstrated that about 90% of summer clothing provides protection that is equivalent to sunscreens of SPF 30 or higher [10], so even wearing long clothes that are not marketed as photoprotective can offer reliable additional protection.

Since sunlight is required in the synthesis of vitamin D, is important to check the level of 25-hydroxyvitamin D in CLE patients, who are actively avoiding sun exposure and routinely

applying sunscreen. Supplementation with at least 400IU of vitamin D3 (cholecalciferol) is recommended in these patients [5].

Topical Therapies

In treating existing lesions, the first class of drugs to consider is topical medications, which includes steroids, calcineurin inhibitors, and physical treatments.

Topical Steroids

Topical corticosteroids are an essential part of treating all subtypes of CLE. Despite their pervasive use, there has only been one randomized controlled trial, which compared a high potency steroid with a low potency steroid, in the treatment of DLE [11]. This study reported 27% (10/37) of patients improving on fluocinonide 0.05% and 10% (4/41) of patients improving on hydrocortisone 1%, suggesting that a high potency steroid is more efficacious than a low potency steroid. One half-side comparison study and two observational studies demonstrated improvement of CLE with topical steroid treatment [4].

When choosing the appropriate topical steroid, both potency and vehicle are important factors to consider. The choice in potency is based on the location of the skin lesion(s). For thin areas of skin (e.g. face), a low potency steroid, such as fluocinolone acetonide 0.01% or hydrocortisone butyrate 1%, is a good option. For the trunk and extremities, a mid potency steroid, such as triamcinolone acetonide or betamethasone valerate, is appropriate. For thick areas of skin (e.g. scalp, soles, palms), a high potency steroid, such as clobetasol propionate, is often required. The choice in vehicle is also an important consideration. For the body, creams and ointments are best. Usually treatment is started with a cream, as most patients can tolerate daily application of them, but some patients may require an ointment. For the scalp, foams and solutions are effective vehicles. Moreover, DLE may be responsive to intralesional steroids.

The side effects of topical steroids are well-known. They include, but are not limited to, skin atrophy, steroid-induced rosacea, and telangiectasias. To minimize these side effects, topical steroids should be applied for a limited number of weeks and intermittently, such that the skin has steroid-free intervals. Similarly, intralesional steroid injections should use the minimum concentration of drug necessary to achieve results and require at least four weeks between injections. To avoid systemic absorption and suppression of the hypothalamic-pituitary axis, no more than 45g per week of high potency or 100g per week of low to mid potency topical steroid should be applied (without occlusion) [12].

Topical Calcineurin Inhibitors

In recent years, there have been multiple reports of using topical calcineurin inhibitors (tacrolimus or pimecrolimus) to treat various subtypes of CLE, including DLE, tumid LE, SCLE, and ACLE [4]. There have been two randomized controlled trials looking at the efficacy of tacrolimus in treating CLE. One double-blind randomized controlled bilateral comparison trial looked at the use of tacrolimus 0.1% ointment versus clobetasol proprionate 0.05% ointment in the treatment of different CLE subtypes on the face [13]. This study found equal efficacy in obtaining partial response over four weeks. A more recent double-blind, vehicle-controlled randomized trial evaluated tacrolimus 0.1% ointment in different CLE subtypes and demonstrated a significantly higher response rate in patients treated with tacrolimus 0.1% compared to the vehicle [5]. There is also data to suggest that the combination of tacrolimus and clobetasol is more effective than tacrolimus alone [14].

Pimecrolimus, more lipophilic than tacrolimus, has been evaluated in several studies [5]. One double-blind randomized controlled trial comparing pimecrolimus 1% cream with

betamethasone 17-valerate 0.1% cream demonstrated significant improvement with both treatments, using each patient as his/her own control [15]. There was no significant difference between groups.

One obvious advantage of these medications is their lack of steroid-associated systemic side effects. Side effects with topical calcineurin inhibitors have been mild or minimal. The most common side effect is pruritis, burning and/or increased erythema at the site of application, however, if tolerable, does not warrant cessation of therapy [16]. Both tacrolimus and pimecrolimus carry a controversial "black box" warning due to a potential increased risk for malignancy, despite no scientific evidence at this time to suggest a causal relationship between topical calcineurin inhibitors and malignancy [17]. Long-term safety studies with postmarketing surveillance data are in progress [17].

Since there is no associated atrophy with tacrolimus or pimecrolimus, calcineurin inhibitors have obvious advantages over steroids for topical treatment of the face and ears. However, topical calcineurin inhibitors are expensive and not always covered by prescription drug plans.

