Lupus erythematosus: considerations about clinical, cutaneous and therapeutic aspects*

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DOI: http://dx.doi.org/10.1590/abd1806-4841.20142146

Abstract: Systemic Lupus Erythematosus is a chronic inflammatory disease with multifactorial etiology. Although clinical manifestations are varied, the skin is an important target-organ, which contributes to the inclusion of skin lesions in 4 out of the 17 new criteria for the diagnosis of the disease, according to the Systemic Lupus International Collaborating Clinics. The cutaneous manifestations of lupus are pleomorphic. Depending on their clinical characteristics, they can be classified into Acute Cutaneous Lupus Erythematosus, Subacute Cutaneous Lupus Erythematosus, Chronic Cutaneous Lupus Erythematosus and Intermittent Cutaneous Lupus Erythematosus. Treatment is based on preventive measures, reversal of inflammation, prevention of damage to target organs and relief of adverse events due to pharmacological therapy. The most commonly used treatment options are topical, systemic and surgical treatment, as well as phototherapy. The correct handling of the cases depends on a careful evaluation of the morphology of the lesions and the patient's general status, always taking into consideration not only the benefits but also the side effects of each therapeutic proposal.
Keywords: Lupus erythematosus, cutaneous; Phototherapy; Skin; Smoking

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease of multifactorial etiology, which is characterized by the involvement of different organs and systems and by presenting important immunological disorders with autoantibodies. Although it can occur in both sexes, it has a higher incidence in women, mainly around 30 years of age.[1]

Although the etiology is poorly defined, it is assumed that different factors together favor the onset of SLE, such as: genetic factors, environmental factors (exposure to ultraviolet rays, viral infections, chemicals, and sexual hormones) and emotional factors. The interaction between these multiple factors is added to the immunoregulatory disarray, loss of immunologic tolerance, development of autoantibodies, deficiency in removal of immune complexes, activation of the complement system and other inflammatory processes that lead to cell and / or tissue injury.[2]

Clinical manifestations of SLE are varied and may involve any organ or system, separately or simultaneously, during any period of the disease.[2] The skin is a target organ that is affected by the disease in a variety of ways, so that cutaneous lesions constitute 4 of the 17 new criteria established by the Systemic Lupus International Collaborating Clinics (SLICC) in 2012, for the diagnosis of systemic lupus erythematosus: acute cutaneous lupus, chronic cutaneous lupus, oral ulcers and non-scarring alopecia.[3,4]

The most widely used classification criteria for SLE are those developed by the American College of Rheumatology (ACR) in 1982.[5] The SLICC group undertook a review of these classification criteria for SLE in order to respond to several questions that had emerged since then.[6] According to the SLICC, the patient must meet at least four criteria, including at least one clinical and one immunologic criterion **OR** he must have biopsy-proven lupus nephritis, in the presence of anti-nuclear and anti-dsDNA.[4]

Received on 20.09.2012.
Approved by the Advisory Board and accepted for publication on 18.01.2013.
* Work performed at Lauro Wanderley University Hospital – Paraiba Federal University (HULW- UFPB) – João Pessoa (PB), Brazil.
Conflict of interest: None
Financial Support: None

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New clinical criteria improved ACR's classification system in several important aspects. In the context of dermatology, we highlight that malar rash and photosensitivity are not regarded as separate items anymore, because they overlap in many respects. A criterion for cutaneous lupus comprehends both the acute and subacute forms, while another separate criterion now encompasses discoid rash and various types of chronic cutaneous lupus not included in the current ACR's classification system. For the proper management of these rules, it is expected that some patients suspected of having SLE will require a dermatological consultation and sometimes even a skin biopsy. Non-scarring alopecia, though not specific for SLE, is included amongst the new criteria, since a good correlation was obtained in the statistical analysis.[4]

According to Berbert and Mantese the expression Cutaneous Lupus Erythematosus is applied to patients with lesions produced by lupus erythematosus, whether the disorder is exclusively cutaneous or part of a systemic disease.[7]

Involvement of the skin is evident, when you consider that about 80% of patients have some cutaneous manifestation in the course of the disease, and in one-fourth of them, the skin lesions are present at the moment of diagnosis.[8,9]

The current classification of skin lesions is still based on the initial observation made by Gilliam in 1977, which classified cutaneous manifestations in specific and non-specific.[10] Non-specific lesions include vascular lesions such as Raynaud's Syndrome, thrombophlebitis and periungual telangiectasias.[11,12] Furthermore, diffuse alopecia associated with telogen effluvium during active disease, erythema multiforme and cutaneous calcinosis can be found. Although non-specific lesions are common in lupus erythematous (SLE), they can also be seen in association with specific skin lesions. Non-specific lesions always indicate disease activity, a period during which patients seek the attention of rheumatologists and intensivists.[13]

Specific lesions in cutaneous lupus erythematosus (CLE) can be allocated and classified into distinct subtypes that may be interpreted variably by dermatologists and rheumatologists. Lesions are classified according to clinical, immune-serological and histological criteria in Acute Cutaneous Lupus Erythematosus (ACLE), Subacute Cutaneous Lupus Erythematosus (SCLE), Chronic Cutaneous Lupus Erythematosus (CCLE) and Intermittent Cutaneous Lupus Erythematosus (ICLE).[13]

CUTANEOUS LESIONS

Keratinocyte apoptosis has been implicated as a key event for the initiation of cutaneous lupus lesions through various apoptotic pathways such as p53, TNFα, Fas/FasL.[14,15] It is assumed that aberrant keratinocytes could not express proteins that are essential for regulating apoptosis, failing to prevent sun-induced apoptosis, for example. Another suggested mechanism is that these keratinocytes could present anomalous major histocompatibility complexes (MHC) or release abnormal cytokines.[14]

