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Review / Derleme

Approach to systemic lupus erythematosus and skin lesions

Sïstemik lupus eritematozus ve deri lezyonlarına yaklaşım

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Abstract

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease that involves a broad spectrum of symptoms. The underlying cause of LE is unknown but the etiology is thought to be multifactorial and polygenic. Although it can occur in both genders, it has a higher incidence in women, commonly around 30 years of age. The cutaneous manifestations of lupus are pleomorphic. Various cutaneous manifestations of LE are divided into LE-specific and LE-nonspecific skin diseases based on histological criteria. Treatment is based on preventive measures, reversal of inflammation, prevention of damage to target organs and relief of adverse events due to pharmacological therapy. In this review, clinical signs, especially skin manifestations of SLE, diagnostic criteria and treatment options have been discussed.

Keywords: cutaneous lupus erythematosus, systemic lupus erythematosus, skin manifestations, therapy

Özet

Sistemik lupus eritematozus (SLE), geniş spektrumda semptomları barındıran, kronik otoimmün bir hastalıktır. Lupus eritematozusun (LE) nedeni tam olarak bilinmemektedir fakat etiyoloji multifaktöryel ve poligenik olabilir. Her iki cinsiyeti etkileyebilse de özellikle 30 yaş civarı kadınlarda insidansı daha yüksektir. Lupusun kutanöz bulguları polimorfiktir. Lupusun kutanöz bulguları histolojik kriterlere göre lupusa spesifik ve lupusa spesifik olmayan lezyonlar olarak ayrılmaktadır. Tedavi, koruyucu önlemler, inflamasyonun baskılanması, hedef organlardaki hasarın önlenmesi ve farmokolojik tedaviye bağlı yan

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etkilerin azaltılmasına dayalıdır. Bu derlemede, klinik bulgular, özellikle LE'un kutanöz bulguları, tanı kriterleri ve tedavi seçenekleri tartışılmıştır.

Anahtar sözcükler: kutanöz lupus eritematozus; sistemik lupus eritematozus; deri bulguları; tedavi

Introduction

SLE is a multisystemic condition that could affect skin, joints, kidneys, lungs, nervous system, serous membranes and blood cells [1]. Although the etiology could not be clearly explained, genetic factors, environmental factors (UV rays, viral infections and chemicals), hormones and emotional factors are accepted as important triggers causing disease initiation. Immunological tolerance loss, autoantibody production, deficiency in removal of immunocomplexes and activation of the complement system result in cell and tissue damage, due to interaction of these factors [2].

In the prevalence studies about SLE, it was found that the prevalence is higher in females (female/male ratio: 4.3-11.7) and in afrocaribbean population; and, the incidence in the United States of America (USA) changes between 1.8 and 5.56 per 100000. Higher prevalence rates in afrocaribbean population in the UK compared to afrocaribbean population in Africa demonstrates that environmental factors are as important as genetic factors [1, 3]. As the majority of cutaneous lupus erythematosus (CLE) patients possess sun sensitivity, especially UVB could cause flaring of the condition [4]. It is known that, 57-73% of the LE patients, 70-90% of the subacute CLE (SCLE) patients, 50% of the discoid lupus erythematosus patients (DLE) and almost 100% of the lupus erythematosus tumidus (LET) patients report photosensitivity. Although it was found that smokers experience more severe clinical symptoms and the treatment, especially antimalarial medications, is affected in a negative aspect, compared to non-smoking patients; no such association was defined for alcohol consumption [5, 6]. Medications like hydrochlorothiazide, calcium channel blockers and terbinafine could lead to creation of SCLE and CLE lesions [5]. The autoantibodies created in SLE target nuclear antigens, especially nucleic acids such as RNA and DNA. As antinuclear antibody (ANA) presence and production is one of the characteristics of LE, it provides a positive result for over 95%. Anti-dsDNA is positive during a period of illness, in 70% of the patients, and specificity is approximately 95% [7].

Clinical properties

SLE could lead to different clinical tables in varying spectrums such as localized cutaneous lupus to systemic lupus, as it is a chronic, autoimmune and multisystemic disease [8]. In SLE cases, at any stage of the disease, cutaneous symptoms are seen at the rate of 72-85%, found as the first symptom in 23-28% [9]. Cutaneous lesions of lupus are divided into two groups: lupus specific and lupus non-specific, according to histopathological symptoms [10].

Cutaneous lesions specific to lupus

Lupus specific cutaneous lesions are grouped as acute, subacute, chronic and intermittent, according to genetic, clinical, histological and immunoserological signs [9].

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Acute cutaneous lupus erythematosus (ACLE)

Localized or generalized lesions demonstrating obvious photosensitivity could be observed.

