Treatment of Cutaneous Lupus Erythematosus

Review and Assessment of Treatment Benefits Based on Oxford Centre for Evidence-based Medicine Criteria

[a]R.R. WINKELMANN, BM, MS-IV; [b]GRACE K. KIM, DO; [c]JAMES Q. DEL ROSSO, DO

[a]Ohio University Heritage College of Osteopathic Medicine, Athens, Ohio; [b]Valley Hospital Medical Center, Las Vegas, Nevada; [c]Valley Hospital Medical Center, Las Vegas, Nevada; Touro University College of Osteopathic Medicine, Henderson, Nevada; Las Vegas Skin and Cancer Clinics, Henderson, Nevada

ABSTRACT

The treatment of cutaneous lupus erythematosus is centered upon formulating a regimen of topical and systemic therapies designed to reduce disease activity and minimize cosmetic damage. Sun avoidance and sunscreen are important preventative measures proven to minimize cutaneous lupus erythematosus exacerbations. Limited disease is typically managed with topical corticosteroids or calcineurin inhibitors. Antimalarial therapy is the gold standard of systemic therapy. Many other treatments have been studied in patients with recalcitrant cutaneous lupus erythematosus, and their use must be evaluated based on individual risk-benefit concerns. R-salbutamol and pulsed dye laser therapy have proven to be effective topical alternatives. Additional systemic agents include retinoids, immunosuppressants, immunomodulators, biologics, and other experimental therapies with novel modes of action. According to the Oxford Centre for Evidence-based Medicine criteria for evaluating the strength of evidence supporting an individual treatment measure, no therapy for cutaneous lupus erythematosus has achieved Level 1 status. This demonstrates the need for randomized, controlled trials and systematic reviews of all cutaneous lupus erythematosus interventions in order to meet increasing standards and demand for evidence-based practice. (*J Clin Aesthet Dermatol.* 2013;6(1):27–38.)

Cutaneous lupus erythematosus (CLE) is the second most common presenting symptom of autoimmune lupus erythematosus (LE). Lesions precede the onset of systemic symptoms in 25 percent of patients, many of whom present to dermatologists for their initial evaluation.[1] Prompt diagnosis of CLE requires a thorough understanding of the cutaneous manifestations and clinical spectrum of lupus. The Gilliam classification scheme differentiates LE-specific CLE based on the presence of interface dermatitis.[2] LE-specific cutaneous lesions are divided into the following three categories: acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE). Further subdivisions of CCLE include discoid LE (DLE) and other atypical LE-specific lesions, including chilblain LE, LE tumidus (LET), and LE panniculitis, which cause cutaneous disease unassociated with interface dermatitis.

ACLE accounts for 6.1 percent of patients with CLE and is characterized by the classic "butterfly rash" overlying the malar cheeks and nose.[3,4] The rash is photosensitive and strongly associated with exacerbations of systemic lupus erythematosus (SLE).[5] Lesions typically resolve without atrophic scarring although areas of postinflammatory dyspigmentation may persist.[4] Of patients with CLE, 18.4 percent are diagnosed with SCLE.[3] Patients experience marked photosensitivity and develop predominantly annular or papulosquamous lesions on sun-exposed areas.[6] Half of the patients with SCLE have four or more diagnostic features of SLE, and 70 percent test positive for anti-Ro antibodies.[7,8] Lesions heal without scarring, but hypopigmentation and telangiectasias often endure.[5] DLE is the most common form of CCLE and affects 67.5 percent of all patients with CLE.[3] Classic DLE presents as erythematous, coin-shaped plaques with central hyperkeratosis.[6] Seventy percent of cases are limited to the head and scalp and are rarely associated with

DISCLOSURE: Mr. Winkelmann and Dr. Kim report no relevant conflicts of interest. Dr. Del Rosso serves as a consultant, researcher, and/or speaker for Allergan, Bayer Dermatology, Eisai, Galderma, LeoPharma, Medicis, Onset Dermatologics, Pharmaderm, Primus, Promius, Ranbaxy, TriaBeauty, Unilever, Valeant, and Warner-Chilcott.

ADDRESS CORRESPONDENCE TO: R.R. Winkelmann; E-mail: rwink@gmail.com

TABLE 1. Oxford Centre for Evidence-Based Medicine 2011 Treatment Benefit Levels of Evidence[15]

QUESTION	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 5
Does this intervention help?	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Nonrandomized controlled cohort/follow-up study	Case series, case-controlled studies, or historically controlled studies	Mechanism-based reasoning

systemic disease.[5,9] Diagnosis is made based on the clinical findings of erythema, follicular plugging, photosensitivity, dyspigmentation, telangiectasias, and skin atrophy.[10,11] In contrast to SCLE, scarring and skin atrophy are characteristic of DLE.[12]

The treatment of CLE is centered upon formulating a regimen of topical and systemic therapies designed to reduce disease activity and minimize cosmetic damage. Dosing adjustments may be necessary throughout treatment due to the unpredictable nature of CLE activity. Although the combined risk of conversion to SLE in patients with SCLE and DLE is 12.2 percent, all patients with CLE should be evaluated initially and throughout follow up for signs of systemic disease (i.e., arthralgia, serositis, oral ulcers, renal disease, and anemia).[13,14]

Currently, no medications have been approved specifically for the treatment of CLE. Many of the drugs described in the literature are licensed for use in SLE or other immunological disorders and are prescribed similarly for each CLE subtype. This review summarizes the current therapeutic options for CLE and highlights studies from the literature supporting their efficacy. Up-to-date information is included on prevention and topical, systemic, experimental, and controversial therapies. Due to the growing emphasis on practicing evidence-based medicine, the strength of studies demonstrating the therapeutic benefits of each treatment has been evaluated based on criteria published by the Oxford Centre for Evidence-Based Medicine (OCEBM)(Table 1).[15] The implications of this classification scheme for the clinical applicability of classic and novel therapeutic interventions are discussed at the end of the manuscript.

PREVENTION

Ultraviolet A (UVA) and B (UVB) irradiation have been shown to induce lesions in patients with CLE.[16] Therefore, educating patients about minimizing sun and UV exposure is an important part of a treatment plan. Kuhn et al[17] recommend patients with CLE avoid sunbathing, tanning salons, travel to regions near the equator, outdoor jobs, and light bulbs with high UV irradiance. Consistent protection with sunscreen has been associated with better clinical outcomes in SLE.[18] Patients should apply 50 or greater sun protection factor (SPF) sunscreen in adequate amounts ($2mg/cm^2$) at least 20 to 30 minutes before known exposure.[17] This recommendation is supported by a vehicle-controlled, randomized, intra-individual, comparative, double-blind study, also by Kuhn et al, demonstrating 100-percent protection from UVA and UVB irradiation in 25 patients with photosensitive CLE using broad spectrum sunscreen.[19] In addition, Vitamin D supplementation (400IU/day) should always be considered in patients advised to avoid the sun.[17]

TOPICAL THERAPY

Topical corticosteroids. Topical corticosteroids (CS) effectively reduce inflammatory symptoms in all types of CLE. Despite years of clinical use, only one randomized, controlled trial exists in which high potency 0.05% fluocinonide cream was more effective than low potency 1.0% hydrocortisone cream in 78 patients with DLE.[9] Topical CS therapy is known to cause atrophy, telangiectasia, and steroid-induced rosacea-like dermatitis with chronic use.[17] To minimize side effects, a topical CS should be prescribed at the lowest potency required to achieve resolution for the shortest amount of time. In general, low-mid-potency CS (e.g., methylprednisolone) should be used on the face, mid-potency CS (e.g., triamcinolone acetonide, betamethasone valerate) on the trunk and extremities, and high-potency CS (e.g., clobetasol) on the palms and soles where skin is thickest.[11] Intralesional therapy with 2.5 to 10mg/mL triamcinolone solution may be of use in patients with localized DLE refractory to other treatment. Injections require careful administration to avoid subcutaneous atrophy.[19]