Acute Cutaneous Lupus Erythematosus (ACLE) may present as the classic butterfly rash, found in the center of the face in its localized form or as a generalized maculopapular exanthema.[11] Typically, patients are critically ill due to systemic lupus erythematosus (SLE) and exhibit underlying manifestations in various organs, as well as the presence of anti-dsDNA antibodies.[13] The typical immunopathological findings of acute lesions are those of dermatitis, without significant hyperkeratosis or epidermic atrophy.[16]

Contrasting with Acute Cutaneous Lupus Erythematosus (ACLE) as a cutaneous manifestation of SLE, Subacute Cutaneous Lupus Erythematosus (SCLE) is sometimes interpreted as the limit between strictly cutaneous and systemic disease. The term Subacute Cutaneous Lupus Erythematosus (SCLE) defines a subgroup of SLE patients with well-defined cutaneous and serological features.[13]

Clinically, cutaneous manifestations of SCLE are characterized by papulosquamous and annular lesions. In both cases, the skin lesions are similar, appearing as a small erythematous slightly desquamative papule or plaque, although papulosquamous lesions progress and converge, forming psoriasiform plaques often arranged in a reticulated pattern, whereas in the annular lesions, there is a peripheral progression, with erythema and thin desquamation on the edges.[17,18] It has been noted that the rash is often photosensitive, i.e. triggered or exacerbated by sun exposure. Thus, the lesions are more frequent in exposed areas, such as the torso and arms, although the face is usually spared.[19]

Histological examinations reveal the involvement of dermis and epidermis; the annular form does not affect the cutaneous adnexa, unlike the psoriasiform variation. The serologic mark of SCLE is positivity for anti-Ro/SS-A and anti-La/SS-B antibodies in approximately 70% of cases.[19] Even though the presence of anti-Ro/SS-A and anti-La/SS-B antibodies indicate systemic disease, only mild arthralgia and myalgia are clinically found in some cases.[13]

Approximately half of the patients with SCLE will develop signs and symptoms of systemic lupus erythematosus (SLE) usually not severe; although the presence of other autoantibodies such as anti-Sm and anti-dsDNA associated with the discovery of lupus

activity in internal organs is rare. Studies have shown that around 10-15% of patients presenting SCLE will develop severe clinical manifestations of SLE.[19,20]

Chronic Cutaneous Lupus Erythematosus (CCLE) can be classified into Discoid (LED), Profundus or Panniculitis (LEP) and Tumidus (LET). Unlike other cutaneous presentations, CCLE can result in atrophy of the skin and scars, making an earlier diagnosis and treatment essential to prevent disfiguring damage.[13]

LED is the most common form of cutaneous lesion in lupus.[13] Discoid lesions are characterized as plaques covered with a thin scaly tissue, which extends to the hair follicle. Initially plaques may be hyperpigmented, but they can evolve with depigmentation and progress to deeper cicatricial lesions, which are in most cases permanent.[21] These lesions are painful to the touch.[13]

Histologic examination shows a predominating lymphocytic infiltrate in the dermis-epidermis junction. Unlike the acute and subacute lesions, involvement of cutaneous adnexa and dermal atrophy are frequent findings.[21]

The discoid form may remain as an exclusively cutaneous disease, or these patients may progress to the systemic form of the disease, which occurs in five to 10% of cases, especially when lesions are disseminated.[22,23]

LEP, also called lupus panniculitis, affects 1% to 3% of patients with CLE.[24,25,26] It is characterized by a localized nodular infiltration in the deep dermis and subcutaneous tissue of proximal extremities, buttocks, face and trunk. These lesions distinctly evolve with deep lipoatrophy and scars; the oldest ones may even calcify.[13] The association of this type of lesion with SLE is rare, and the presence of lymphocytic panniculitis is the predominant histological finding.[27,28]

LET is a rare form of CLE and is characterized by erythematous urticarial papules and plaques with annular or centrifugal presentation on the face, proximal upper extremities and chest.[13,29] Histological findings show perivascular and periadnexal lymphocytic infiltrate and the distinctive presence of mucin. Association with SLE is unusual.[30]

Non-specific lesions, however, such as alopecia and urticaria vasculitis, are the ones that predict the clinical activity of systemic disease.[31] The presence of urticarial vasculitis associated with decreased serum levels of C1q suggest a predisposition to the development of renal lesions.[32] Livedo reticularis may appear associated with antiphospholipid antibodies, which occur in 30 to 40% of patients with SLE, worsening the prognosis.[33]

Thus, knowing the spectrum of cutaneous manifestations in a patient with SLE is very important, because the analysis of this clinical component, easily accessible to inspection, can provide essential clues to better understanding the case.[8]

TREATMENT

The treatment of SLE is based on preventive measures, reversal of inflammation, organ damage prevention and relief of symptoms. The most employed therapeutic tools are immunosuppression, cytotoxic treatment and immunoglobulin therapy.[34]

Exposure to ultraviolet radiation and smoking are lifestyle habits related to the emergence and worsening of cutaneous lesions in lupus erythematosus.[24,35]

Sun exposure can be considered one of the main external factors implicated in the pathogenesis of this disease. Some studies have investigated the role of ultraviolet radiation in the immunological events involved in SLE's pathogenesis. Patients should be counseled about the risks of sun exposure and the importance of protection through the use of clothing, accessories, and sunscreen.[36,37,38,39] Sunscreens are chemical agents applied to the skin, in different presentations, which contain in their formulation ingredients capable of interfering with solar radiation, by reflection, dispersion and absorption, thus reducing their harmful effects.[40]