R-salbutamol

R-salbutamol is a β_2-adrenergic receptor agonist that binds $CD4^+$ T lymphocytes, Langerhans cells, and macrophages, thereby inhibiting expression of inflammatory genes and the production of their proinflammatory gene products. Although it did not meet its primary endpoint, a double-blind placebo-controlled randomized study of R-salbutamol for treatment of DLE demonstrated significantly better secondary outcomes (scaling, hypertrophy, induration, pain, itching, and patient global assessment) in the R-salbutamol group compared to the placebo group [18]. The primary endpoint, involving change in an unvalidated outcome measure, was equivalent between both groups.

Imiquimod

Imiquimod is a topical immunomodulator with potent antiviral and antineoplastic properties, most commonly prescribed for warts, basal cell carcinoma, and actinic keratoses. There have been several case reports of improvement in DLE with its use [5]. A disadvantage of imiquimod is that it stimulates toll-like receptors on dendritic cells, which are abundant in the skin, and thus could, at least in theory, exacerbate inflammatory conditions.

Physical Treatments

As trauma to the skin is known to induce DLE lesions, the consideration of physical treatments, such as laser therapy, cryotherapy, and dermabrasion, requires a comprehensive discussion on the risks and benefits of these procedures. Laser therapy, pulsed dye or argon, has been described in case reports and series to be helpful in treating CLE [4]. An open prospective study assessing pulsed dye laser therapy demonstrated a decrease in skin activity in patients with recalcitrant DLE [19]. Side effects of laser therapy include purpura, pain, and post-inflammatory dyspigmentation. Cryotherapy has also been shown to be effective in patients refractory to topical and systemic treatments [5].

Systemic Therapies

When topical therapies alone are ineffective in CLE or disease is widespread, systemic therapies are the next step. There are essentially three groups of drugs to consider: antimalarials, immunosuppressives, immunomodulators. Note that it is often helpful to continue treating topically, as there can be therapeutic benefit from adjuvant spot treatment of individual lesions.

Antimalarials

Three antimalarials are currently used in the treatment of CLE: hydroxychloroquine, chloroquine, and quinacrine. Several mechanisms have been proposed to explain the therapeutic benefit of antimalarials in CLE: antigen presentation suppression, inhibition of prostaglandin and cytokine synthesis, lysosomal stabilization, inhibition of toll-like receptor signaling, and photoprotective properties [20,21]. There have been two randomized controlled trials demonstrating improvement in patients taking hydroxychloroquine or chloroquine, though neither was placebo-controlled [22,23]. These data are supported by numerous case reports and case series. The benefit of hydroxychloroquine-quinacrine combination therapy in the treatment of CLE has been explored in a study using a validated outcome measure, though the outcome measure was used in an unvalidated manner by retrospective assignment [24]. The benefit of chloroquine-quinacrine combination therapy in CLE patients has been reported in two studies, which used clinical criteria to demonstrate improvement [25,26].

Hydroxychloroquine is first-line antimalarial therapy, due to a lower incidence of retinal toxicity compared to chloroquine [27]. In the CLE population, response to hydroxychloroquine ranges from 50% to 70% [28,29]. Quinacrine, which can only be obtained at a compounding pharmacy, is used in combination with hydroxychloroquine or chloroquine. Use of antimalarials involves an algorithmic approach. If a patient fails first-line hydroxychloroquine, quinacrine is usually added. If the patient has previously failed hydroxychloroquine-quinacrine combination therapy or does not have access to a compounding pharmacy, chloroquine is considered. Chloroquine-quinacrine combination therapy is used when a patient has failed hydroxychloroquine-quinacrine combination therapy and/or chloroquine monotherapy.

Since hydroxychloroquine and chloroquine are not stored in fat, dosing is based on ideal body weight: 6.5 mg/kg/day and 3 mg/kg/day, respectively. Quinacrine is generally dosed at 100mg per day. Aplastic anemia has been reported to be associated with the use of quinacrine at higher doses [30]. It is important to remember that antimalarials take six to eight weeks to take effect and also remain in the tissue for months after discontinuation. Screening guidelines for hydroxychloroquine and chloroquine-induced retinal toxicity vary, with the most recent from the American Academy of Ophthalmology which recommends screening patients based on their risk status [31]. One approach is to obtain a visual field test and dilated retinal exam every six months for patients on hydroxychloroquine and every three to four months for patients on chloroquine. Generally, antimalarials are well-tolerated, though gastrointestinal upset can occur. Hydroxychloroquine and chloroquine can cause gray/blue-black hyperpigmentation of the skin, myopathy, and white discoloration of lighter hair. In rare patients that develop an adverse non-urticarial cutaneous reaction to hydroxychloroquine, chloroquine can be used without recurrence of the rash. Quinacrine can cause yellow discoloration of the skin. Although the literature recommends laboratory evaluation for hematologic, hepatic, and renal toxicity associated with antimalarials, this recommendation does not appear to be cost-effective [5], and routine laboratory tests for toxicity related to antimalarials are not recommended.

