THERAPEUTIC ASPECTS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Summary

Lupus erythematosus is a multisystem disease with a wide range of manifestations, from relatively benign forms limited to the skin, to severe multivisceral damages with reserved prognosis.

Lupus erythematosus is still of great interest for clinicians and immunologists today, despite a century having passed since Biett's first description of what he called "erytheme centryfuge" (1823), the term "lupus erythematosus" being used for the first time by Cazenave in 1838.

Lately a lot of issues have been clarified and new concepts came to light regarding LE. However, this disease attracts the attention of researchers as its etiology is still incompletely understood, its evolution is variable, with exacerbations and remissions, and the treatment is still a challenge, even considering the discovery of biological therapy acting at different stages in the immune pathogenesis of the autoimmune diseases, which changed the therapeutic strategy.

Treatment for patients with lupus erythematosus is intended to achieve disease remission and maintenance for as long as possible, also preventing side effects of therapies.

This article intends to underline the importance and complexity of treatment in lupus erythematosus, through research of recent scholarly literature.

Keywords: *systemic lupus erythematosus, cutaneous lupus erythematosus, treatment, remission.*

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Introduction

Lupus erythematosus is an autoimmune disease characterized by auto-antibodies and immune complexes, causing cutaneous and/or multisystem damages which translate to inflammation, tissue injury and a wide range of clinical signs.

The term "Lupus" = wolf, ulcer (lat.) is an ancient one, used in Greek and Arab medicines, and having no defined meaning until the 19th century; it designates all terebrant ulcers with chronic evolution.

The disease is present all over the world but with geographical variations, and is more frequent in females, having a women: men ration of 3:1.

This disease has clinical, histological and biological aspects that are currently well defined, and are variable depending on the clinical form.

According to Düsseldorf classification (2003), cutaneous LE is divided into:

1. Chronic lupus;
2. Subacute lupus;
3. Acute lupus;
4. Intermittent lupus;

Cutaneous lupus erythematosus (CLE) is the most frequent clinical form of the disease, characterized by lesions (erythema, squamae, atrophy) with chronic evolution, rarely accompanied by visceral damage.

Treatment of lupus erythematosus aims to obtain a balance between preventing vital organ damage, maintaining a high quality of life and

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minimizing side effects. In this regard, a lupus patient must be closely observed and monitored.

Preventive treatment may reduce the risk of exacerbations.

General recommendations include avoiding ultraviolet radiation exposure, covering the exposed areas, using wide-brimmed hats, and consistently using sunscreen formulations. These creams with a sun protection factor over 30 will be applied in any season, 30-60 minutes before exposure, then every 4-6 hours. Avoiding other factors that could aggravate eruption, e.g. cold, wind, trauma, is also recommended. Protective measures are crucial for treatment success. [1, 2]

Disease progression is not significantly altered by diet, but a balanced diet adapted to weight, physical activity and disease is recommended. During exacerbation periods, a slightly higher caloric intake is recommended.

In patients with confirmed vitamin D deficiency, 800 IU vitamin D/day and 1.500 mg calcium/day are recommended, possibly associated with biophosphates in those with chronic use of corticosteroids and in post-menopausal women. [3, 4, 5]

Influenza and pneumococcal vaccination is recommended although vaccines have been involved in reactivation of the disease due to immunosuppression. [4, 5]

Lupus patients should avoid medications that induce photosensitivity or are involved in drug-induced lupus, as well as foods that increase skin sensitivity to UV radiation (parsley, celery).[4]

An adequate lifestyle is essential in treating lupus, as it reduces frequency and severity of outbursts, thus helping improve the quality of life.

It includes: regular physical activity, knowing and understanding the disease, avoidance of smoking and excessive alcohol consumption, a balanced diet, emotional support from friends and family. Friends and family of the patient must understand his/her disease, how it affects his/her life, the limitations and needs brought on by an active outburst, and how they can help him/her. In such cases, support groups can be helpful.[6,7.8]

Stress control is essential, as stress can trigger symptoms of lupus, so it is recommended to simplify the daily schedule, to delegate daily chores to other people, to take daily walks, to use relaxation techniques (meditation or yoga, massage, imagination stimulation). Relaxation therapies could help patients cope with a chronic disease, and increase the quality of life.

The prognosis of the disease improved very much in the last decades, due to improvements in diagnosis methods and discoveries in the therapeutic area.