Cigarette smoking has been linked to the pathogenesis of lupus.[24] It has been observed that CLE is more prevalent among smokers.[41,42] Some studies suggest that cigarette smoking increases the activity of the disease, affects the efficiency of antimalarial therapies and has a direct deleterious effect on cutaneous lesions.[43-45] Smokers have an increased level of epidermal surface molecules, such as intercellular adhesion molecule-1, that are involved both in the development of primary skin lesions, as well as in those induced by ultraviolet light.[46,47]

Smoke activates metalloproteinases, that damage the tissue, and cytokines such as interleukin-6, an important marker of inflammation in lupus.[46,48] Studies also report the reduction of chloroquine efficacy in smokers, due to the effect of tobacco on cytochrome P450, which enzymatic system is responsible for the metabolism of this drug.[44,49] In addition, smoking is usually related to other risk factors that may also influence treatment adherence.[50]

Pharmacological therapy used in the treatment of LE usually includes corticosteroids, antimalarials and topical or systemic immunosuppressants.[51] Recently, new immunotherapy strategies that act on specific molecules or immune cells have emerged, resulting in lower toxicity and higher selectivity. This is the case of B and/or T-cell depletion therapy and anti-cytokine treatments.[52,53]

SYSTEMIC TREATMENT

Antimalarials must be highlighted in the systemic treatment of CLE.[54] Since the 1950s they persist as first-line agents, with response rates between 75-95%, in the treatment of cutaneous lupus erythematosus.[55]

Although controlled studies comparing the efficacy of antimalarials (such as chloroquine and hydroxychloroquine) versus placebo and other treatments are scarce, many case reports confirm the therapeutic efficacy of these agents in the treatment of cutaneous lesions in lupus.[55] The most widely used antimalarial agent is hydroxychloroquine sulfate, which is well tolerated, with chloroquine and quinacrine as alternatives.[56]

Immunosuppressive drugs play an important role in the treatment of patients which are refractory to antimalarial drugs, and may be used as adjuvants to spare doses of corticosteroids.[57,58,59] Methotrexate (MTX) has been found effective in several subtypes of CLE.[57,58] Recent studies have linked the anti-inflammatory properties of MTX to its effects on adenosine, a purine nucleoside that has potent anti-inflammatory effects on different target cells. In addition, MTX selectively induces apoptosis in activated and proliferating CD4+ T- cells and has also been shown to inhibit the activity of IL-1.[60] In a study of 43 patients with several subtypes of refractory CLE, low doses of MTX were administered orally or intravenously. Nearly all patients (98%) showed improvement of skin lesions; the greater clinical improvement was observed in patients with SCLE and LED.[58] Thus, MTX is considered as a second-line treatment for patients with CLE refractory to antimalarials, especially those with localized SCLE and LED, or patients who do not tolerate antimalarials.[60] MTX is administered at a dose of 7.5-25mg (0.2 mg/kg) once a week, orally, intravenously, or subcutaneously (by the patient himself).[59]

Mycophenolate mofetil (MMF) is a drug that inhibits the proliferation of B and T lymphocytes, involved in the pathogenesis of lupus.[61] Some case reports demonstrated good results with MMF in the treatment of cutaneous lesions that were non-responsive to therapy with antimalarials and other immunosuppressive agents.[62,63] Recent studies have also shown satisfactory clinical response, with regression of skin lesions after the use of this drug.[64,65] The adverse events are varied, however gastrointestinal intolerance, leukopenia and infections are noteworthy. There must be a dose adjustment in patients with renal failure, and the use of MMF is not recommended during pregnancy.[66]

Retinoids comprise a group of compounds that have structure and function similar to those of vitamin A. Synthetic retinoids (isotretinoin and acitretin) are second-line drugs in the treatment of cutaneous lupus erythematosus, being a therapeutic option in case of failure with antimalarials.[24] Retinoids have been used in cases of subacute and chronic cutaneous lupus erythematosus, achieving more relevant success in patients with discoid lupus.[67] Prolonged treatment with retinoids is restricted due to extensive adverse events, including drug-induced hepatitis, hypertriglyceridemia, cutaneous and mucocutaneous dryness, bone changes consistent with diffuse idiopathic skeletal hyperostosis (DISH) and teratogenicity, being mandatory the use of contraceptive methods. Moreover, the careful use of sunscreens is recommended, since retinoids may exacerbate photosensitivity.[68]

Dapsone, known for its antimicrobial properties, is also an effective immunomodulatory agent in the treatment of bullous lupus erythematosus, lupus panniculitis, SCLE and possibly LED, due to its effects on neutrophils and possible TNFα modulation.[59,69] The use of dapsone should only be considered for inflammatory, but not hyperkeratotic, forms of CLE.[59] The dose of dapsone ranges from 25 to 150 mg per day, with the maximum permitted dose being 200 mg. When dapsone is initiated, the dosage is usually 50 mg daily, with increments of 25 mg every subsequent week.[69,70]

Thalidomide is especially effective in deep LE (LEP) and LED. With good clinical response and tolerability, the dose between 50 and 200 mg / day should be reduced to a minimum. This drug's action is explained by its influence on the activity of macrophages and on the modulation of TNF-α expression.[59] Several side effects were linked to the use of thalidomide: constipation, drowsiness, rash, swelling, and xerostomia, however, the most important one is peripheral polyneuropathy.[71] This adverse event may occur early during the first four weeks of treatment and it is not always reversible, making it mandatory to perform neurological monitoring of these patients.[59] Due to its teratogenic risk, thalidomide should only be prescribed for women of childbearing age in cases of refractory CLE and always associated with effective contraceptive measures.[72] In the U.S., thalidomide derivatives are being developed in order to reduce the adverse events spectrum.[59]