Calcineurin inhibitors. Due to the unwanted side effects of topical CS, calcineurin inhibitors, tacrolimus and pimecrolimus, have been studied for their long-term therapeutic potential in CLE. Drugs in this class work by forming a complex with macrophilin-12 that inhibits the calcineurin mediated dephosphorylation of nuclear transcription factor of activated T cells (NF-AT).[20] Phosphorylated NK-AT is responsible for the transcription of many inflammatory modulators within T cells.[21] Since the first reports of success with calcineurin inhibitors treating lupus skin lesions in 2002, several studies have demonstrated their efficacy in CLE.[22] Side effects are limited to transient burning, erythema, and irritation.[22] Without the risk of skin atrophy, calcineurin inhibitors are particularly effective in sensitive areas of skin including the face, neck, and intertriginous areas.[23,24]

Tacrolimus, available in a 0.1% and 0.03% ointment formulation, is licensed for use in atopic dermatitis and has had off-label success treating psoriasis, lichen planus, pyoderma gangrenosum, and CLE.[25–27] In a randomized, double-blind trial, 20 patients with CLE (13 malar rash of SLE, 4 DLE, 1 SCLE) were treated with 0.1% tacrolimus and 0.05% clobetasol proprionate ointments, each applied to one

side of the face twice daily for four weeks.[28] Improvement of CLE lesions was observed in both treatment groups without a significant difference in overall efficacy. However, 61 percent of patients treated with steroids developed telangiectasias, a finding that highlights the steroid-sparing effects of tacrolimus.

In 2011, a multicenter, randomized, double-blind, vehicle-controlled trial evaluated the efficacy of 0.1% tacrolimus ointment in 20 patients treated twice per day for 12 weeks.[29] Significant improvement of erythema and edema was found in lesions treated with tacrolimus after 28 and 56 days, but not after 84 days when compared to vehicle-treated lesions. The least improvement was noted in patients with older, hyperkeratotic DLE lesions. No major side effects were reported. Findings of this study suggest tacrolimus provides temporary benefit especially in acute, edematous, nonhyperkeratotic CLE lesions. Another recent study also found tacrolimus 0.3% in combination with clobetasol proprionate 0.05% may be more effective than 0.1% tacrolimus ointment monotherapy in the treatment of recalcitrant CLE.[30]

Pimecrolimus has the same functional activity as tacrolimus, but is more lipophilic, has higher epidermal affinity, lower penetration into the skin, and lower resorption.[22] Zabawski[31] was the first to describe moderate improvement in a single patient with facial DLE treated with pimecrolimus 1% cream.[31] In 2007, a double-blind, placebo-controlled study evaluated the use of 1% pimecrolimus cream in CLE.[32] Twenty-five patients with DLE or SCLE were treated twice daily for four weeks and evaluated by skin scores based on erythema, infiltration, scaling, and lesion diameter. Therapy was well tolerated and skin scores were reduced after four weeks of therapy from an average of 5.5 at baseline to 2.8.

A 2009 double-blind, randomized, controlled trial compared the efficacy of pimecrolimus 0.1% cream with betamethasone 17-valerate 0.1% cream in 10 patients with severe facial DLE.[33] Each drug was applied to one side of the face twice daily for eight weeks. An 87- and 73-percent decrease in clinical severity was observed in pimecrolimus and clobetasol treatment groups, respectively. No major adverse effects were reported with either therapy. The difference in outcomes between treatment groups was not statistically significant and shows pimecrolimus 0.1% cream is just as effective as betamethasone 17-valerate 0.1% cream in the treatment of DLE.

Studies indicate calcineurin inhibitors are comparable to topical CS in the treatment of CLE. The lack of atrophic side effects suggests calcineurin inhibitors are particularly appropriate for topical therapy of CLE lesions affecting the face. However, before specific recommendations can be made regarding their use, a larger number of multicenter studies on a sufficient number of patients are necessary.

R-salbutamol. R-salbutamol is a B2 adrenergic receptor agonist commonly used in the treatment of asthma.[34] Its effects are largely attributed to activation of B2 receptors on CD4 cells, monocytes, macrophages, and Langerhans cells.[35–37] In these cells, activation of B2 receptors inhibits transcription of inflammatory genes and the subsequent production of interleukin (IL)-2 and interferon (INF)-gamma. In a 2009 multicenter, randomized, placebo-controlled phase 2 trial, 37 patients with at least one new DLE lesion were randomly treated with 0.5% R-salbutamol cream (n=19) or placebo (n=18) twice daily for eight weeks.[38] Actively treated patients displayed statistically significant improvement of scaling/hypertrophy, pain, itching, ulceration, and global assessment when compared with placebo. No adverse effects were reported. This study and an earlier pilot study suggest R-salbutamol may be an effective new topical therapy alternative for DLE.[39]

Physical therapies. Therapeutic success has been reported with laser and cryotherapy in patients with CLE.[40] Although the use of argon and carbon dioxide lasers has been documented in a handful of case reports, several case studies support the effectiveness of pulsed-dye laser (PDL) therapy.[41–45] The effectiveness of PDL is attributed to the selective destruction of blood vessels within the skin followed by inflammatory modulation and disease regression.[42] Side effects of PDL are limited to localized hypopigmentation, transitory hyperpigmentation, and slight scarring.[49]

In a 1999 study, a clearance rate of 70 percent was observed in nine patients with DLE following treatment with PDL.[46] Two patients developed transient hyperpigmentation as a result of therapy. Another series of 12 patients with recalcitrant DLE demonstrated a significant reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score following three PDL treatments.[47,48] A recent, prospective, open-label study achieved a clearance rate of more than 60 percent in 14 patients with different types of CLE. Clinical analysis demonstrated improvement in telangiectatic, erythema, and scaling components, but none in atrophy, hyperkeratosis, scarring, and pigmentation. Histopathological evaluation revealed a marked decrease in dermal lymphocytic infiltrate and basal damage.[49] These studies collectively show PDL is an effective treatment of CLE, especially in patients with chronic DLE. However, when considering any physical treatment for CLE, a risk-benefit analysis is necessary due to the well-documented risk of inducing lesions with physical or laser treatments in CLE via the Koebner phenomenon.[17]

SYSTEMIC THERAPY

Antimalarial therapy. First-line systemic therapy for patients with all subtypes of CLE is the use of an oral antimalarial medication. The anti-inflammatory activity of antimalarials in CLE is not understood but attributed to its lysosomotropic properties, interference with antigen presentation, and inhibition of pro-inflammatory cytokine (e.g., IL-1, IL-2, tumor necrosis factor [TNF]-alpha) release.[17,50] Use of antimalarials in CLE was first reported in 1894 with the successful treatment of DLE with chinine.[51] Today, hydroxychloroquine (HQ), chloroquine (CQ), and quinacrine are the most commonly used antimalarials in the treatment of CLE. Contraindications to antimalarial therapy include patients with hypersensitivity to 4-amino-quinolones, retinopathy, hematopoetic disorders, glucose-6-phosphate

TABLE 2. Combination therapy in cutaneous lupus erythematosus

DRUG	IN COMBINATION WITH	REFERENCE
Topical Corticosteroids	Tacrolimus	Madan et al[30]
HQ or CQ	Quinacrine	Feldmann et al[62]
	Tacrolimus	Averginou et al[65]
	Pimecrolimus	Averginou et al[65]
	Methotrexate	Wenzel et al[66]
	Dapsone	Lindskov et al[67]
	Mycophenolate mofetil	Sadlier et al[68]
Methotrexate	Cyclosporine	Klein et al[145]

deficiency, and myasthenia gravis.[52]

HQ has been called the cornerstone of lupus therapy due to its lower incidence of side effects compared to chloroquine.[53] In 1992, a randomized, double-blind, multicenter study related the effectiveness of HQ to acitretin in patients with different types of CLE.[54] Thirty patients receiving 400mg/day HQ exhibited 50-percent improvement and fewer side effects compared to 46-percent improvement in 28 patients receiving 50mg/day of acitretin.

The efficacy of CQ was demonstrated in a 2005 prospective, double-blind, randomized, controlled trial.[55] Seventeen patients were treated with 250mg/day CQ and 16 with 100mg/day clofazimine for six months. Of patients treated with CQ and clofazimine, 82.4 and 75 percent, respectively, had complete or near-complete remission of skin lesions. Gastrointestinal side effects were frequent in both groups and no significant difference in outcomes was evident for either treatment.