Treatment goals are early diagnosis, regular and thorough monitoring, initiation of adequate treatment to achieve disease remission and maintenance for as long as possible, also preventing the side effects of therapies.[4]

1. Treatment of chronic cutaneous lupus erythematosus

– Local treatment includes:

Dermocorticoid preparations with medium or high potency, administered topically or intralesionally.

Active lesions must be promptly treated in order to limit the risk of scar formation.

Topical corticoids with high potency are preferred, such as methylprednisolone (Advantan), mometasone (Elocom), fluocinolone (Fluocinolon acetonid). In certain cases, dermocorticoids can be applied as occlusive patches or local hydrocortisone infiltrations 2 times/week. Ointments are more efficient than creams. On the scalp lotions, gels or solutions can be used. [2, 4, 9, 10]

Corticoids are the most potent and efficient topical anti-inflammatory drugs, also having the ability to inhibit cell division as well as collagen synthesis. The efficacy of topical corticoids depends on their potency, as well as their ability of percutaneous penetration, their activity depending on their capacity of binding to a specific receptor in the cytosol, and on the vehicle that incorporates them. Thus, a correlation has been established between the vasoconstrictor action of a topical corticoid, highlighted by the McKenzie and Stoughton vasoconstriction assay, and the anti-inflammatory potency of various glucocorticoid drugs. However, the side effects of local cortisone therapy must be considered:

cutaneous atrophy, telangiectases, hypertrichosis, local hypersensitivity. [1, 2]

Concerning the frequency of application of topical glucocorticoids, those with lower intensity of effect are applied more frequently, 2-3 times/day, while the strong ones only once a day. Due to the occurrence of tolerance phenomenon for both vasoconstrictor and antimitotic effects, discontinuous administration might be prescribed, using a double dose every other day. While some authors highlight a superior efficacy of the alternative treatment, the occurrence of another specific phenomenon, the "reservoir effect", contraindicates this type of therapy. [1, 2]

Pimecrolimus cream 1%, tacrolimus ointment 0.1%, 2 applications/day, for at least 6 weeks, could be used in discoid LE that does not respond to other treatments.[1, 12, 13, 14]

In some cases refractory to classic treatment, with lesions causing aesthetic complaints, vitamin A derivatives have been used with good results: **etretinate, acitretin .[15, 16, 17]**

Calcipotriol and imiquimode had reported efficiency in some patients.

Carbonic ice or liquid nitrogen cryotherapy may be used for old, fixed, keratotic lesions, one 10-15 second application every 2-3 weeks. [1, 9]

Cosmetic camouflage is used to conceal inaesthetic plaques.[18]

ND-YAG 1067 **vascular laser** can be used for telangiectasia reduction.

– Systemic treatment can use:

Synthetic antimalarial drugs, used for their anti-inflammatory and antibacterial effect through DNA binding, molecule stabilization, and inhibition of DNA replication and RNA transcription; these drugs have immunosuppressive effects through reduction of interleukin synthesis by monocytes and macrophages, they inhibit cell, antinuclear antibody and rheumatoid factor formation, as well as dissociation of circulating immune complexes; they reduce the activity of collagenase and hyaluronidase, have photoprotective effects, antiplatelet and membrane stabilizing properties. [9, 10]

Hydroxychloroquine (Plaquenil) is the first-line drug, with good tolerability and doses ranging between 200-600 mg/day (not more than 6 mg/kg) for several months. Therapeutic response is assessed after 4-8 weeks.[1, 2, 19]

Other synthetic antimalarial drugs, such as **Chloroquine** (Nivaquin 200-400 mg/zi) which is less well tolerated, Damoquine (Amodiaquine) and Atabrine (Mepacrine 100 mg/day) which have higher hepatotoxicity, are currently used only in forms that do not respond to other antipalludic drugs.[1, 2]

Notable side effects:

Hemolytic crises in patients with glucose-6-phosphate dehydrogenase deficiency, hemolytic anemia, aplastic anemia, thrombocytopenia, peripheral neuropathy, digestive intolerance.[19]

Cloroquine can cause bluish-grey or blackish-purple skin pigmentation, especially on pretibial areas and cephalic extremity, slowly reversible after treatment discontinuation. Polymorphous light eruptions are also possible: rash, lichen planus-type eruptions, fixed pigmented erythema, erythema annulare centrifugum, polymorphous erythema.[1, 9]

Alopecia and photosensitivity, mild transient headache, fatigue, irritability, toxic psychosis, apathy, confusion, depression, neural hearing loss, vertigo may also occur. Cardiovascular adverse effects that may occur: hypotension, ECG changes, cardiomyopathy.[20]

Antimalarial therapy can be also administered during pregnancy, as it does not affect the fetus.[21]

Ocular toxicity is the most problematic, because it causes irreversible retinal damage. Therefore ophthalmological examinations are recommended before starting the treatment, than every 6 months in order to detect premaculopathies.