Clofazimine is a lipophilic agent with antimicrobial, anti-inflammatory and immunosuppressant activities.[73] The most frequent adverse event is a brownish discoloration of the skin and bodily secretions, which is associated with high drug dosage and is reversible. Other adverse events include dry skin, occasional nausea and diarrhea and, in rare cases, eosinophilic enteritis and splenic infarction.[60] In

2005, a randomized, double-blind, controlled study compared clofazimine (100 mg daily) with chloroquine (250 mg daily) in 33 patients with SLE and active cutaneous lesions. After six months, a good response was observed in 12 of 16 patients (75%) in the clofazimine group and 14 out of 17 patients (82.4%) in the cloroquine group. This result suggests that clofazimine and chloroquine are equally effective in the control of cutaneous lesions in patients with SLE.[74] It is recommended that clofazimine should be used only in patients presenting exclusively cutaneous manifestations of the disease, at a dose of 100 mg per day, orally.[60,74]

Rituximab (RTX) is an anti-CD20 monoclonal antibody, that causes a specific depletion of peripheral B-lymphocytes that have transmembrane protein CD20. Through the induction of cellular lysis via antibody-dependent cellular toxicity, RTX significantly decreases the levels of these B-lymphocytes in peripheral blood, leading to the remission of cutaneous symptoms in most cases. RTX is ellected as the first choice therapy in patients with severe autoimmune diseases and is indicated in cases that are resistant to conventional treatment.[75] Tanaka et al., in their study, used RTX at 375 mg per square meter of body surface area, in weekly infusions, for two weeks, associated with an initial dose of prednisolone (15-40 mg) to treat five patients with CLE refractory to conventional treatment. They achieved good results, with improvement of clinical manifestations in all patients, maintaining remission of symptoms for up to 20 months.[76]

Anti-cytokine therapy has more restricted indications due to the need for further studies. In this category, Llorenteet al. conducted a research with anti-interleukin-10 therapy and observed clinical improvement in a group of six patients, comprehending cutaneous and joint lesions, with a significant reduction in the dose of prednisolone that was associated to the treatment.[77] Anti-tumor necrosis factor alpha (anti-TNFα) therapy with infliximab is still controversial, because literature reports that the administration of this medication to patients with rheumatoid arthritis is associated with the development of anti-dsDNA and, to a lesser extent, to the emergence of clinically active lupus.[52] However, it is known that, in lupus, TNFα levels are elevated, which would justify further research in this area. Aringeret al. demonstrated, through the association of infliximab with azathioprine or methotrexate, that there may be clinical improvement of the disease, despite the detection of anti-dsDNA.[53]

Such therapeutic approaches cause adverse effects that, to a greater or lesser extent, lead to immune disorders such as leukopenia, increasing the predisposition to infections and in the long term, to the development of malignancies. Nevertheless, immunosuppressants, antimalarials and immunotherapy have their established uses in the treatment of systemic disease and often lead to the remission of cutaneous lesions.[60]

TOPICAL TREATMENT

In some situations, cutaneous lesions are the only manifestations of disease and, considering the risk of adverse events that may be induced by the various drugs employed for systemic treatment, it is difficult to justify their use in such cases.[78] Topical treatment is also recommended when there are resistant or refractory lesions despite the systemic therapy.[79]

Topical treatment of skin lesions arising from systemic lupus erythematosus can be accomplished with corticosteroids, macrolide immunomodulators and UVA radiation.[60]

The topical application of corticosteroids (CE) can improve cutaneous manifestations related to all types of CLE.[59,80] They are used in isolated or refractory lesions, since the more chronic ones respond poorly to treatment with topic CE. Corticosteroids may be classified as fluorinated and non-fluorinated.[24] The latter cause more adverse events, such as atrophy, depigmentation, striae, telangiectasia, acne, folliculitis and superinfection by *Candida* therefore, it is recommended that they should be used for less than two weeks.[81] Because of the known side effects, treatments with EC should run for a limited time and rather intermittently. Depending on the affected area, topical applications for a few days to several weeks, followed by reduction in frequency and treatment pauses, can help minimize the risks of local adverse reactions.[47]

The choice of CE's class must be made considering the body area that is affected and the skin lesion's activity. For example: in the face, a brief application of mild to moderately potent CE, such as methylprednisolone; on the trunk and extremities, moderately potent CE, such as mometasone furoate, betamethasone valerate and triamcinolone; on the scalp, palms of hands and soles of feet, superpotent CE as clobetasol. In areas with hair, CE may be used as solution, lotion or foam.[47]

Due to the adverse events triggered by repeated or long-term use of corticosteroids, macrolide immunomodulators were introduced. They act on T-lymphocytes, hindering the transcription of interleukin-2 (IL-2) and other cytokines, through the inhibition of the calcineurin system.[65,82,83] Its efficacy in topical treatments is similar to or better than that of corticosteroids, especially in facial lesions or in children, situations in which only less potent

corticosteroids may be employed.[84] Topical immunomodulators have many advantages because they produce less systemic adverse events – as a consequence of their lower bioavailability – and also local ones - since they do not affect endothelial cells and skin fibroblasts - besides being an alternative therapy for patients with lesions that do not respond to available conventional treatments.[13,85] Some adverse events associated with the use of these drugs are: burning, redness, itching and folliculitis.[86] However, the intensity of these reactions tend to be reduced with regular use of the medication.[79] Recently, two inhibitors of the calcineurin system became available for topical use: tacrolimus (0.03% and 0.1% ointment) and pimecrolimus (1% cream).[13] Several studies have addressed the use of calcineurin inhibitors in dermatology, and reported positive outcomes on autoimmune skin diseases.[65,83,87] While cutaneous lesions of SLE usually respond well to treatment, only minor effects are observed in SCLE. For LEDs, the results are even less convincing, since hyperkeratosis will hinder the penetration of the drug into the skin. However, the need for more clinical studies on the use of calcineurin inhibitors is a consensus amongst researchers.[13]