Although the most common side effects of antimalarial therapy are xerosis and skin hyperpigmentation, ocular toxicity is the most well known.[56] HQ and CQ are particularly associated with maximum daily dose related ophthalmological toxicity. However, if dosed correctly, prolonged therapy carries a minimal risk of inducing retinopathy.[57] Current maximum dosing recommendations in adults are 6.0 to 6.5 and 3.5 to 4.0mg/kg ideal body weight for HQ and CQ, respectively. Ideal body weight is calculated using the equation: [(body length (cm)-100)-10%] in male patients and [(body length (cm)-100)-15%] for female patients.[17] HQ has a lower risk of retinal toxicity than CQ, but is less efficacious.[58] Other side effects of HQ and CQ are gastrointestinal discomfort, central nervous system effects, white discoloration of the hair, myopathy, pruritus, and hyperpigmentation of the skin, nails, and mucous membranes.[17]

Quinacrine was shown to be successful in the treatment of CLE by several studies in the mid-20th century.[17,59,60] However, due to its unique risks of bone marrow suppression and yellow discoloration of the skin and mucosa, its use diminished in favor of HQ and CQ. Despite the efficacy of HQ and CQ in CLE, their use is limited by the risk of irreversible retinopathy and should never be prescribed together.[15] Recent studies show that combination therapy of HQ or CQ with quinacrine, which has no retinal toxicity, has synergistic efficacy without an increased risk of retinopathy.[61–64] The synergistic effects of combination therapy have also been reported for patients on HQ or CQ in combination with calcineurin inhibitors, methotrexate, dapsone, and mycophenolate mofetil (Table 2).[65–68] More studies are needed to examine the use of combination therapy in CLE therapy. Currently, 100mg/day quinacrine is advised as an adjuvant to HQ and CQ in patients with refractory disease or as monotherapy in patients with ocular alterations or other contraindications to HQ or CQ.[69]

Despite recommendations in the literature for routine laboratory evaluation of patients on antimalarial therapy, this has not been shown to be a particularly cost-effective measure.[17] However, due to the risks of retinopathy, approval from an ophthalmologist is recommended prior to initiating therapy. Patients taking antimalarials should be advised that the drugs take several weeks to achieve full effects (4–6 weeks for HQ and CQ, 6–8 weeks for quinacrine) and stay in the tissue for several months following drug cessation.[70] Smokers have decreased response to antimalarial therapy.[71–73] Therefore, smoking cessation is advised for all CLE patients and especially those receiving antimalarial therapy.

Systemic corticosteroids. Long-term therapy with systemic CS is avoided in CLE patients due to the well-known risks of developing diabetes, osteoporosis, and Cushing's syndrome. However, short courses of oral CS take advantage of their rapid onset to treat highly acute lesions or as bridge therapy until antimalarial drugs reach therapeutic levels. Generally, a standard dose of 0.5 to 1.0mg/kg/day is tapered after 2 to 4 weeks of therapy.[17]

Oral retinoids. Acitretin and isotretinoin are classified as second-line therapies for the treatment of CLE by the American Academy of Dermatology guidelines.[74] Retinoids are commonly employed for the treatment of acne, psoriasis, and T cell lymphomas.[76] The first successful use of a vitamin A derivative in the treatment of CLE was reported using etretinate in 1985.[75] Acitretin has since replaced etretinate because of its shorter half-life. The use of acitretin in CLE is

supported by a previously mentioned randomized, double-blind, multicenter study in which 50mg/day of acitretin was as successful in treating 28 patients with CLE as 400mg/day HQ in 30 patients.[54] Retinoids are particularly useful in patients with hypertrophic lesions on the palms and soles.[11] Treatment of DLE and SCLE with isoretinoin has been reported in approximately 50 patients with a success rate of up to 86.9 percent.[76–80]

The recommended dose for acitretin and isotretinoin in CLE is 0.2 to 1.0mg/kg bodyweight/day.[52] Common side effects include xerosis and xerophthalmia while gastrointestinal problems, skeletal toxicity, hair loss, depression, pseudotumor cerebri, myalgia, and arthralgia occur less frequently.[11,81] Isotretinoin and acitretin are both teratogenic and potential for pregnancy must be carefully assessed in female patients. Contraception is necessary before and after treatment (1 month for isoretinoin, 2 months for acitretin) to ensure full elimination of the drug from the body. Hyperlipidemia and hepatotoxicity are also common with retinoid use due to their effects on lipid metabolism.[82] Therefore, the risks and benefits of retinoid therapy must be considered in patients with dyslipidemias, diabetes, metabolic syndrome, and other cardiovascular risk factors.

IMMUNOSUPPRESSANTS

Methotrexate. Methotrexate (MTX) is a folic acid analog that inhibits the enzyme dihydrofolate reductase and, as a result, the proliferation of T cell populations.[83] MTX is well known for its use in rheumatoid arthritis and was first considered for the treatment of SLE in 1965.[84,85] The use of MTX as a second-line therapy in CLE patients refractory to antimalarial therapy has been supported over the last 15 years in the literature.[60,86–93] The current recommended dose is 7.5 to 25mg administered via subcutaneous injection for up to five days a week.[17] Side effects of MTX include gastrointestinal discomfort, bone marrow toxicity, nephrotoxicity, hepatotoxicity, and interstitial pneumonitis.[17] Folate replacement is necessary with treatment as well as routine laboratory monitoring for bone marrow and hepatotoxicity.[70]

A 1998 retrospective analysis of 12 patients with various CLE subtypes (6 SCLE, 4 DLE, 1 lupus erythematosus panniculitis, 1 chilblain lupus) examined the effects of 10 to 25mg intravenous (IV) or oral MTX.[88] Six patients exhibited complete remission of CLE lesions, four achieved partial remission, and two did not respond. Five patients achieved a long-standing remission 5 to 24 months following therapy. Another retrospective study examined the efficacy and safety of MTX in recalcitrant CLE. Forty-three patients with various subtypes of CLE were treated with low-dose IV or oral MTX.[66] Ninety-eight percent demonstrated significant decline in disease activity. The most improvement was observed in patients with DLE and SCLE. Seven patients discontinued treatment due to side effects: four had increased liver enzymes, two experienced nausea, and one developed panleukocytopenia that resolved after cessation of MTX. Currently, MTX is recommended as a second-line treatment for SCLE and localized DLE refractory to antimalarial therapy.[17]

Mycophenolate mofetil and mycophenolate sodium. Mycophenolate mofetil (MMF) is a specific, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase. Decreased activity of this enzyme affects proliferation of B and T lymphocytes and directly induces apoptosis of activated T lymphocytes.[17] Case reports have shown MMF is effective in autoimmune bullous dermatoses, lupus nephritis, and various subtypes of CLE.[94–101] MMF is well tolerated and clinical results are achieved in 1 to 2 months with doses from 1 to 3g/day.[17] The most common side effects are gastrointestinal symptoms, urinary tract infections, and immunosuppression.[15] Routine laboratory monitoring for hematological, renal, and hepatic toxicity is necessary.[70]

A 2007 prospective, nonrandomized, open pilot study assessed the efficacy of mycophenolate sodium, the enteric-coated form of MMF, in 10 patients with SCLE refractory to antimalarial therapy.[102] Remarkable results were achieved with 1,440mg/day MMF monotherapy for three months. No serious side effects were reported. The use of MMF as an adjuvant to other therapies was studied in a 2011 retrospective study of 24 patients with various subtypes of recalcitrant CLE.[103] The average final dose of MMF was 2,750mg/day. One hundred percent of patients demonstrated improvement and 62 percent achieved complete or near-complete resolution of CLE lesions. Therapy was well tolerated and the mean time to initial response was 2.76 months. The beneficial effects of MMF in combination with HQ are highlighted in a recent case series of three patients with recalcitrant CLE.[104] Doses of MMF from 1,000 to 1,500mg/day were effective within 5.6 weeks. Although effective as monotherapy or in combination with other agents for refractory disease, more studies are necessary to further identify a role for MMF in the treatment of CLE.

