



Cutaneous Lupus: A Brief Review of Old and New Medical Therapeutic Options

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Systemic lupus erythematosus is a chronic inflammatory condition which affects predominantly women in their 30s. It has several clinical manifestations, including skin lesions that can be classified as acute cutaneous lupus erythematosus, subacute cutaneous lupus erythematosus, and chronic cutaneous lupus erythematosus. A multifaceted approach to treating cutaneous lupus is advocated.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organ systems in the body, including the skin and/or mucous membranes. These can be involved in over 80% of the patients with SLE. There are lupus-specific skin lesions and lupus nonspecific skin lesions (Berbert et al., 2005; Gilliam, 1977). Cutaneous lupus erythematosus (CLE) most often affects women ages 20–50 years and is often induced by sunlight. It is categorized into three main entities: acute cutaneous lupus erythematosus (ACLE), subacute CLE, and chronic cutaneous lupus erythematosus (CCLE) (Sticherling, 2011). The latter is the most common subtype of CLE, accounting for 75% of all cases of CLE. It is crucial to properly evaluate the extent of skin involvement versus systemic involvement, because they do not always directly correlate. Up to 28% patients with CCLE are susceptible to developing SLE, and earlier diagnosis and treatment might affect the onset of SLE.

According to the new Systemic Lupus International Collaborating Clinics criteria published in 2012, ACLE lesions, CCLE lesions, oral and nasal ulcers, and non-scarring alopecia form four of the 11 clinical criteria for the diagnosis of SLE (Petri et al., 2012). Malar rash, discoid rash, photosensitivity, and oral ulcers are four of the 11 criteria from the American College of Rheumatology-approved SLE diagnosis criteria (Tan et al., 1982).

Incidence of CLE is similar to incidence of SLE. CLE is three times more common than SLE in men. About 33% of patients

with subacute CLE have lesions that are related to the use of drugs including terbinafine, thiazides, proton pump inhibitors, and statins (Gronhagen et al., 2012). Therefore, stopping these medications is an important part of management.

BRIEF PATHOPHYSIOLOGY

Pathogenesis of CLE is a complex, multistep process, and much knowledge has gained in recent years. The end product of skin injury and abnormal immune response expresses as histopathological change of atrophy of the epidermis, hydropic degeneration of the basal cell layer with apoptotic keratinocytes, hyperkeratosis, follicular plugging, and basement membrane thickening with dermal edema (Oke and Wahren-Herlenius, 2013). Abnormal expression of both T helper (Th) cells Th1, Th2, and Th17 and cytokines are important in pathogenesis of tissue injury. Plasmacytoid dendritic cells play a central role in antigen presentation and produce IFN type 1 in response to nuclear antigens with immune complexes and drive cutaneous inflammation (Robinson and Werth, 2015). Multiple new agents are being introduced with targeted effect on the various cytokines and chemokines.

GENERAL PRINCIPLES OF THERAPY

The treatment of CLE should be divided into non-pharmacological and pharmacological approaches. Under the nonpharmacological approach, it is important to address patient adherence at each visit. Physical protection like broad-brimmed hats and sun-protective clothing, along with proper use of sunscreen, is essential.

Smoking enhances toll-like receptor 9 responsiveness and IFN type 1 production in plasmacytoid dendritic cells. Tobacco is also phototoxic and up-regulates expression of metalloproteinases 1 through 8 (Ortiz and Grando, 2012). Hence, smoking cessation is of paramount importance. Moreover, research studies have found that vitamin D repletion helps with better response to medications (Abou-Raya et al., 2013).

Within the pharmacological therapy approach, the use of topical corticosteroids (CSs) and calcineurin inhibitors is widely accepted. Intralesional CSs could be used in localized areas. When a patient with CLE does not respond appropriately to topical therapy and/or the cutaneous disease is widespread, the use of systemic therapy should be considered.

Finding the appropriate therapy for a patient could be challenging. It is well known that 66% of patients with CCLE will respond appropriately to antimalarials (hydroxychloroquine, chloroquine, quinacrine). Another group of people would respond appropriately when immunomodulators or immunosuppressive medications are added to the

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Abbreviations: ACLE, acute cutaneous lupus erythematosus; CCLE, chronic cutaneous lupus erythematosus; CLE, cutaneous lupus erythematosus; CS, corticosteroid; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus; Th, T helper

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regimen; however, 10% of patients are intolerant or have recalcitrant lesions.

New advances in basic and translational research in autoimmunity have been crucial in the development of these new options, which include biological agents. These new medications target key inflammatory pathways, which play an important role in the pathogenesis of the disease. The next challenge is to be more precise and predict the response of these new medications in an individual with CLE. Tailoring treatment to each person's unique disease is the next goal. The goals of therapy is to improve the appearance of the skin, limit scarring, and prevent new skin lesions. In this article we briefly discuss the various medical therapeutic options for patients with CLE.