PHOTOTHERAPY

The main action of phototherapy with UVA radiation is to induce leukocyte apoptosis, especially on B-lymphocytes.[88,89] This type of radiation decreases the amount of cells secreting IFN-γ - a key substance involved in the pathogenesis of SLE - thereby reducing the symptoms of the disease.[90] McGreath et al. reported encouraging results in patients with SLE treated with a fraction of UVA light spectrum's wavelength (340 to 400nm), called UVA-1. In these patients, there was a significant improvement in symptoms.[91] Furthermore, Polderman et al. and Szegedi et al. demonstrated positive results with UVA-1 in the treatment of patients with cutaneous lesions from SLE, thus claiming this to be an effective adjuvant therapy.[88,90] Caution is recommended in the treatment with UVA-1 radiation, on account of the extensively studied deleterious effects of ultraviolet radiation on cutaneous lupus.[92,93,94]

Regarding phototherapy, its consequences to human health can be beneficial but also adverse. This form of therapy can promote protection against polymorphic light eruption and immune diseases mediated by T cells, as well as cause skin cancer, trigger cutaneous lupus erythematosus and infectious diseases. However, due to its high cost, this treatment option should be restricted to patients with cutaneous lupus erythematosus who are resistant to standard therapies.[95]

SURGICAL TREATMENT

Cosmetic surgery treatments are of limited value in chronic scar lesions, especially given the risk of disease exacerbation - Koebner phenomenon - secondary to invasive procedures.[96,97] However, studies have shown that methods such as dermabrasion, hair transplant or autologous fat transplant were safe when performed in non-inflamed areas and in patients with controlled disease.[98]

OTHERS

Recent advances in biotechnology have lead to the development of novel systemic agents, but randomized controlled trials are still needed to approve new strategies for the treatment of CLE.[99]

CONCLUSION

Cutaneous lesions are the most frequent manifestations of systemic lupus erythematosus. They are important for providing information about the diagnosis and prognosis of the disease.

Lately, there has been a quest for topical treatment alternatives, especially when there is little systemic damage and the main manifestation of the disease is cutaneous involvement. Thus, new topical therapies for cutaneous lupus have emerged every day. Most recently, biologic agents, some widely used in the treatment of autoimmune diseases and other still under investigation, appear to have a promising role in the treatment of refractory cases. However, further studies confirming the therapeutic efficacy of these medications to treat cutaneous lupus are still needed. This represents a new approach in the treatment of CLE, since these drugs are effective in the desired site of action and have the advantage of not causing the inconvenient systemic manifestations.

Histopathological and morphological alterations in cutaneous lupus are diverse, thus deserving attention in the clinical management and the choice of the most effective therapy, while taking into consideration their spectrum of adverse events.❑