Azathioprine. Azathioprine is the prodrug of 6-mercaptopurine, a purine antimetabolite with cytotoxic and immunosuppressive activity attributed to the disruption of nucleic acids in the s-phase of the cell cycle.[17] Side effects include bone-marrow toxicity, hepatotoxicity, and gastrointestinal symptoms.[17] Approximately 10 patients with CLE in the literature have been successfully treated with azathioprine.[105–108] Therapeutic doses range between 1 and 2.5mg/kg body weight/day and require routine laboratory monitoring for hematological and hepatic toxicity.[70] Levels of the enzyme thiopurine methyltransferase should be assessed prior to therapy because deficiencies are associated with a higher risk of hematopoietic toxicity.[17] Due to its large side effect profile, lack of studies, and high cost, the use of azathioprine in CLE is reserved for patients with SLE-associated lesions.

Clofazimine. Clofazimine is an antibiotic with anti-inflammatory and immunosuppressive activity traditionally used in the treatment of leprosy. Common side effects include reddish-brown discoloration of the skin, dry skin, nausea, and diarrhea.[17] The first time clofazimine was used to treat CLE was in a 1974 study in which 65 percent of 26 patients with DLE were successfully treated.[109] A more recent randomized, double-blind, controlled trial compared the

efficacy of 100mg clofazimine to 250mg CQ in 33 patients with active SLE lesions.[55] A good response was noted in 75 and 82.4 percent of patients treated with clofazimine and CQ, respectively. Although clofazimine was as effective as CQ in controlling cutaneous SLE lesions, five patients with a serious flare of lesions were withdrawn from the study. Due to the inability to determine if there is a risk of inducing CLE lesions with clofazimine, it is only indicated in patients with exclusively cutaneous manifestations of disease.[17]

IMMUNOMODULATORS

Dapsone. Dapsone is a sulfone that inhibits dihydrofolic acid synthesis and exhibits both antibiotic and anti-inflammatory properties. The main indication for use of oral dapsone is dermatitis herpetiformis, although it has been used to treat many other dermatological disorders. Three case series collectively demonstrate an improvement in 35 percent of 55 CLE patients treated with oral dapsone.[70] Therapeutic doses range from 25 to 150mg/day. Treatment limited to the lowest effective dose reduces the risk of dose-dependent hemolysis and methemoglobinemia.[17] Prior to initiating therapy with dapsone, it is suggested that patients be screened for glucose-6-phosphate deficiency. Other side effects include a hypersensitivity reaction with mononucleosis-type symptoms, potentially fatal agranulocytosis, and acral motor neuropathy.[70] The risks of hematological side effects are greatest in the first three months of therapy and complete blood counts need to be obtained routinely during this time. Despite its risky side effect potential, dapsone is recommended as an alternative or adjuvant therapy in antimalarial-resistant CLE.[17]

Thalidomide. The effects of thalidomide are attributed to the inhibition of TNF-alpha synthesis and UVB-induced keratinocyte apoptosis.[17] Thalidomide is a well-known teratogen and must only be considered in women of reproductive age with an effective form of contraception. Other side effects include potentially irreversible peripheral neuropathy, secondary amenorrhea, and an increased risk of thromboembolic events.[70] Therapeutic doses range from 50 to 100mg/day and clinicians should refer to the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) program to ensure safe administration.[110]

Use of thalidomide in the treatment of CLE was first reported in a 1983 series in which 60 cases of chronic DLE were treated with 50 to 100mg/day.[111] Fifty-four patients (90%) had complete or marked regression of lesions. Relapse occurred in 30 of 41 (71%) successfully treated patients following discontinuation of thalidomide. Lesions were not as severe as before treatment and 16 of 41 (39%) responded well to a second course of thalidomide. Reported side effects included drowsiness, constipation, rash, edema, xerostomia, and most importantly, peripheral neuropathy in 25 percent of patients. A 2005 study of 48 patients receiving different doses of thalidomide produced similar results in patients with various subtypes of CLE.[112] Twenty-nine (60%) achieved complete remission, 10 (21%) partial remission, and nine (19%) reported no response. Relapse occurred in 26 (67%) patients who had attained a complete or partial remission. Thirteen (27%) patients reported non-dose-dependent neuropathy. Finally, a 2011 study examined the long-term experience of thalidomide's efficacy and safety in the treatment of refractory CLE.[113] Sixty total patients with DLE (42%), SCLE (30%), or lupus profundus unresponsive to therapy with CQ, HCQ, topical/oral steroids, dapsone, or oral immunosuppressives were treated with 100mg/day thalidomide. Patients were evaluated using the CLASI scoring system and demonstrated a reduction in activity score (e.g., erythema and scaling) from 7±4 to 0.25±0.82 and damage score (e.g., scarring and dyspigmentation) from 0.67±1.34 to 1.4±1.7. Complete response was observed in 50 (85%) patients, partial response in eight (14%), and no response in one. Thirty-five (70%) patients with a complete response suffered a relapse after withdrawal from thalidomide. Paresthesia was reported in 18 percent of patients and seven women reported secondary amenorrhea. Due to the risks associated with using thalidomide, it should only be used to treat severe recalcitrant CLE, particularly DLE, or as a remission-inducing agent.

Lenalidomide. Lenalidomide is a structural analog of thalidomide with more potent immunomodulatory effects and lower risk of polyneuropathy.[114–116] Side effects are similar to those of thalidomide, but generally milder. Lenalidomide was developed in 2004 for the treatment of multiple myeloma, myelodysplastic syndrome, and solid tumors.[17] A 2012 non-blinded, open-label study examined the effects of lenalidomide as an adjunctive therapy in recalcitrant CLE.[114] Four patients with DLE or SCLE were started on 5mg oral lenalidomide daily for six weeks in addition to their prescribed regimens. Four of five patients had a clinically satisfactory response and an average reduction in CLASI activity score from 21.4 to 10.4. One nonresponder had new onset symptoms of SLE despite initial improvement of skin lesions. The risk of lenalidomide triggering systemic disease has been described in the literature.[117] Due to the possibility that lenalidomide may exacerbate disease and the lack of supporting studies in the literature, lenalidomide is not currently recommended for the routine treatment of CLE.

BIOLOGIC AGENTS

Intravenous immunoglobulin (IVIG). IVIG is the product of pooling immunoglobulin G (IgG) immunoglobulins extracted from donor blood. The precise mechanism of action is poorly understood, but IVIG has proven effective in the treatment of immune deficiency and autoimmune disease. Headaches are the most common side effect, with rare reports of cutaneous eruptions, acute renal failure, and thromboembolic events.[118] Overall, complete resolution or good response has been reported in a total of 21 patients with CLE from six case reports.[119–124] In contrast, another study found IVIG was not effective in treating CLE lesions in five patients with ACLE and two with SCLE.[125] IVIG is a promising therapy for recalcitrant CLE, but its routine use is limited due to high cost and lack of strong clinical studies.

Rituximab. Rituximab is a chimeric anti-CD20 monoclonal antibody that induces depletion of B cells through both antibody dependent and independent

TABLE 3. Therapies for cutaneous lupus erythematosus and the levels of evidence supporting therapeutic benefit according to Oxford Centre for Evidence-Based Medicine Criteria

INTERVENTION	LEVEL 1	LEVEL 2	LEVEL 3	LEVEL 4	LEVEL 5
	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Nonrandomized controlled cohort/follow-up study	Case-series, case-controlled studies, or historically controlled studies	Mechanism-based reasoning
Prevention	—	Sunscreen	—	—	—
Topical Therapy	—	Corticosteroids Tacrolimus Pimecrolimus R-salbutamol	—	Pulsed dye laser	Photodynamic therapy Cryotherapy Argon laser CO_2 laser
Systemic Therapy	—	Hydroxychloroquine Chloroquine Retinoids Clofazime	Mycophenolate mofetil	Quinacrine Methotrexate Dapsone Thalidomide Lenalidomide Intravenous immunoglobulin	AZA INF-alpha Rituximab
Experimental Therapy	—	—	—	—	Tociluzimab Anti-CD4 antibody Sulfasalazine Cefuroxime axetil Danazol Extracorporeal phoresis Chaperonin 10
Controversial Therapy	—	—	Leflunomide	Phenytoin Cyclophosphamide Efalizumab	Gold TNF-alpha antagonists Cyclosporine Imiquimod

pathways.[126] Side effects include infusion reactions, neutropenia, and thrombocytopenia.[127,128] Studies within the literature support the use of rituximab in dermatological conditions, such as pemphigus vulgaris, paraneoplastic pemphigus, graft-versus host disease, dermatomyositis, and cutaneous B-cell malignancies.[129–131] In four case reports, skin lesions were successfully treated in three patients with refractory SLE and two patients with SCLE.[128,132–134] Most patients demonstrated an excellent response to rituximab monotherapy or in combination with other systemic agents. More studies are required to determine the optimal dose and scheduling of rituximab therapy in CLE.