Localized form is more commonly observed and is characterized by malar rash. The erythema on bilaterally and symmetrically nose bridge and with defined margins on cheeks, in the shape of a butterfly, does not involve the nasolabial folds. The erythema that develops after being prone to sunlight is in a temporary character, ranging from few hours to few weeks, heals without creating scars [8]. Telangiectasia, pigmentation disorder and epidermal atrophy could accompany the lesion that is commonly in the shape of erythematous edematous plaque. Primarily epidermis and superficial dermis are involved. Localized form is observed in 60% of SLE and 15% of SCLE cases [9].

Generalized form is observed symmetrically in the entire body as morbiliform or maculopapular exanthema. Palmoplantar region, hand and foot dorsums, especially interphalangeal region extensors are involved. Although interphalangeal region is involved, different to dermatomyositis, knuckle regions are not involved. Erythema, telangiectasia and red lunula could be spotted on nail folds. Mucosal enanthema, erosion and superficial ulcerations commonly accompany acute flaring. Although mucosal lesions are settled generally on hard palate, they could also be observed at gingival or buccal mucosa. Also, erosive or dry chelitis could be detected [9]. It is related to acute form SLE activity, 40-90% Anti Ds-DNA and 10-30% Anti-Sm antibody positivity could be detected [4].

As localized and generalized form ACLE lesions demonstrate a non-scarring healing, occasionally post inflammatory hyperpigmentation can arise [4]. Diffuse thinning could be observed on hair in the scalp border and this is named as the “lupus hair” [9].

Subacute cutaneous lupus erythematosus (SCLE)

Photosensitive skin lesions symmetrically involve regions outside the midline of the face, neck V, superior regions of back, shoulders, extensor regions of upper extremities and hand dorsums [11]. Lesions could initiate as erythematous papules or plaques and develop into wide annular polycyclic lesions or psoriasiform plaques healing from the centre [8]. Non-scarring lesions generally heal by a residual hyperpigmentation.

Lesions involve epidermis and superficial dermis. Arthralgia and myalgia are the commonest observed extracutaneous symptoms. ANA is 60-80% positive. Conversion to SLE is at the rate of 10-15%. Positivity rate is 70-90% for Anti-Ro and 30-50% for Anti-La [9].

Calcium channel blockers, especially hydrochlorothiazide and terbinafine; non-steroidal anti- inflammatory medications, griseofulvin and antihistamines could be related to SCLE [9, 12].

Chronic cutaneous lupus erythematosus (CCLE)

Discoid lupus, lupus erythematosus tumidus, lupus panniculitis and chilblain lupus are present in this group.

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Discoid lupus erythematosus (DLE)

Discoid lesions are the most commonly observed cutaneous lesions in chronic form. Localized form (60-80%) is limited to the superior section of neck, scalp; and, skin lesions are the primarily affected regions; in generalized form (20-40%) lesions can be observed in inferior section of the neck additional to the superior section of the neck.

Erythematous, keratotic plaques with defined borders could demonstrate peripheral development and acquire a discoid character. Central depigmentation heals by leaving an atrophic scar in lesions with peripheral hyperpigmentation. Mucosal involvement could be observed in the ratio of 25%. Lips, cheeks and palate mucosa are in the most commonly affected regions [8]. Lesions could settle to sun-exposed and sun-protected areas. Histopathologically epidermal, superficial and deep dermal; and, adnexal structure involvement is observed.

As discoid lesions possess scarring potential, scalp involvement could result with cicatricial alopecia [9]. ANA positivity with high titres are seen at the ratio of 5%, low titre positivity could be detected up to 50 % [13].

There is no obvious systemic disease in a great majority of patients. Rarely, squamous cell carcinoma could develop on long term discoid lesions.

Lupus panniculitis

It is observed as painful subcutaneous nodules or endurated plaques in the adipose tissue, developing secondary to intensive inflammation. Lobular panniculitis is characterized by hyaline necrosis in adipose lobule and high grade lymphocytic infiltration.

It is characterized by endurated subcutaneous nodules and plaques on proximal extremity trunk, face and scalp [4].Cases reporting periorbital edema as the initial symptom are also present. It could create depressed scars secondary to deep lipoatrophy or could ulcerate. 70% of the patients demonstrate a relationship with DLE and ANA positivity is at a ratio as high as 75% [9].

Chilblain lupus (Hutchinson lupus)

In women, especially in winter months at cold extremities of body such as toes, fingers, nose, knees, heels and ears, it is characterized with pernio-like painful, blue-purple coloured plaques or nodules. Histologically, superficial and deep perivascular infiltration, edema and variable mucin deposition is observed. Although the mechanism is not clearly explained, vasoconstriction and microvascular damage induced by cold is thought to be responsible from the sporadic results [4].