REFERENCES

1. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus. 2006;15:308-18.
2. Freire EAM, Souto LM, Ciconelli RM. Medidas de avaliação em lúpus eritematoso sistêmico (Assessment measures in systemic lupus erythematosus). Rev Bras Reumatol. 2011;51:75-80.
3. Sontheimer RD. Clinical manifestations of cutaneous lupus erythematosus. In: Wallace DJ, Hahn BH. Dubois' lupus erythematosus. Pennsylvania: Lea &Febiger; 1993. p.285-301
4. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and Validation of the Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus Arthritis Rheum. 2012;64:2677-86.
5. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25:1271-7.
6. Petri M, Magder L. Classification criteria for systemic lupus erythematosus: a review. Lupus. 2004;13:829-37.
7. Berbert ALCV, Mantese SA. Lúpus eritematoso cutâneo: aspectos clínicos e laboratoriais (Cutaneous lupus erythematosus - Clinical and laboratorial aspects). An Bras Dermatol. 2005;80:119-31.
8. Machado APB, Dykyj MT, Vandresen N, Skare TL. Mucocutaneous involvement in systemic lupus erythematosus and its association with autoantibodies. An Bras Dermatol. 2008;83:323-8.
9. Zecević RD, Vojvodić D, Ristić B, Pavlović MD, Stefanović D, Karadaglić D. Skin lesions: an indicator of disease activity in systemic lupus erythematosus? Lupus. 2001;10:364-7.
10. Gilliam JN. The cutaneous signs of lupus erythematosus. Cont Educ Fam Phys. 1977; 6:37-40.
11. Renner R, Sticherling M. The different faces of cutaneous lupus erythematosus. G Ital Dermatol Venereol. 2009;144:135-47.
12. Provost TT. Nonspecific cutaneous manifestations of systemic lupus erythematosus. In: Kuhn A, Lehmann P, Ruzicka T, editors. Cutaneous lupus erythematosus. Heidelberg: Springer; 2004. p. 93-106.
13. Sticherling M. Update on the use of topical calcineurin inhibitors in cutaneous lupus erythematous. Biologics. 2011;5:21-31.
14. Seitz CS, Bröcker EB, Trautmann A. Linear variant of chronic cutaneous lupus erythematosus: a clue for the pathogenesis of chronic cutaneous lupus erythematosus? Lupus. 2008;17:1136-9.
15. Martin DA, Elkon KB. Apoptosis. In: Wallace DJ, Hayn BH, editors. Dubois' lupus erythematosus. Philadelphia: Lippincott Willians & Willians; 2007. p. 118-32.
16. David-Bajar KM, Davis BM. Pathology, immunopathology and immunohistochemistry in cutaneous lupus erythematosus. Lupus. 1997;6:145-57.
17. Sontheimer RD, Maddison PJ, Reichlin M, Jordon RE, Stastny P, Gilliam JN. Serologic and HLA associations in subacute cutaneous lupus erythematosus, a clinical subset of lupus erythematosus. Ann Intern Med. 1982;97:664-71.
18. Amato L, Coronella G, Berti S, Moretti S, Fabbri P. Subcutaneous lupus erytematosus in childhood. Pediatr Dermatol. 2003;20:31-4.
19. Sontheimer RD. Subacute cutaneous lupus erythematosus: 25-year evolution of a prototypic subset (subphenotype) of lupus erythematosus defined by characteristic cutaneous, pathological, immunological, and genetic findings. Autoimmun Rev. 2005;4:253-63.
20. Sontheimer RD, Thomas JR, Gilliam JN. Subacute cutaneous lupus erythematosus: a cutaneous marker for a distinct lupus erythematosus subset. Arch Dermatol. 1979;115:1409-15.
21. Wallace DJ. The relationship between discoid and systemic lupus erythematosus. In: DJ Wallace, Hahn BH, Quismorio FP, Klinemberg JR, editors: Dubois' lupus erythematosus. Philadelphia and London: Lea & Febiger; 1993. p. 310-2.
22. Dubois EL, Wallace DJ. Clinical and laboratory manifestations of systemic lupus erythematosus. In: Dubois EL, Wallace DJ, editors. Dubois' Lupus erythematosus. Philadelphia: Lea & Ferbiger; 2002. p. 317-449.
23. Patel P, Werth V. Cutaneous lupus erythematosus: a review. Dermatol Clin. 2002;20:373-85, v.
24. Ribeiro LH, Nunes MJ, Lomonte ABV, Latorre L. Atualizações no tratamento do lúpus cutâneo (Updates in Cutaneous Lupus Treatment). Rev Bras Reumatol. 2008;48:283-90.
25. Massone C, Kodama K, Salmhofer W, Abe R, Shimizu H, Parodi A, et al. Lupus erythematosus panniculitis (lupus profundus): clinical, histopathological and molecular analysis of nine cases. J Cutan Pathol. 2005;32:396-404.
26. Requena L, Sánchez Yus E. Panniculitis (Part II). Mostly lobular panniculitis. J Am Acad Dermatol. 2001;45:325-61
27. Costner MI, Sontheimer RD, Provost TT. Lupus erythematosus. In: Sontheimer RD, Provost TT, editors. Cutaneous Manifestations of Rheumatic Diseases. Philadephia: Williams & Wilkins; 2003. p. 15-64.