EXPERIMENTAL THERAPY

Some newer therapies have demonstrated promising results in a limited number of patients with CLE. Biological monoclonal antibodies, tocilizumab and anti-CD4 antibody, have each successfully treated refractory CLE lesions in single reports.[135,136] Cefuroxime axetil is an oral cephalosporin antibiotic that appears to exhibit some immunomodulatory activity, with complete clearance of lesions demonstrated in three patients with SCLE.[137] Danazol is a testosterone derivative used to treat endometriosis, fibrocystic breast disease, and hereditary angioneurotic edema that suppresses the pituitary-ovarian axis and may decrease immunoglobulin levels. Oral danazole has been used effectively to treat two patients with DLE associated with premenstrual exacerbations.[138,139] Extracorporeal photophoresis is a technique that separates and irradiates white blood cells used with favorable results in a total of seven patients with severe CLE.[140–142] UVB hardening therapy has also been implicated as a novel intervention in patients with photosensitive CLE.[143] Chaperonin 10 is a heat shock protein and secretory molecule that can suppress innate and adaptive immunity. A recent study demonstrated recombinant chaperonin 10 selectively prevents cutaneous lupus and suppresses lupus nephritis in SLE-induced mice.[144] More studies are needed on a larger number of patients to

TABLE 4. Summary of cutaneous lupus erythematosus therapeutic interventions

	1ST LINE	2ND LINE	EXPERIMENTAL
PREVENTION	Sun avoidance	n/a	n/a
	Sunscreen (SPF ≥50)		
TOPICAL TREATMENT	Corticosteroids	Tacrolimus	Pulsed dye laser
		Pimecrolimus	Cryotherapy
		R-salbutamol	Phototherapy
SYSTEMIC TREATMENT	Hydroxychloroquine	Retinoids	Azathioprine
	Chloroquine	Methotrexate	Clofazimine
	n/a	Dapsone	Lenalidomide
		Mycophenolate mofetil	IVIG
		Quinacrine	Rituximab
		Corticosteroids	Tocilizumab
		Thalidomide	Anti-CD4 antibody
		n/a	Cefuroxime axetil
			Extracorporeal photophoresis
			Danazol

support the efficacy of these promising therapies and their routine use in CLE treatment.

CONTROVERSIAL THERAPY

Over the years, many different therapies have been tested for efficacy in CLE and have gone in and out of favor based on one reason or another. This subject is thoroughly addressed in previous review articles.[4,9,16,17,19] Drugs no longer recommended due to an unfavorable risk-benefit profile include phenytoin, gold, efalizumab, cyclosporine, and cyclophosphamide. Other drugs, such as TNF-alpha antagonists (e.g., infliximab, etanercept, adalimumab), interferon alpha, imiquimod, phototherapy, sulfasalazine, and leflunomide are not used or strictly limited due to reports questioning their potential to exacerbate underlying disease.[17] Although risky as monotherapy, some of these agents may still prove useful at lower doses as an adjuvant to standard medications by taking advantage of the synergistic effects of combination therapy (Table 2). Such an effect has been reported in a recent case report of two patients with recalcitrant SCLE successfully treated with 22.5 to 30mg/week MTX in combination with 3mg/kg/day cyclosporine in the absence of unfavorable side effects.[145]

DISCUSSION

Many treatment options have been used successfully to treat skin lesions of CLE (Tables 3 and 4). Sun avoidance and high SPF sunscreen are highly effective preventative measures. Topical therapy is the staple of CLE treatment. Systemic interventions range from older, clinically proven treatments, such as antimalarial therapy, to newer, cutting edge immunological and biological drugs with novel mechanisms of action. The concept of combination therapy is also on the horizon for the treatment of CLE. Studies demonstrating the safety and efficacy of different combinations of therapy may provide a route in which medications with broader side effect profiles may return to routine use.

The main issue regarding treatment of CLE is the paucity of well-powered and adequately sized studies supporting the benefits of therapy. Currently, there is only one systematic review of drugs for DLE on the Cochrane Database of Systemic Reviews and no therapeutic intervention is supported by enough clinical evidence to achieve a Level 1 distinction according to OCEBM criteria (Table 3).[10] Due to the current climate of healthcare and increasing emphasis on practicing evidence-based medicine, physicians will likely be required to make clinical judgments based on the strength of evidence from the literature. Although some therapeutic

interventions have been supported for decades by anecdotal and historical evidence, the future of medicine may warrant more concrete proof of their risks and benefits. Unfortunately, agents with immunological effects are often a "double-edged sword," with the use of some newer therapies remaining controversial because the promising results in treating recalcitrant CLE are contradicted by a handful of reports suggesting these drugs may actually exacerbate disease. With better-designed trials on a sufficient number of patients, this ambiguity may resolve allowing dermatologists to take advantage of these novel therapeutic interventions and practice confidently under the aegis of evidence-based medicine.