Intermittent cutaneous lupus erythematosus (ICLE)

Lupus erythematosus tumidus (LET)

Papule and plaque shaped lesions with clear borders, smooth surface, erythema and urticaria are mostly located on regions prone to sunlight. Annular, centrifugal and crescent shapes could be formed. It is characterized by dermal infiltration without epidermal

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involvement. Lesions heal without causing atrophy, scar, hypopigmentation or hyperpigmentation. ANA positivity is between 10-30% [4, 9].

Other variants Bullous lupus

Bullous lupus is a rarely observed clinical condition with subepidermal involvement; and, is generally associated with acute and severe SLE. Bullous skin signs could develop due to severe basal cell damage in ACL, SCLE or DLE lesions. In some cases, lesions like erythema multiforme or toxic epidermal necrolysis could be observed [9].

Neonatal lupus erythematosus

This condition develops as a result of transfer of maternal antibodies to the fetus through transplacental pathway. Anti-Ro or Anti-La antibody presence in mother and fetus are characteristic diagnostic signs. Frequently, SCLE-like erythematous annular lesions are observed in sun prone regions. Although skin lesions generally appear in the first week of life, they could sometimes be present at birth as well. Skin lesions spontaneously regress in six months due to disappearance of antibodies. It could result in development of haematological or hepatic anomalies and congenital atrioventricular block [8, 9].

Non-genuine cutaneous lesions

Although non-specific signs of lupus are greatly associated with systemic lupus, they could accompany other diseases as well. Raynaud phenomena, livedo reticularis, thrombophlebitis, erythromelalgia, periungal telangiectasia could be named as vascular lesions. Purpura, urticarial vasculitis-like lesions, Degos disease or atrophic blanchia-like cutaneous infarcts could develop secondary to vasculitis. Urticeria, erythema multiforme, lichen planus-like lesions, sclerodactyly, acanthosis nigricans, calcinosis cutis, rheumatoid nodules, papulonodular mucinosis, anetoderma, leg ulcers and cicatricial alopecia are the other non- specific cutaneous signs [9].

SLE diagnosis

Skin, joints, kidneys, lungs, cardiovascular system, nervous system, serous membranes, haematological system and other organs could be affected in SLE. In Table 1, SLE classification criteria updated by ACR in 1997 is demonstrated. SLE diagnosis is made if [4] or more criteria are fulfilled by the patients out of the total of 11 criteria [14].

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Table 1. SLE classification criteria

1. Malar rash (fixed erythema on the malar region, radiating to cheeks from base of the nose, where nasolabial sulcus is protected)
2. Discoid rash (erythematous plaques involving keratotic and follicular occlusions, atrophic scar can develop on old lesions)
3. Photosensitivity (skin rash that is elicited from the history or clinical examination, resulting from exposure to sunlight)
4. Oral ulcers (oral or nasopharyngeal ulcers detected in clinical examination, are generally painless)
5. Arthritis (arthritis that is not erosive characterized by sensitivity affecting two or more peripheral joints, swelling and effusion)
6. Serositis Pleuritis: Detection of pleuritic pain history or pleurisy symptoms Pericarditis: Demonstration of pericardial effusion by echocardiography and clinical examination signs
7. Renal signs 0.5g/day proteinuria or >3 +proteinuria presence Presence of cell factors (erythrocyte, haemoglobin, granules, tubular or mixed)
8. Neurological signs (Attack or psychosis: unrelated to medications or a known cause (uraemia, ketoacidosis, electrolyte imbalance)
9. Haematological signs Haemolytic anaemia: with reticulocytosis Leucopenia: <4000/mm3 Lymphopenia: <1500/mm3 (two or more measuring are required) Thrombocytopenia: <100.000/mm3 (unrelated to medications) (two or more measuring are required)
10. Immunological signs Anti-dsDNA positivity Anti-Sm positivity Antiphospholipid antibody positivity Anticardiolipin antibody IgG or IgM positivity Lupus anticoagulant test positivity False positive syphilis test
11. Anti-nuclear antibody (ANA) positivity (unrelated to the use of any medications related to drug induced lupus syndrome)

However, in everyday clinical use, according to the clinical signs of the patients, occasionally SLE diagnosis could be made by presence of two or three criteria; or, it could

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be followed up as lupus-like disease. Finally, in 2012, SLICC study group has developed SLE classification criteria that is demonstrated in the Table 2. The most important updates in this are inclusion of signs like hair loss, low complement values and Coombs test positivity; clinical and immunological separation of the criteria; and, separate evaluation of haematological criteria. According to the classification criteria demonstrated in Table 2, SLE diagnosis could be made by presence of at least one immunological one clinical sign and again, fulfillment of 4 criteria is necessary [3].