TOPICAL TREATMENTS

Topical CSs and calcineurin inhibitors are the most widely used topical treatments. Topical CSs have been used the longest and can be classified as fluorinated and non-fluorinated. They are first-line agents but unfortunately are associated with local and sometimes systemic adverse effects if used for long durations and on large body surface areas (Ting and Sontheimer, 2001). Topical calcineurin inhibitors (tacrolimus 0.1% and pimecrolimus 0.3%) have the same efficacy as topical steroids. They are especially useful in children and on facial lesions with avoidance of telangiectasias and atrophy (unlike topical CSs) because they have no effect on endothelial cells and skin fibroblasts. Most ACLE and CCLE lesions respond well to treatment, but only minor effects are noted in lesions of subacute CLE and tumid lupus (Sardy et al., 2009).

R-salbutamol is β_2 adrenergic receptor agonist that inhibits IL-2 and IFN- γ production. A 0.5% cream applied twice per day has shown significant improvement in scaling/hypertrophy, pain, and itching with ulceration in patients with CCLE (Tokunaga et al., 2005).

SYSTEMIC TREATMENTS

Older treatments (pre-biologicals era)

Antimalarials. Antimalarials were the oral first-line therapy in cutaneous lupus, introduced in 1953. Hydroxychloroquine, chloroquine, and quinacrine are the three drugs that belong to this class. The first case series of chloroquine sulfate in CLE was published in the *British Medical Journal* in 1955 by Lewis (1955).

Mechanism of action is proposed to be immunomodulating effects with influencing antigen presentation, stabilizing lysosomes, suppression of toll-like receptor signaling (toll-like receptor 9), and reducing plasmacytoid dendritic cell production of IFN by preventing nucleic acids from acting on toll-like receptors.

Dosage recommendations are as follows: hydroxychloroquine, 6.0–6.5 mg/kg of ideal body weight; chloroquine, 3.5–4 mg/kg of ideal body weight; quinacrine, 100 mg/day. For low-weight patients, use of actual weight for dosage is recommended.

Adverse effects include nausea, vomiting, irreversible retinopathy (rare and total, dose dependent), and yellow discoloration of the skin/mucous membranes. Response rates of 75–95% are seen.

Methotrexate. Methotrexate was introduced in 1965 and is considered a second line of therapy, especially in ACLE and CCLE. It is also used in lesions refractory to antimalarials and as a CS-sparing agent. The mechanism of action includes action on adenosine, which is a purine nucleoside and has potent anti-inflammatory effects. It induces apoptosis in CD4⁺ T cells. In a study of patients with lupus, significant reduction in autoantibodies (92.3%) compared with the control group (50%) was found with the use of methotrexate (Miyawaki et al., 2013).

The dosage ranges from 7.5 mg to 25 mg once per week orally, intravenously, or subcutaneously. Adverse effects include gastrointestinal complaints, which can be alleviated with administration of folic acid before or after methotrexate administration; hepatotoxicity; nephrotoxicity; and bone marrow suppression. Interstitial pneumonitis, which is extremely rare, can potentially be fatal.

Retinoids. Introduced in 1983, retinoids are also considered second-line therapy for treatment of CCLE, according to the American Academy of Dermatology guidelines (Drake et al., 1996). Lesions of discoid lupus have shown more response with retinoids, and retinoids have been especially useful in hypertrophic/verrucous CLE (Al-Mutairi et al., 1987).

Retinoids inhibit the expression of the proinflammatory cytokines (IL-6), MRP-8, and IFN- γ (markers of hyperproliferation and abnormal keratinocyte differentiation). They are also anti-inflammatory and antiproliferative, and they normalize keratinocyte differentiation in the epithelium.

Recommended dosages of acitretin and isotretinoin are 0.2–1.0 mg/kg/body weight daily. Adverse effects include cheilitis and hair loss (dose dependent) and elevation of triglyceride levels. Birth defects are noted, and hence contraception for 1 month with isotretinoin use and 3 years with acitretin use is strictly enforced. Drug-induced hepatitis is also to be monitored for.

In the only double-blind, randomized, multicenter trial comparing the efficacy of acitretin and hydroxychloroquine in 28 and 30 patients with CCLE, improvements in 13 patients (46%) treated with acitretin and 15 (50%) patients with hydroxychloroquine were noted (Ruzicka et al., 1992).

Dapsone. Introduced in the 1980s, dapsone is recommended for vasculitic lesions, urticarial lesions, oral ulceration, the nonscarring form of CCLE, chloroquine intolerance, bullous lupus, and lupus panniculitis. Although lesions of the hyperkeratotic form do not respond to dapsone (Ruzicka et al., 1981), bullous lesions respond very well (Hall et al., 1982).

Dapsone is an antibiotic that blocks the myeloperoxidase enzyme. This may explain its anti-inflammatory and immunomodulatory effect. Even this does not explain its mechanism of action when it is used in skin conditions in which bacteria do not have a role. Other theories used are its action on neutrophils and possible tumor necrosis factor- α modulation.

Dapsone is started at 50 mg daily, with increments of 25 mg added every subsequent week until a maximum dosage of 200 mg daily. Adverse effects can be pharmacologic in nature and include hemolytic anemia and methemoglobinemia, and hence glucose 6 phosphate deficiency must be excluded before initiation of treatment. Idiosyncratic reactions include agranulocytosis, drug hypersensitivity syndrome, peripheral neuropathy, gastrointestinal adverse effects, and psychosis.

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