REFERENCES

1. Yell JA, Mbuagbaw J, Burge SM. Cutaneous manifestations of systemic lupus erythematosus. *Br J Dermatol.* 1996;135: 355–362.
2. Gilliam JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. *J Am Acad Dermatol.* 1981;4:471–475.
3. Moghadam-Kia S, Chilek K, Gaines E, et al. Cross-sectional analysis of a collaborative web-based database for lupus erythematosus associated skin lesions: prospective enrollment of 114 patients. *Arch Dermatol.* 2009;145:255–260.
4. Walling HW, Sontheimer RD. Cutaneous lupus erythematosus: issues in diagnosis and treatment. *Am J Clin Dermatol.* 2009;10:365–381.
5. Fabbri P, Cardinali C, Giomi B. Cutaneous lupus erythematosus: diagnosis and management. *Am J Clin Dermatol.* 2003;4: 449–465.
6. Obermoser G, Sontheimer RD, Zelger B. Overview of common, rare and atypical manifestations of cutaneous lupus erythematosus and histopathological correlates. *Lupus.* 2010;19:1050–1070.
7. Cohen MR, Crosby D. Systemic disease in subacute cutaneous lupus erythematosus; a controlled comparison with systemic lupus erythematosus. *J Rheumatol.* 1994;21:1665–1669.
8. Sontheimer RD, Maddison PJ, Reichlin M, et al. Serologic and HLA associations in subacute cutaneous lupus erythematosus, a clinical subset of lupus erythematosus. *Ann Intern Med.* 1982;97:664–671.
9. Lee HJ, Sinha AA. Cutaneous lupus erythematosus: understanding of clinical features, genetic basis, and pathobiology of disease guides therapeutic strategies. *Autoimmunity.* 2006;39:433–444.
10. Jessop S, Whitelaw DA, Delamere FM. Drugs for discoid lupus erythematosus. *Cochrane Database Syst Rev.* 2009;CD002954.
11. Callen JP. Management of "refractory" skin disease in patients with lupus erythematosus. *Best Pract Res Clin Rheumatol.* 2005;19:767–784.
12. Callen JP. How frequently are drugs associated with the development or exacerbation of subacute cutaneous lupus? *Arch Dermatol.* 2003;139:89–90.
13. Durosaro O, Davis MD, Reed KB, Rohlinger AL. Incidence of cutaneous lupus erythematosus, 1965-2005: a population-based study. *Arch Dermatol.* 2009;145:249–253.
14. Tsokos GC. Systemic lupus erythematosus. *N Engl J Med.* 2011;365:2110–2121.
15. Oxford Center for Evidence Based Medicine. http://www.cebm.net/index.aspx?o=5653. Accessed June 6, 2012.
16. Kuhn A, Sonntag M, Richter-Hintz D, et al. Phototesting in lupus erythematosus: a 15-year experience. *J Am Acad Dermatol.* 2001;45:86–95.
17. Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update of therapeutic options part I and II. *J Am Acad Dermatol.* 2011;65:e179–e213.
18. Vila LM, Mayor AM, Valentin AH, et al. Association of sunlight exposure and photo- protection measures with clinical outcome in systemic lupus erythematosus. *P R Health Sci J.* 1999;18:89–94.
19. McCauliffe DP. Cutaneous lupus erythematosus. *Semin Cutan Med Surg.* 2001;20:14–26.
20. Gisondi P, Ellis CN, Girolomoni G. Pimecrolimus in dermatology: atopic dermatitis and beyond. *Int J Clin Pract.* 2005;59:969–974.
21. Marsland AM, Griffiths CE. The macrolide immunosuppressants in dermatology: mechanisms of action. *Eur J Dermatol.* 2002;12:618–622.
22. Sticherling M. Update on the use of topical calcineurin inhibitors in cutaneous lupus erythematosus. *Biologics.* 2011;5:21–31.
23. Queille-Roussel C, Paul C, Duteil L, et al. The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. *Br J Dermatol.* 2001;144:507–513.
24. Draelos ZD. Use of topical corticosteroids and topical calcineurin inhibitors for the treatment of atopic dermatitis in thin and sensitive skin areas. *Curr Med Res Opin.* 2008;24:985–994.
25. Luger T, Paul C. Potential new indications of topical calcineurin inhibitors. *Dermatology.* 2007;215:45–54.
26. Wollina U, Hansel G. The use of topical calcineurin inhibitors in lupus erythematosus: an overview. *J Eur Acad Dermatol Venereol.* 2008;22:1–6.
27. Sárdy M, Ruzicka T, Kuhn A. Topical calcineurin inhibitors in cutaneous lupus erythematosus. *Arch Dermatol Res.* 2009;301:93–98.
28. Tzung TY, Liu YS, Chang HW. Tacrolimus vs. clobetasol propionate in the treatment of facial cutaneous lupus erythematosus: a randomized, double-blind, bilateral comparison study. *Br J Dermatol.* 2007;156:191–192.
29. Kuhn A, Gensch K, Haust M, et al. Efficacy of tacrolimus 0.1% ointment in cutaneous lupus erythematosus: a multicenter, randomized, double-blind, vehicle-controlled trial. *J Am Acad Dermatol.* 2011;65:54–64.
30. Madan V, August PJ, Chalmers RJ. Efficacy of topical tacrolimus 0.3% in clobetasol propionate 0.05% ointment in therapy-resistant cutaneous lupus erythematosus: a cohort study. *Clin Exp Dermatol.* 2010;35:27–30.
31. Zabawski E. Treatment of cutaneous lupus with Elidel. *Dermatol Online J.* 2002;8:25.
32. Sticherling M, Gelbrich G, Rogalski C. Topical pimecrolimus for cutaneous lupus erythematosus-results of a double-blind, placebo controlled study. *J Deutsch Dermatol Ges.* 2007;5:S188–S189.
33. Barikbin B, Givrad S, Yousefi M, et al. Pimecrolimus 1% cream versus betamethasone 17-valerate 0.1% cream in the treatment

of facial discoid lupus erythematosus: a double-blind, randomized pilot study. *Clin Exp Dermatol.* 2009;34:776–780.
34. Prenner BM. Role of long-acting beta2-adrenergic agonists in asthma management based on updated asthma guidelines. *Curr Opin Pulm Med.* 2008;14:57–63.
35. Baramki D, Koester J, Anderson AJ, et al. Modulation of T-cell function by (R)- and (S)-isomers of albuterol: anti-inflammatory influences of (R)-isomers are negated in the presence of the (S)-isomer. *J Allergy Clin Immunol.* 2002;109:449–454.
36. Volcheck GW, Kelkar P, Bartemes KR, et al. Effects of (R)- and (S)-isomers of beta-adrenergic agonists on eosinophil response to interleukin-5. *Clin Exp Allergy.* 2005;35:1341–1346.
37. Leff AR, Herrnreiter A, Naclerio RM, et al. Effect of enantiomeric forms of albuterol on stimulated secretion of granular protein from human eosinophils. *Pulm Pharmacol Ther.* 1997;10: 97–104.
38. Jemec GB, Ullman S, Goodfield M, et al. A randomized controlled trial of R-salbutamol for topical treatment of discoid lupus erythematosus. *Br J Dermatol.* 2009;161:1365–1370.
39. Wulf HC, Ullman S. Discoid and subacute lupus erythematosus treated with 0.5% R-salbutamol cream. *Arch Dermatol.* 2007;143:1589–1590.
40. Molin L, Tarstedt M. Discoid lupus erythematosus treated with cryotherapy. *J Dermatolog Treat.* 2003;14:182–183.
41. Zachariae H, Bjerring P, Cramers M. Argon laser treatment of cutaneous vascular lesions in connective tissue diseases. *Acta Derm Venereol.* 1988;68:179–182.
42. Nurnberg W, Algermissen B, Hermes B, et al. Successful treatment of chronic discoid lupus erythematosus with argon laser. *Hautarzt.* 1996;47:767–770.
43. Kuhn A, Becker-Wegerich PM, Ruzicka T, Lehmann P. Successful treatment of discoid lupus erythematosus with argon laser. *Dermatology.* 2000;201:175–177.
44. Henderson DL, Odom JC. Laser treatment of discoid lupus (case report). *Lasers Surg Med.* 1986;6:12–15, 44–45.
45. Walker SL, Harland CC. Carbon dioxide laser resurfacing of facial scarring secondary to chronic discoid lupus erythematosus. *Br J Dermatol.* 2000;143:1101–1102.
46. Raulin C, Schmidt C, Hellwig S. Cutaneous lupus erythematosus-treatment with pulsed dye laser. *Br J Dermatol.* 1999;141: 1046–1050.
47. Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol.* 2005;125:889–894.
48. Erceg A, Bovenschen HJ, van de Kerkhof PC, et al. Efficacy and safety of pulsed dye laser treatment for cutaneous discoid lupus erythematosus. *J Am Acad Dermatol.* 2009;60:626–632.
49. Díez MT, Boixeda P, Moreno C. Histopathology and immunohistochemistry of cutaneous lupus erythematosus after pulsed dye laser treatment. *Dermatol Surg.* 2011;37:971–981.
50. Cooper RG, Magwere T. Chloroquine: novel uses & manifestations. *Indian J Med Res.* 2008;127:305–316.
51. Payne JF. A postgraduate lecture on lupus erythematosus. *Clin J.* 1894;4:223–239.
52. Kuhn A, Ochsendorf F, Bonsmann G. Treatment of cutaneous lupus erythematosus. *Lupus.* 2010;19:1125–1136.
53. Ruiz-Irastorza G, Khamashta MA. Hydroxychloroquine: the cornerstone of lupus therapy. *Lupus.* 2008;17:271–273.
54. Ruzicka T, Sommerburg C, Goerz G, Kind P, Mensing H. Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. *Br J Dermatol.* 1992;127:513–518.
55. Bezerra EL, Vilar MJ, da Trindade Neto PB. Double-blind, randomized, controlled clinical trial of clofazimine compared with chloroquine in patients with systemic lupus erythematosus. *Arthritis Rheum.* 2005;52:3073–3078.
56. Thelma Skare T, Ribeiro CF, Souza FH. Antimalarial cutaneous side effects: a study in 209 users. *Cutan Ocul Toxic.* 2011;30:45–49.
57. Levy GD, Munz SJ, Paschal J, et al. Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. *Arthritis Rheum.* 1997;40:1482–1486.
58. McGrath H, Martinez-Osuna P, Lee FA. Ultraviolet-A1 (340–400 nm) irradiation therapy in systemic lupus erythematosus. *Lupus.* 1996;5:269–274.
59. Dubois EL. Antimalarials in the management of discoid and systemic lupus erythematosus. *Semin Arthritis Rheum.* 1978;8:33–51.
60. Wallace DJ. The use of quinacrine (Atabrine) in rheumatic diseases: a reexamination. *Semin Arthritis Rheum.* 1989;18: 282–296.
61. Chung HS, Hann SK. Lupus panniculitis treated by a combination therapy of hydroxychloroquine and quinacrine. *J Dermatol.* 1997;24:569–572.
62. Feldmann R, Salomon D, Saurat JH. The association of the two antimalarials chloroquine and quinacrine for treatment- resistant chronic and subacute cutaneous lupus erythematosus. *Dermatology.* 1994;189:425–427.
63. Von Schmiedeberg S, Ronnau AC, Schuppe HC, et al. Combination of antimalarial drugs mepacrine and chloroquine in therapy refractory cutaneous lupus erythematosus [in German]. *Hautarzt.* 2000;51:82–85.
64. Lipsker D, Piette JC, Cacoub P. Chloroquine-quinacrine association in resistant cutaneous lupus. *Dermatology.* 1995;190:257–258.
65. Avgerinou G, Papafragkaki DK, Nasiopoulou A, et al. Effectiveness of topical calcineurin inhibitors as monotherapy or in combination with hydroxychloroquine in cutaneous lupus erythematosus. *J Eur Acad Dermatol Venereol.* 2011 Jun 28.
66. Wenzel J, Brahler S, Bauer R, et al. Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. *Br J Dermatol.* 2005;153:157–162.
67. Lindskov R, Reymann F. Dapsone in the treatment of cutaneous lupus erythematosus. *Dermatologica.* 1986;172:214–217.
68. Sadlier M, Kirby B, Lally A. Mycophenolate mofetil and hydroxychloroquine: an effective treatment for recalcitrant cutaneous lupus erythematosus. *J Am Acad Dermatol.* 2012;66:160–161.
69. González-Sixto B, García-Doval I, Oliveira R et al. Quinacrine in the Treatment of Cutaneous Lupus Erythematosus: Practical Aspects and a Case Series. *Actas Dermosifiliogr.* 2010;101: 54–58.
70. Chang AY, Werth VP. Treatment of cutaneous lupus. *Curr Rheumatol Rep.* 2011;13:300–307.