Systemic corticotherapy, Prednisone 30-60 mg/day is used in short-term therapies, associated with antimalarial drugs after careful risk/benefit assessment, in disseminated CLE, in patients with arthralgia or scar tissue of the scalp,[2, 9] and also when antinuclear antibodies are present.

Use of corticosteroids comes with a series of adverse reactions that may occur, such as: acne, Cushingoid appearance, fragile skin fostering the emergence of ecchymoses, irritability, restlessness, depression, insomnia. In long-term

corticotherapy adverse reactions may occur, which include: cataract, avascular bone necrosis, osteoporosis, infections. Some diseases may be aggravated, such as diabetes, hypertension, glaucoma, gastric ulcer may occur, as well as increase in cholesterol and triglyceride serum levels.

Dapsone in 25-100 mg/day doses for 6-16 weeks is used for treatment of bulous lesions, panniculitis, oral ulcerations, in non-scarring types of LE, and also as alternative treatment in patients that did not respond to corticotherapy or synthetic antimalarial drugs. The antiinflammatory mechanism of action is the most important one for dapsone.

Dapsone use comes with side effects that include methemoglobinemia, hemolysis, agranulocytosis. To prevent these, it is recommended to associate iron, vitamin E, vitamin C, cimetidine. [21]

Retinoids (isotretinoin, etretinate, acitretin) have been used in cutaneous CLE, especially in verrucous, hypertrophic forms. [1, 9, 22]

The mechanism of action of retinoids consist of decrease in proliferation and increase in epidermal differentiation, decrease in erythema and cellular infiltration, inhibition of polymorphonuclear leukocyte migration, etc.

Etretinate may be used in doses of 1 mg/kg/day, but should be avoided in women that use oral contraceptives, due to its 100-day long half-life.

Acitretin (Soriatane) is a retinoic acid analogue, similar to etretinate and isotretinoin, but with a shorter half-life - 50 hours - which makes it preferable to etretinate. Adverse effects include: pruritus, xerosis, desquamation, dermatitis, mucosal dryness, alopecia, paronychia, gastro-intestinal symptoms, disruptions in lipid, calcium and phosphate metabolism, etc.

Clofazimine 50-200 mg/day has antimalarial effect and suppresses cutaneous lesions in 2/3 cases of CLE.[23] It is used in disseminated CLE, and as a side effect causes pink discoloration of the skin.

Cyclophosphamide (50-200 mg/day) is used in cases with multiple lesions, biological syndrome and a tendency towards systemic lupus, and in cases that did not respond to antimalarial drugs or topical corticoids.[2, 9, 10]

Azathioprine (Azasan, Imuran) is a purine antagonist which inhibits DNA, RNA and protein synthesis. It can reduce proliferation of immune cells, which results in a decreased autoimmune activity.

Azathioprine showed good results in LE with palmoplantar lesions, resistant to other treatments.[23]

Cyclosporin A had uneven results in cutaneous CLE. It induces expression of helper T cells, and stimulates the ability of T cells for lymphokine synthesis and release. The adverse effects that can occur are: gingival hyperplasia, tremor, nephrotoxicity, hepatotoxicity, bone marrow suppression. [24, 25]

Immunomodulators:

Thalidomide - initially administered in doses of 200 mg/day for several weeks, than progressively reduced to a maintenance dose of 25-50 mg/day, the treatment being no longer than 3-5 months.[2]

Thalidomide might suppress excessive production of tumoral necrosis factor alpha (TNF-alpha), and can regulate the adhesion of surface molecules involved in leukocyte migration.

Side effects of thalidomide include: drowsiness, hallucinations, headache, nausea, vomiting, constipation, abdominal pain, impotence, hypotension, oral and ocular dryness, pruritus, erythematous or papular rash, oedema of the face and limbs, genital bleeding, as well as severe effects such as: distal sensory polyneuropathy and teratogenicity.[26, 27] For these reasons, Thalidomide is no longer used.