Data from several retrospective cohort studies suggest that smokers have a decreased response to antimalarials in the treatment of CLE [32,33,34]. It has been proposed that nicotine may enhance the elimination of antimalarials at the level of the cytochrome p450 enzyme complex, or nicotine may inhibit antimalarials from lysosomal uptake, since both are sequestered in the lysosome [32]. Aside from the overall health benefits of smoking cessation, these data suggest that smoking cessation may be beneficial in CLE patients being treated with antimalarials.

Immunosuppressives

As with other inflammatory conditions, CLE can respond to systemic corticosteroids, though response to steroids in DLE is unreliable. A short course of steroids can be very helpful during flares and when initiating antimalarials or non-steroidal immunosuppressive drugs, which may take several weeks to demonstrate benefit. Systemic steroids should not be used as long-term therapy, given their well-known serious side effects.

Immunosuppressives play a valuable role in treating antimalarial-refractory patients. Methotrexate has been shown in multiple case reports and two retrospective studies to be effective in multiple subtypes of CLE [35,36]. Folate replacement and routine laboratory monitoring for bone marrow suppression and hepatotoxicity is required. For patients who do not tolerate oral delivery of the drug, intramuscular delivery is an option. Mycophenolate has been shown in multiple case reports to be effective in treating all subtypes of CLE [4]. In a prospective nonrandomized open pilot study, mycophenolate was shown to be beneficial in treating SCLE patients who had been resistant to at least one standard therapy, defined as steroids (topical or systemic) or antimalarials [37]. Routine laboratory monitoring for hematologic, renal, and hepatic toxicity is necessary. Mycophenolate mofetil is generally well-tolerate though gastrointestinal upset and diarrhea are the more commonly reported side effects. Mycophenolate sodium, which is enteric-coated, has been associated with fewer gastrointestinal side effects. Azathioprine can also be effective in DLE [38]. When starting azathioprine, a low dose of 50mg a day is used initially and increased by 25mg every two weeks, as laboratory monitoring allows, until the minimum effective dose is achieved. An alternative approach is checking the enzyme activity of thiopurine methyltransferase (TPMT) prior to initiating treatment and then starting at a higher dose if TPMT activity is sufficient. Routine laboratory monitoring for hematologic and hepatic toxicity is also required.

Cyclophosphamide and cyclosporine can be used, usually in the context of significant organ involvement beyond the skin. Improvement of CLE lesions with these medications has been reported [5]. However, due to their significant toxicity profile, they are rarely used in CLE patients and reserved for refractory CLE patients with SLE.

Rituximab has been used successfully in several case reports involving patients with CLE, including bullous lupus, that were refractory to combinations of antimalarials, immunomodulators, and immunosuppressives [5,39]. Other biologic therapies, such as tumor necrosis factor-alpha (TNF-α inhibitors, have also been reported as useful in the treatment of CLE, although infliximab, etanercept, and adalimumab have also been associated with the induction of various CLE subtype lesions [5]. Systematic studies are needed to further evaluate biologic therapies.

Immunomodulators

Dapsone, known for its antimicrobial properties, is also an immunomodulatory agent effective in the treatment of bullous lupus erythematosus, lupus panniculitis, SCLE, and possibly DLE. Three case series, when combined, demonstrated an improvement in 55% (30/55) of CLE patients [4]. Dapsone causes a dose-related hemolysis and methemoglobinemia. All patients should be screened for glucose-6-phosphate dehyrogenase (G6PD) deficiency prior to initiation. Rarely, dapsone causes agranulocytosis or a hypersensitivity reaction, which is characterized by fever, skin eruption, and internal organ involvement. Dosing of dapsone ranges from 25 to 150mg per day, though a maximum of 200mg is allowable. When initiating dapsone, low doses of 50mg a day are used initially, and increased by 25mg a week, with weekly monitoring of blood counts and liver tests until

the minimum effective dose is achieved. Routine monitoring for hematologic and hepatic toxicity is required.

Thalidomide is an immunomodulatory agent that has multiple modes of action on the immune system. There is a host of case series supporting the use of thalidomide for CCLE, SCLE, and tumid LE [40]. Dosing of thalidomide generally ranges from 50 to 100mg per day. Patients often experience relapse of their disease when thalidomide is stopped so continuation may be necessary to maintain remission [40]. Thalidomide is teratogenic, causing phocomelia, and can only be used in women of childbearing potential if they have an effective form of contraception. The manufacturer has established a System for Thalidomide Education and Prescribing Safety (S.T.E.P.S) program, to control access to the drug, educate practitioners, pharmacists, and patients, and monitor compliance [41]. Peripheral neuropathy from thalidomide typically presents as a distal sensory neuropathy characterized by paresthesia. This neuropathy may be slow to resolve and can be irreversible. Patients should obtain nerve conduction testing prior to initiation and every six months thereafter. Although the relationship between dose and peripheral neuropathy is controversial, the lowest effective dose should always be used [42]. Thromboembolic events have been reported in dermatologic patients taking thalidomide [40]. Guidelines for thrombotic prophylaxis do not exist, but the continuation of antimalarials is likely beneficial due to their anti-platelet effects [43]. If this is not possible, then use of aspirin may be helpful [40]. More common and less severe side effects of thalidomide include drowsiness and constipation.