71. Sugano M, Shintani Y, Kobayashi K, et al. Successful treatment with topical tacrolimus in four cases of discoid lupus erythematosus. *J Dermatol.* 2006;33:887–891.
72. Walker SL, Kirby B, Chalmers RJ. The effect of topical tacrolimus on severe recalcitrant chronic discoid lupus erythematosus. *Br J Dermatol.* 2002;147:405–406.
73. Madan V, August PJ, Chalmers RJ. Efficacy of topical tacrolimus 0.3% in clobetasol propionate 0.05% ointment in therapy-resistant cutaneous lupus erythematosus: a cohort study. *Clin Exp Dermatol.* 2010;35:27–30.
74. Drake LA, Dinehart SM, Farmer ER, et al. Guidelines of care for cutaneous lupus erythematosus: American Academy of Dermatology. *J Am Acad Dermatol.* 1996;34:830–836.
75. Ruzicka T, Meurer M, Braun-Falco O. Treatment of cutaneous lupus erythematosus with etretinate. *Acta Derm Venereol.* 1985;65:324–329.
76. Newton RC, Jorizzo JL, Solomon AR Jr, et al. Mechanism-oriented assessment of isotretinoin in chronic or subacute cutaneous lupus erythematosus. *Arch Dermatol.* 1986;122: 170–176.
77. Vena GA, Coviello C, Angelini G. Use of oral isotretinoin in the treatment of cutaneous lupus erythematosus [in Italian]. *G Ital Dermatol Venereol.* 1989;124:311–315.
78. Furner BB. Subacute cutaneous lupus erythematosus response to isotretinoin. *Int J Dermatol.* 1990;29:587–590.
79. Shornick JK, Formica N, Parke AL. Isotretinoin for refractory lupus erythematosus. *J Am Acad Dermatol.* 1991;24:49–52.
80. Richardson TT, Cohen PR. Subacute cutaneous lupus erythematosus: report of a patient who subsequently developed a meningioma and whose skin lesions were treated with isotretinoin. *Cutis.* 2000;66:183–188.
81. Bacman D, Kuhn A, Ruzicka T. Dapsone and retinoids. In: Kuhn A, Lehmann P, Ruzicka T, eds. *Cutaneous Lupus Erythematosus.* Berlin: Springer; 2004:373–390.
82. Klör HU, Weizel A, Augustin M. The impact of oral vitamin A derivatives on lipid metabolism. What recommendations can be derived for dealing with this issue in the daily dermatological practice? *J Dtsch Dermatol Ges.* 2011;9:600–606.
83. Bangert CA, Costner MI. Methotrexate in dermatology. *Dermatol Ther.* 2007;20:216–228.
84. Islam MN, Hossain M, Haq SA. Efficacy and safety of methotrexate in articular and cutaneous manifestations of systemic lupuserythematosus. *Int J Rheum Dis.* 2012;15:62–68.
85. Miescher PA, Riethmuller D. Diagnosis and treatment of systemic lupus erythematosus. *Semin Hematol.* 1965;2:1–28.
86. Kuhn A, Specker C, Ruzicka T, Lehmann P. Methotrexate treatment for refractory subacute cutaneous lupus erythematosus. *J Am Acad Dermatol.* 2002;46:600–603.
87. Bohm L, Uerlich M, Bauer R. Rapid improvement of subacute cutaneous lupus erythematosus with low-dose methotrexate. *Dermatology.* 1997;194:307–308.
88. Boehm IB, Boehm GA, Bauer R. Management of cutaneous lupus erythematosus with low-dose methotrexate: indication for modulation of inflammatory mechanisms. *Rheumatol Int.* 1998;18:59–62.
89. Bottomley WW, Goodfield MJ. Methotrexate for the treatment of discoid lupus erythematosus. *Br J Dermatol.* 1995;133:655–656.
90. Goldstein E, Carey W. Discoid lupus erythematosus: successful treatment with oral methotrexate. *Arch Dermatol.* 1994;130:938–939.
91. Picco P, Gattorno M, Buoncompagni A, et al. A case of pediatric discoid lupus erythematosus evolving into SLE. *Clin Exp Rheumatol.* 1998;16:620.
92. Sato ET. Methotrexate in systemic lupus erythematosus. *Lupus.* 2001;10:162–164.
93. Sanchez Y, Carvallo A. Methotrexate use in patients with systemic lupus erythematosus. *Rev Med Chil.* 2004;132;195–201.
94. Beissert S, Werfel T, Frieling U, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol.* 2007;143:1536–1542.
95. Beissert S, Werfel T, Frieling U, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of pemphigus. *Arch Dermatol.* 2006;142: 1447–1454.
96. Walsh M, James M, Jayne D, et al. Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2007;2:968–975.
97. Appel AS, Appel GB. An update on the use of mycophenolate mofetil in lupus nephritis and other primary glomerular diseases. *Nat Clin Pract Nephrol.* 2009;5:132–142.
98. Boehm I, Bieber T. Chilblain lupus erythematosus Hutchinson: successful treatment with mycophenolate mofetil. *Arch Dermatol.* 2001;137:235–236.
99. Goyal S, Nousari HC. Treatment of resistant discoid lupus erythematosus of the palms and soles with mycophenolate mofetil. *J Am Acad Dermatol.* 2001;45:142–144.
100. Schanz S, Ulmer A, Rassner G, Fierlbeck G. Successful treatment of subacute cutaneous lupus erythematosus with mycophenolate mofetil. *Br J Dermatol.* 2002;147:174–178.
101. Cetkovska P, Pizinger K. Coexisting subacute and systemic lupus erythematosus after terbinafine administration: successful treatment with mycophenolate mofetil. *Int J Dermatol.* 2006;45:320–322.
102. Kreuter A, Tomi NS, Weiner SM, et al. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *Br J Dermatol.* 2007;156:1321–1327.
103. Gammon B, Hansen C, Costner MI. Efficacy of mycophenolate mofetil in antimalarial-resistant cutaneous lupus erythematosus. *J Am Acad Dermatol.* 2011;65:717–721.
104. Sadlier M, Kirby B, Lally A. Mycophenolate mofetil and hydroxychloroquine: an effective treatment for recalcitrant cutaneouslupus erythematosus. *J Am Acad Dermatol.* 2012;66: 160–161.
105. Callen JP, Spencer LV, Burruss JB, Holtman J. Azathioprine: an effective, corticosteroid-sparing therapy for patients with recalcitrant cutaneous lupus erythematosus or with recalcitrant cutaneous leukocytoclastic vasculitis. *Arch Dermatol.* 1991;127:515–522.
106. Ashinoff R, Werth VP, Franks AG. Resistant discoid lupus erythematosus of palms and soles: successful treatment with azathioprine. *J Am Acad Dermatol.* 1988;19:961–965.
107. Tsokos GC, Caughman SW, Klippel JH. Successful treatment of generalized discoid skin lesions with azathioprine: its use in a patient with systemic lupus erythematosus. *Arch Dermatol.* 1985;121:1323–1325.