Mycophenolate mofetil (CellCept) is administered for 6 months, 1-3 g/day. It inhibits inosine monophosphate dehydrogenase and suppresses de novo purine synthesis by the lymphocytes, thus inhibiting their proliferation. The drug inhibits antibody production.

Methotrexate – reversibly inhibits dihydrofolate reductase, limits the availability of one-carbon fragments needed for purine synthesis and conversion of deoxyuridine monophosphate to thymidine monophosphate during DNA synthesis and cell division.[28]

Gold compounds can regulate immune cell function and are used rarely, in CLE forms with fixed keratotic lesions. [1, 2]

Auranofin (Ridaura) - gold is taken up by macrophages, which in turn inhibit phagocytosis and stabilization of lysosomal membrane. It modifies immunoglobulins by decreasing prostaglandin synthesis and the activity of lysosomal enzyme.

Interferon alpha-2 - used on average in doses of 35 mil U/week for 4-8 weeks, with good results in controlling the immune function, but with rapid relapse after treatment discontinuation. [29, 30]

IV immunoglobulins can be administered to patients with severe forms of cutaneous CLE.

2. Treatment of systemic lupus

Synthetic antimalarial drugs and/or **glucocorticoids** are recommended for treatment of SLE without major organ manifestations.

NSAIDs can be used in patients having low risk of complications.

Azathioprine, mycophenolate mofetil and methotrexate are recommended to non-responsive patients or to those for whom the cortisol dose cannot be lowered to a level deemed acceptable for chronic use. These drugs must be used soundly, taking into account their side effects.

During aggravation stages corticoids in high doses are administered, 60-80 mg predisone/day, the dose being progressively lowered to 5-10 mg/day as soon as the situation seems under control.

In rapid progressive cases with kidney and CNS damage, pneumonia, and in some cases of refractory thrombocytopenia, bolus corticotherapy has been tempted, using high doses of over 100 mg methylprednisolone/day, administered in iv perfusion over a period of 4 hours, with 500 ml isotonic saline solution. This dose is repeated for 3 consecutive days. [31, 32]

High doses of corticosteroids associated with cyclophosphamide has been the golden standard in treatment of proliferative lupus nephritis for many years; while effective, this treatment is limited by significant toxicity.

Monthly pulse **cyclophosphamide** therapy can be useful in renal damage; 1 g/m^2 body surface area/month is administered for 6 months, followed by a 3-month pause, then the treatment is resumed, up to a 2-year duration while monitoring the active inflammation through renal biopsy, and the level of serum creatinine.

In 2002 the so called Euro-Lupus regimen was published, which argues the use of "low dose" cyclophosphamide (500 mg pulses once every 2 weeks), leading to the reduction of infertility risk, with no negative impact on renal disease.[33]

In SLE with renal damage cortisol and immunosuppressants are used. Cyclophosphamide improves long-term prognosis, but with the risk of important side effects in proliferative forms of lupus nephritis.

Mycophenolate improves short- and medium-term prognosis, with less significant adverse reactions.

Cyclophosphamide associated with corticotherapy slows down the progression of renal damage more than individual corticotherapy, but does not impact mortality.

Plasmapheresis is used only in exceptional cases, when no other treatment proved efficient (alveolar hemorrhage, thrombocytopenic purpura, hyperviscosity syndromes, cryoglobulinemia). It must be associated with Cyclophosphamide immunosuppression. [34]

IV immunoglobulins - used in 400 mg/kg/day doses for 5 consecutive days, in thrombocytopenia, hemolytic anemia refractory to corticotherapy and immunosuppression, neurological impairment refractory to conventional treatments, severe cutaneous damage refractory to conventional treatments.

Hormone therapy – **Danazol** is used in thrombocytopenia refractory to other types of treatment.

Anticoagulant treatment - used for treating thromboses within the syndrome.

DHEA treatment - it is an androgenetic food supplement extracted from wild yam; its use seems to reduce symptoms of lupus, but research results are inconsistent. Adverse effects are acne and hirsutism in women, and alopecia in men, so it is recommended to monitor DHEA blood levels every 6 months.

Surgical treatment is recommended for patients with severe impairment of kidney function, final stage lupus nephritis. Kidney

transplant or dialysis are preferred for these patients, instead of administering long-term treatment with high doses and important side effects. Kidney transplant or dialysis area also the best option for patients who do not respond to high-dose corticosteroid treatment or immunosuppressive medication.