28. Watanabe T, Tsuchida T. Lupus erythematosus a cutaneous marker for a distinct, profundus clinical subset? Br J Dermatol. 1996;134:123-5.
29. Ruiz H, Sánchez JL. Tumid lupus erythematosus. Am J Dermatopathol. 1999;21:356-60.
30. Dekle CL, Mannes KD, Davis LS, Sangueza OP. Lupus tumidus. J Am Acad Dermatol. 1999 Aug;41:250-3.
31. Zecević RD, Vojvodić D, Ristić B, Pavlović MD, Stefanović D, Karadaglić D. Skin lesions: an indicator of disease activity in systemic lupus erythematosus? Lupus. 2001;10:364-7.
32. Enríquez R, Sirvent AE, Amorós F, Pérez M, Matarredona J, Reyes A. Crescentic membranoproliferative glomerulonephritis and hypocomplementemic urticarial vasculitis. J Nephrol. 2005;18:318-22.
33. Khamashta MA, Hugues GRV. The clinical aspects of antiphospholipid syndrome In: Lahita RG, editor. Systemic Lupus Erythematosus. London: Elsevier; 2004. p. 1017-23.
34. Diamanti AP, Rosado MM, Carsetti R, Valesini G. B cells in SLE: differentbiological drugs for different pathogenic mechanisms. Autoimmun Rev. 2007;7:143-8.
35. Wallace DJ. Principles of therapy and local measures. In: Wallace DJ, Hahn BH. Dubois' lupus erythematosus. 6th ed. Philadelphia: Lippincott Willians & Wilkins; 2002. p. 1131-40.
36. Lin JH, Dutz JP, Sontheimer RD, Werth VP. Pathophysiology of cutaneous lupus erythematosus. Clin Rev Allergy Immunol. 2007;33:85-106.
37. Bijl M, Kallenberg CG. Ultraviolet light and cutaneous lupus. Lupus. 2006;15:724-7.
38. Bang B, Rygaard J, Baadsgaard O, Skov L. Increased expression of Fas on human epidermal cells after in vivo exposure to single-dose ultraviolet (UV) B or long-wave UVA radiation. Br J Dermatol. 2002;147:1199-206.
39. Reefman E, Kuiper H, Jonkman MF, Limburg PC, Kallenberg CG, Bijl M, et al. Skin sensitivity to UVB irradiation in systemic lupus erythematosus is not related to the level of apoptosis induction in keratinocytes. Rheumatology (Oxford). 2006;45:538-44.
40. Osterwalder U, Lim HW. Novel developments in photoprotection: Part I. In: Lim HW, Hönigsmann H, Hawk JLM. Photodermatology. New York: Informa Healthcare USA; 2007. p. 279-95
41. Miot HA, Bartoli Miot LD, Haddad GR. Association between Discoid Lupus erythematosus and Cigarette Smoking. Dermatology. 2005;211:118-22.
42. Boeckler P, Milea M, Meyer A, Uring-Lambert B, Heid E, Hauptmann G, et al. The combination of complement deficiency and cigarette smoking as risk factor for cutaneous lupus erythematosus in men; a focus on combined C2/C4 deficiency. Br J Dermatol. 2005;152:265-70.v.
43. Ghaussy NO, Sibbitt W Jr, Bankhurst AD, Qualls CR. Cigarette smoking and disease activity in systemic lupus erythematosus. J Rheumatol. 2003;30:1215-21.
44. Jewell ML, McCauliffe DP. Patients with cutaneous lupus erythematosus who smoke are less responsive to antimalarial treatment. J Am Acad Dermatol. 2000;42:983-7.
45. Leroux G, Costedoat-Chalumeau N, Hulot JS, Amoura Z, Francès C, Aymard G,, et al. Relationship between blood hydroxychloroquine and desethylchloroquine concentrations and cigarette smoking in treated patients with connective tissue diseases. Ann Rheum Dis. 2007;66:1547-8.
46. Bermudez EA, Rifai N, Buring JE, Manson JE, Ridker PM. Relation between markers of systemic vascular inflammation and smoking in women. Am J Cardiol. 2002;89:1117-9.
47. Kuhn A, Sonntag M, Sunderkötter C, Lehmann P, Vestweber D, Ruzicka T. Upregulation of epidermal surface molecule expression in primary and ultraviolet-induced lesions of lupus erythematosus tumidus. Br J Dermatol. 2002;146:801-9.
48. Seagrave J, Barr EB, March TH, Nikula KJ. Effects of cigarette smoke exposure and cessation on inflammatory cells and matrix metalloproteinase activity in mice. Exp Lung Res. 2004;30:1-15.
49. Schein JR. Cigarette smoking and clinically significant drug interactions. Ann Pharmacother. 1995;29:1139-48.
50. Jessor R, Turbin MS, Costa FM. Protective factors in adolescent health behavior. J Pers Soc Psychol. 1998;75:788-800.
51. Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update of therapeutic options part I. J Am Acad Dermatol. 2011;65:e179-93.
52. Karim MY, Pisoni CN, Khamashta MA. Update on immunotherapy for systemic lupus erythematosus - what's hot and what's not! Rheumatology (Oxford). 2009;48:332-41
53. Aringer M, Steiner G, Graninger WB, Höfler E, Steiner CW, Smolen JS. Effects of short-term infliximab therapy on autoantibodies in systemic lupus erythematosus. Arthritis Rheum. 2007;56:274-9.
54. Dubois EL. Antimalarials in the management of discoid and systemic lupus erythematosus. Semin Arthritis Rheum. 1978;8:33-51.