108. Shehade S. Successful treatment of generalized discoid skin lesions with azathioprine. *Arch Dermatol.* 1986;122:376–377.
109. Mackey JP, Barnes J. Clofazimine in the treatment of discoid lupus erythematosus. *Br J Dermatol.* 1974;91:93–96.
110. Zeldis JB, Williams BA, Thomas SD, Elsayed ME. S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. *Clin Ther.* 1999;21:319–330.
111. Knop J, Bonsmann G, Happle R, et al. Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. *Br J Dermatol.* 1983;108:461–466.
112. Cuadrado MJ, Karim Y, Sanna G, et al. Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med.* 2005;118:246–250.
113. Cortés-Hernández J, Torres-Salido M, Castro-Marrero J, et al. Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome. *Br J Dermatol.* 2012;166:616–623.
114. Braunstein I, Goodman NG, Rosenbach M. Lenalidomide therapy in treatment-refractory cutaneous lupus erythematosus: histologic and circulating leukocyte profile and potential risk of a systemic lupus flare. *J Am Acad Dermatol.* 2012;66(4):571–582.
115. Dimopoulos MA, Kastritis E, Rajkumar SV. Treatment of plasma cell dyscrasias with lenalidomide. *Leukemia.* 2008;22:1343–1353.
116. Layzer R, Wolf J. Myeloma-associated polyneuropathy responding to lenalidomide. *Neurology.* 2009;73:812–813.
117. Jian X, Guo G, Ruan Y, et al. Severe cutaneous adverse drug reaction to leflunomide: a report of two cases. *Cutan Ocul Toxicol.* 2008;27:5–9.
118. Fernandez AP, Kerdel FA. The use of i.v. IG therapy in dermatology. *Dermatol Ther.* 2007;20:288–305.
119. Genereau T, Chosidow O, Danel C, et al. High-dose intravenous immunoglobulin in cutaneous lupus erythematosus. *Arch Dermatol.* 1999;135:1124–1125.
120. Lampropoulos CE, Hughes GR, D'Cruz DP. Intravenous immunoglobulin in the treatment of resistant subacute cutaneous lupus erythematosus: a possible alternative. *Clin Rheumatol.* 2007;26:981–983.
121. Kreuter A, Hyun J, Altmeyer P, Gambichler T. Intravenous immunoglobulin for recalcitrant subacute cutaneous lupus erythematosus. *Acta Derm Venereol.* 2005;85:545–547.
122. Espirito Santo J, Gomes MF, Gomes MJ, et al. Intravenous immunoglobulin in lupus panniculitis. *Clin Rev Allergy Immunol.* 2010;38:307–318.
123. Goodfield M, Davison K, Bowden K. Intravenous immunoglobulin (IVIg) for therapy-resistant cutaneous lupus erythematosus (LE). *J Dermatolog Treat.* 2004;15:46–50.
124. Piette JC, Frances C, Roy S, et al. High-dose immunoglobulins in the treatment of refractory cutaneous lupus erythematosus. Open trial in 5 cases. *Arthritis Rheum.* 1995;38:304.
125. De Pita O, Bellucci AM, Ruffelli M, et al. Intravenous immunoglobulin therapy is not able to efficiently control cutaneous manifestations in patients with lupus erythematosus. *Lupus.* 1997;6:415–417.
126. Silverman GJ, Weisman S. Rituximab therapy and autoimmune disorders: prospects for anti-B cell therapy. *Arthritis Rheum.* 2003;48:1484–1492.
127. Boye J, Elter T, Engert A. An overview of the current clinical use of the anti-CD20 monoclonal antibody rituximab. *Ann Oncol.* 2003;14:520–535.
128. Cieza-Díaz DE, Avilés-Izquierdo JA, Ceballos-Rodríguez C. Refractory subacute cutaneous lupus erythematosus treated with rituximab. *Actas Dermosifiliogr.* 2012 Apr 4 [Epub ahead of print].
129. Goh MS, McCormack C, Dinh HV, et al. Rituximab in the adjuvant treatment of pemphigus vulgaris: a prospective open-label pilot study in five patients. *Br J Dermatol.* 2007;156:990–996.
130. Dinh HV, McCormack C, Hall S, Prince HM. Rituximab for the treatment of the skin manifestations of dermatomyositis: a report of 3 cases. *J Am Acad Dermatol.* 2007;56:148–153.
131. Fatourechi MM, el-Azhary RA, Gibson LE. Rituximab: applications in dermatology. *Int J Dermatol.* 2006;45:1143–1155.
132. Risselada AP, Kallenberg CG. Therapy-resistant lupus skin disease successfully treated with rituximab. *Rheumatology.* 2006;45:915–916.
133. Uthman I, Taher A, Abbas O, et al. Successful treatment of refractory skin manifestations of systemic lupus erythematosus with rituximab: report of a case. *Dermatology.* 2008;216:257–259.
134. Kieu V, O'Brien T, Yap LM, et al. Refractory subacute cutaneous lupus erythematosus successfully treated with rituximab. *Australas J Dermatol.* 2009;50:202–206.
135. Makol A, Gibson LE, Michet CJ. Successful use of interleukin 6 antagonist tocilizumab in a patient with refractory cutaneous lupus and urticarial vasculitis. *J Clin Rheumatol.* 2012;18:92–95.
136. Prinz JC, Meurer M, Reiter C, et al. Treatment of severe cutaneous lupus erythematosus with a chimeric CD4 monoclonal antibody, cM-T412. *J Am Acad Dermatol.* 1996;34:244–252.
137. Rudnicka L, Szymanska E, Walecka I, Slowinska M. Long-term cefuroxime axetil in subacute cutaneous lupus erythematosus: a report of three cases. *Dermatology.* 2000;200:129–31.
138. Torrelo A, Espana A, Medina S, Ledo A. Danazol and discoid lupus erythematosus. *Dermatologica.* 1990;181:239.
139. Englert HJ, Hughes GV. Danazol and discoid lupus. *Br J Dermatol.* 1988;119:407–409.
140. Richter HI, Krutmann J, Goerz G. Extracorporeal photopheresis in therapy-refractory disseminated discoid lupus erythematosus [in German]. *Hautarzt.* 1998;49:487–491.
141. Wollina U, Looks A. Extracorporeal photochemotherapy in cutaneous lupus erythematosus. *J Eur Acad Dermatol Venereol.* 1999;13:127–130.
142. Richard MA, Saadallah S, Lefevre P, et al. Extracorporeal photochemotherapy in therapy refractory subacute lupus [in French]. *Ann Dermatol Venereol.* 2002;129:1023–1026.
143. Sanders CJ, Lam HY, Bruijnzeel-Koomen CA, et al. UV hardening therapy: a novel intervention in patients with photosensitive cutaneous lupus erythematosus. *J Am Acad Dermatol.* 2006;54:479–486.
144. Kulkarni OP, Ryu M, Kantner C, et al. Recombinant chaperonin 10 suppresses cutaneous lupus and lupus nephritis in MRL-(Fas)lpr mice. *Nephrol Dial Transplant.* 2012;27:1358–1367.
145. Klein A, Vogt T, Wenzel SM, et al. Cyclosporin combined with methotrexate in two patients with recalcitrant subacute cutaneous lupus erythematosus. *Australas J Dermatol.* 2011;52:43–47.