For unknown reasons, lupus progression during dialysis or following kidney transplant is less severe, and it is possible that recurring lupus nephritis does not occur in allograft.

Therapeutic methods currently under research include stem cell transplant and biological therapies.

Stem cell transplant consists of replacing bone marrow cells affected by disease with new, healthy ones - stem cells.

Umbilical cord blood-derived stem cells (uMSCs) have been used for treating lupus nephritis in SLE mouse models, beneficial results being reported in a study by Taiwanese researchers.[35]

3. Biological treatments

These therapies include new immunosuppressive agents, biological medication, tolerance agents, immunoablation and hormone medicines. Some of these therapies are currently involved in research studies, and others are ready to begin clinical testing.

Genetics and phenotypic heterogeneity characteristic to SLE, as well as the fluctuant activity of the disease made it difficult to get a beneficial response from these therapies, especially considering that many effects were the same as the ones of immunosuppressive therapies.

The first biological agent used against B-cells for treating SLE was rituximab, a mouse/human chimeric monoclonal antibody targeted against CD20. CD20 is expressed ever since the early phases of lymphocyte B development. Use of rituximab led to fast depletion of CD20-positive B lymphocytes. After administering rituximab, some patients restored native B cells and went into remission. [9, 22, 30]

Rituximab was used in open studies and an improvement in disease progression was reported. Additionally, it proved safe to use and well tolerated. Two large, multicenter, placebo-controlled trials that used rituximab in patients with moderate and severe forms of LE (EXPLORER) and in patients with proliferative lupus nephritis (LUNAR) were not able to demonstrate a positive effect of the drug as compared to placebo. Adverse effects of rituximab are generally mild: perfusion accidents (30-35%), neutropenia (8%), and human anti-heme antibodies (9%). However, two fatal cases of progressive multifocal leukoencephalopathy were reported in patients treated with rituximab. Rituximab had inconclusive results in lupus nephritis.

Belimumab is a human monoclonal antibody that binds BlyS and inhibits its activity.

A multicenter, two-phase trial was done to study efficacy, tolerability, and safety of belimumab in SLE therapy, which reported a decrease in disease activity and recurrence after 52 weeks of analysis.[36]

Atacicept is another BlyS blocker; it is a soluble transmembrane activating receptor, dependent on calcium, also an interactive ligand for cyclophilin that binds BLyS and APRIL with antagonistic effects. It was used in patients with generalized SLE to diminish signs of disease, and in patients with lupus nephritis in order to improve kidney response to treatment.

Ocrelizumab, a recombinant humanized anti-CD20 monoclonal antibody, has been studied in phase 3 trials for extrarenal SLE and lupus nephritis. Use of ocrelizumab was firstly discontinued in the BEGIN trial due to negative results obtained in a similar trial with rituximab anti-CD20 antibody, and more recently in the BELONG trial due to occurrence of opportunistic infections in patients treated with ocrelizumab and standard therapy, as compared to those receiving only standard therapy.

New monoclonal anti-CD20 antibodies were discovered, either completely humanized - ofatumumab and GA-101-RO5072759, or 90% humanized - veltuzumab. They were only used in lymphomas and rheumatoid arthritis, and there are no data regarding their use in SLE. [19,22]

While there are a large number of biological medications that target specific lymphocyte receptors, only few of them proved useful.

Conclusions

Treatment for patients with lupus erythematosus is intended to achieve disease remission and maintenance for as long as possible, at the same time preventing the side effects of therapies.

It was found that antimalarial drugs halve the exacerbation episodes in SLE, methotrexate shows good compliance on articular and cutaneous components and on disease activity, while azathioprine proved beneficial in SLE without kidney and neurological damage.

Biological agents are promising therapeutic alternatives, as they avoid unspecified immunosuppression which translates to high risk of infections and neoplasia. Their use is based on the understanding of the pathogenic mechanisms of the disease, these substances trying to interfere with the immune processes, such as T-cell activation and collaboration with B cell, production of autoantibodies, immune complex deposition, complement and cytokine activation. However, the results of many studies have been inconclusive.

There are many treatment attempts where classic drugs (corticoids and cytostatic) are associated with titrated doses of biological therapies.

There is no fully adequate medication at the moment to induce durable and long-term remission of lupus erythematosus.

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Conflict of interest
NONE DECLARED

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