55. Ezra N, Jorizzo J. Hydroxychloroquine and smoking in patients with cutaneous lupus erythematosus. Clin Exp Dermatol. 2012;37:327-34.
56. Bolognia J, Jorizzo J, Rapini R. Dermatology, 2nd ed. Spain: Mosby Elsevier; 2008. p.527-3.
57. 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.
58. Wenzel J, Brähler S, Bauer R, Bieber T, Tüting T. Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. Br J Dermatol. 2005;153:157-62.
59. Sticherling M, Bonsmann G, Kuhn A. Diagnostic approach and treatment of cutaneous lupus erythematosus. J Dtsch Dermatol Ges. 2008;6:48-59.
60. Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update of therapeutic options: part II. J Am Acad Dermatol. 2011;65:e195-213.
61. Zwerner J, Fiorentino D. Mycophenolate mofetil. Dermatol Ther. 2007;20:229-38.
62. Pisoni CN, Obermoser G, Cuadrado MJ, Sanchez FJ, Karim Y, Sepp NT, et al. Skin manifestations of systemic lupus erythematosus refractory to multiple treatment modalities: poor results with mycophenolate mofetil. Clin Exp Rheumatol. 2005;23:393-6.
63. Schanz S, Ulmer A, Rassner G, Fierlbeck G. Successful treatment of subacute cutaneous lupus erythematosus with mycophenolate mofetil. Br J Dermatol. 2002;147:174-8.
64. Wenzel J, Bieber T, Uerlich M, Tüting T. Systemic treatment of cutaneous lupus erythematosus. J Dtsch Dermatol Ges. 2003;1:694-704.
65. Luger T, Paul C. Potential new indications of topical calcineurin inhibitors. Dermatology. 2007;215:45-54.
66. Davis JC, Klippel JH: Antimalarials and immunosuppressive therapies. In: Lahita RG, editor. Systemic lupus erythematosus. 4th ed. Massachusetts: Elsevier, Academic Press; 2004. p. 1279-81.
67. Fabbri P, Cardinali C, Giomi B, Caproni M. Cutaneous lupus erythematosus: diagnosis and management. Am J Clin Dermatol. 2003;4:449-65.
68. Sontheimer RD, McCauliffe DP: Cutaneous manifestations of lupus erythematosus. In: Wallace DJ, Hahn BH. Dubois' lupus erythematosus. 6th. ed. Philadelphia: Lippincott Willians& Wilkins; 2002. p. 573-618
69. Chang AY, Werth VP. Treatment of cutaneous lupus. Curr Rheumatol Rep. 2011;13:300-7.
70. Duna GF, Cash JM. Treatment of refractory cutaneous lupus erythematosus. Rheum Dis Clin North Am. 1995;21:99-115.
71. Knop J, Bonsmann G, Happle R, Ludolph A, Matz DR, Mifsud EJ, et al. Thalidomide in the treatment of sixty cases of chronic discoid lupus erythematosus. Br J Dermatol. 1983;108:461-6.
72. Tseng S, Pak G, Washenik K, Pomeranz MK, Shupack JL. Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. J Am Acad Dermatol. 1996;35:969-79.
73. Arbiser JL, Moschella SL. Clofazimine: a review of its medical uses and mechanisms of action. J Am Acad Dermatol. 1995;32:241-7.
74. Bezerra EL, Vilar MJ, da Trindade Neto PB, Sato EI. Double blind, randomized, controlled clinical trial of clofazimine compared with chloroquine in patients with systemic lupus erythematosus. Arthritis Rheum. 2005;52:3073-8.
75. García-Carrasco M, Jiménez-Hernández M, Escárcega RO, Mendoza-Pinto C, Galarza-Maldonado C, Sandoval-Cruz M, et. Al. Use of rituximab in patients with systemic lupus erythematosus: An update. Autoimmun Rev. 2009;8:343-8.
76. Tokunaga M, Fujii K, Saito K, Nakayamada S, Tsujimura S, Nawata M, et al. Down-regulation of CD40 and CD80 on B cells in patients with life-threatening systemic lupus erythematosus after successful treatment with rituximab. Rheumatology (Oxford). 2005;44:176-82.
77. Llorente L, Richaud-Patin Y, García-Padilla C, Claret E, Jakez-Ocampo J, Cardiel MH, et al. Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. Arthritis Rheum. 2000;43:1790-800.
78. Lampropoulos CE, Sangle S, Harrison P, Hughes GR, D'Cruz DP. Topical tacrolimus therapy of resistant cutaneous lesions in lupus erythematosus: a possible alternative. Rheumatology (Oxford). 2004;43:1383-5.
79. Rangel LV, Santiago JM, Souza JCC, Nascimento LFL, Santiago MB. Terapia Tópica com Pimecrolimus em Lesão Cutânea Refratária de Lúpus Eritematoso Sistêmico (Topical therapy with pimecrolimus in refractory cutaneous lesion of systemic lupus erythematosus.) Rev Bras Reumatol. 2006;46:230-3.
80. Ting WW, Sontheimer RD. Local therapy for cutaneous and systemic lupus erythematosus: practical and theoretical considerations. Lupus. 2001;10:171-84.
81. Werth T. Current treatment of cutaneous lupus erythematosus. Dermatol Online J. 2001;7: 174-8.
82. Ho S, Clipstone N, Timmermann L, Northrop J, Graef I, Fiorentino D, et al. The mechanism of action of cyclosporin A and FK506. Clin Immunol Immunopathol. 1996;80:S40-5.
83. Wollina U, Hansel G. The use of topical calcineurin inhibitors in lupus erythematosus: an overview. J Eur Acad Dermatol Venereol. 2008;22:1-6.
84. Bos JD. Non-steroidal topical immunomodulators provide skin-selective and self-limiting treatment in atopic dermatitis. Eur J Dermatol. 2003;13:455-61.
85. Gisondi P, Ellis CN, Girolomoni G. Pimecrolimus in dermatology: atopic dermatitis and beyond. Int J Clin Pract. 2005;59:969-74.
86. Tlacuilo-Parra A, Guevara-Gutiérrez E, Gutiérrez-Murillo F, Soto-Ortiz A, Barba-Gómez F, Hernández-Torres M, et al. Pimecrolimus 1% cream for the treatment of discoid lupus erythematosus. Rheumatology (Oxford). 2005;44:1564-8.
87. Sárdy M, Ruzicka T, Kuhn A. Topical calcineurin inhibitors in cutaneous lupus erythematosus. Arch Dermatol Res. 2009;301:93-8.
88. Polderman MC, le Cessie S, Huizinga TW, Pavel S. Efficacy of UVA-1 cold light as an adjuvant therapy for systemic lupus erythematosus. Rheumatology (Oxford). 2004;43:1402-4.
89. Godar DE. UVA1 radiation triggers two different final apoptotic pathways. J Invest Dermatol. 1999;112:3-12.
90. Szegedi A, Simics E, Aleksza M, Horkay I, Gaál K, Sipka S, et al.. Ultraviolet-A1 phototherapy modulates Th1/Th2 and Tc1/Tc2 balance in patients with systemic lupus erythematosus. Rheumatology (Oxford). 2005;44:925-31.
91. McGrath H, Martínez-Osuna P, Lee FA. Review: Ultraviolet-A1 (340-400nm) irradiation therapy in systemic lupus erythematosus. Lupus. 1996;5:269-74.
92. Lehmann P, Hölzle E, Kind P, Goerz G, Plewig G. Experimental reproduction of skin lesions in lupus erythematosus by UV-A and UV-B radiation. J Am Acad Dermatol. 1990;22:181-7.
93. Nived O, Johansen PB, Sturfelt G. Standardized ultraviolet-A exposure provokes skin reaction in systemic lupus erythematosus. Lupus. 1993;2:247-50.
94. Dawe RS. Ultraviolet A1 phototherapy. Br J Dermatol. 2003;148:626-37.
95. Norval M, Halliday GM. The consequences of UV-Induced immunosuppression for human health. Photochem Photobiol. 2011;87:965-77.
96. Rothfield NF, Braverman IM, Moschella S et al. Classification of lupus erythematosus. An open forum. Fitzpatrick's. J Clin Dermatol. 1994;1:9-12.
97. Ueki H. Koebner phenomenon in lupus erythematosus with special consideration of clinical findings. Autoimmun Rev. 2005;4:219-23.
98. Pinski KS, Roenigk HH Jr. Autologous fat transplantation. Long-term follow-up. J Dermatol Surg Oncol. 1992;18:179-84.
99. Kuhn A, Ochsendorf F, Bonsmann G. Treatment of cutaneous lupus erythematosus. Lupus. 2010;19:1125-36.

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How to cite this article: Moura Filho JP, Peixoto RL, Martins LG, Melo SD, Carvalho LL, Pereira AKFTC, Freire EAM. Lupus erythematosus: considerations about clinical, cutaneous and therapeutic aspects. An Bras Dermatol. 2014;89(1):118-25.