More recently, lenalidomide, a structural derivative of thalidomide, has been shown to be a potential treatment for patients with refractory severe DLE, though larger studies are necessary [44]. There is some concern for increased activation of T cells with lenalidomide, which potentially could trigger SLE symptoms, although there does not appear to be as great a risk of peripheral neuropathy [5].

Improvement of SCLE lesions with leflunomide has been described in one case report [5]. However, the induction of SCLE with leflunomide has been described in eight patients [5]. The risk of CLE induction and toxicity profile of leflunomide argues against routine use of this medication in CLE patients.

Other systemic therapies

Intravenous immunoglobulins (IVIG) have been reported in several case reports to be effective [5]. IVIG is generally well-tolerated. Headaches are reported as the most common side effect, but rarely skin eruptions, renal insufficiency, and thrombotic events can occur [45]. IVIG is a promising therapy for severe CLE refractory to all other forms of treatment, but systematic studies evaluating its efficacy are needed.

Systemic retinoids, a group of compounds structurally similar to vitamin A, are most commonly used in treating acne and psoriasis but have also been evaluated in the treatment of CLE. In a double-blinded randomized controlled trial comparing acitretin to hydroxychloroquine, about half of patients demonstrated subjective improvement with acetretin [22]. Isotretinoin has also been used successfully in treating DLE and SCLE, as reported in multiple case reports and open studies [5]. Importantly, isotretinoin and acetretin are teratogens and thus effective contraception is required during and after treatment. Routine laboratory monitoring for hyperlipidemia and hepatotoxicity is required. Retinoids are also associated with xerostomia, xerophthalmia, joint pains, and arthralgia. They are not used frequently due to their unfavorable mucocutaneous and musculoskeletal side effect profile, particularly as patients with CLE may also have SLE or Sjögren’s Syndrome.

Future Directions

In 2005, the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) was developed and validated as an outcome measure for CLE that measures disease activity and damage separately, demonstrating good content validity, as well as excellent inter-rater and intra-rater reliability amongst both dermatologists and rheumatologists [46,47]. Since its development, the CLASI has been used in several prospective studies involving the most common subsets of CLE [19,37]. The CLASI, favored by international consensus, is a useful clinical instrument to evaluate response of patients to therapies [48,49]. Recent studies have determined the minimal change in CLASI activity score that correlates with clinically significant improvement [48].

The CLASI was designed to capture disease severity for all common subsets of CLE, which is possible since erythema and scale are seen in nearly all patients who would be examined systemically in clinical trials. As such, the CLASI is a simple tool that measures signs that have been proven to be amenable to change and unambiguous in their meaning [50,51]. Specifically, surface area is not measured because of the small surface area frequently involved in CLE, particularly in patients with DLE of the scalp and face. It has been proposed that more complicated instruments may be needed for rarer subsets, such as lupus panniculitis, which is seen in 2–3% of CLE patients [52]. Nevertheless, complex instruments that describe features of rare CLE subsets are not optimal for the majority of studies.

The CLASI provides a standardized objective outcome measure when evaluating treatments for CLE and also facilitates design of randomized controlled trials that are lacking in this field. Currently, there are two new investigational drugs being evaluated for the treatment of CLE (http://clinicaltrials.gov), using the CLASI as an outcome measure. In addition, the CLASI is being used to evaluate skin disease in a number of international SLE trials.

Conclusion

The management of CLE includes routine assessment for systemic disease, as well prevention of new lesions and treatment of existing lesions. Prevention is achieved by optimal protection against UV exposure, with broad-spectrum sunscreen as an effective means of preventing development of UV-induced CLE. Treatment includes topical and systemic options. There is good evidence to support the use of topical steroids and topical calcineurin inhibitors. While there are no randomized placebo-controlled trials evaluating the efficacy of antimalarials, they are accepted as first-line systemic therapy when topical therapies are ineffective. If the antimalarial treatment algorithm detailed earlier is insufficient, an immunosuppressive or immunomodulator is added. IVIG and rituximab are considered in patients refractory to various combinations of antimalarials and immunosuppressives/immunomodulators. With the introduction of a validated outcome measure for CLE, improved evaluation of treatment efficacy and promising new therapies are on the horizon.

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