Table 2. 2012 SLICC classification criteria for SLE

Clinical Signs	
Acute cutaneous lupus	Cutaneous lupus-psoriasis like or non-scarring annular polycyclic lesions without malar rash, bullous lupus, maculopapular lupus rash, photosensitive lupus rash
Chronic cutaneous lupus	Classical discoid rash (localized on the superior region of neck or widespread), lupus panniculitis, mucosal lupus, chilblain lupus, discoid/lichen planus overlap
Oral or nasal ulcers	On hard palate or tongue
Alopecia	Diffuse thinning and breaking in non-medicated hair
Synovitis/Arthritis	Characterized by swelling and effusion affecting 2 or more joints Sensitivity in the joint (together with morning stiffness in 2 or more joints lasting for longer than 30 minutes)
Serositis	Typical pleurisy (>1 day) or pleural effusion or pleural frontman Typical pericardial pain (>1 day) (increasing on lying down, easing with leaning front) or pericardial effusion or rubbing sound or pericarditis signs on ECG
Renal involvement	Urine protein/keratine ratio or proteinuria over 500 mg or erythrocyte cylinders in 24 hour urine, kidney biopsy
Neurological involvement	Attack, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state
Haemolytic anaemia	Leucopenia (at least once below 4000) *Lymphopenia (at least once below 1000) Thrombocytopenia (at least once below 100000)
Immunological criteria	
ANA positivity	
Anti-ds DNA positivity	
Anti-Sm	
Anti-phospholipid antibody positivity	Lupus anticoagulant, anticardiolipin IgG, IgM, IgA, anti-Beta2-glycoprotein I IgG, IgM, IgA, false positive syphilis test

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Low complement levels	C3, C4, CH50
Direct Coombs test positivity	Without haemolytic anaemia

Treatment

SLE does not have a standardized treatment pathway, the treatment pathway demonstrates variations according to the disease activity and affected organs [3].Immunosuppressive, cytotoxic and immunoglobulin methods could be counted as the most commonly used treatment modalities [2].It is advised to avoid UV exposure, cigarette smoking and the lifestyle that could trigger and alleviate cutaneous lesions. In skin, joint, light haematological inclusion and serositis cases, low-medium dose steroid and antimalarial medications are used. In resistant cases, medications like azathioprine and methotrexate are prescribed. Dapsone or thalidomide is preferred for the patients with resistant cutaneous involvement. In the last years, B cell treatment methods like Anti CD-20 (Rituximab) and LJP-394 (Abetimus Sodium) has been introduced as a treatment modality for patients with SLE. Phase experimentations for Anti CD-40 and CD-40L, which are medications developed for helper stimulator molecules, is still continuing [15].

In cutaneous LE treatment, it is essential to primarily avoid the triggering factors like sun exposure and smoking. Topical steroid and calcineurin inhibitors are advised as the first line treatment. For the systemic treatment, the first choice is antimalarials. In 75% of patients, response to treatment is achieved with topical treatment and antimalarial use. Retinoids, methotrexate, thalidomide, mycophenolate, azathioprine and dapsone could be tried in resistant cases [8].

Protection from the sunlight

Avoidance of sun exposure, artificial UV radiation and potential photosensitizing medication use are vital for the CLE and SLE patients. Beside cutaneous signs, it is proven that internal organ involvement, especially nephritis, could be triggered by sun exposure [16]. Octocrylene provides UVB protection, chemicals like mexoryl SX, mexoryl XL and parsol 1789 provide UVA protection, titanium dioxide is a physical barrier and provides protection from both UV rays and visible light [5, 16].Sunscreens need to be applied 20-30 minutes before the exposure. Clinical evidence is present that renal involvement and immunosuppressive treatment requirement is lower in SLE patients using sunscreen. In sun avoidance and daily regular sunscreen use, 25-hydroxyvitamin D levels were demonstrated to be significantly lower; and, in CLE and SLE patients, 400 IU/day vitamin D3 use is advised [16].

Topical treatment options

Topical steroids

Topical steroids could be used in all CLE lesions. Products with different potencies should be preferred according to localization of the lesions. Low potency products like methylprednisolone for the face; mometasone furoate, betamethasone valerate and triamcinolone for the trunk and extremities; clobetasol for scalp and palmoplantar region,

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could be used. Intralesional steroid injection could be applied in DLE lesions unresponsive to topical steroids. Triamcinolone acetonide could be applied with intervals, not for shorter than 4-6 weeks, with the dose of 2,5-5 mg/ml on face and with varying concentrations up to 10 mg/ml on other regions [5, 16].

Topical immunomodulators

Topical immunomodulators should be preferred especially in face lesions and children, due to the side effects that could develop because of long term topical steroid use. In DLE and SCLE lesions, pimecrolimus cream (1%) and tacrolimus pomade (0.03% and 0.1%) 2x1 dose could be used; and, result in visible improvement within 4-8 weeks. Pimecrolimus is 20 times more lipophilic compared to tacrolimus, and it is a calcineurin inhibitor with a higher skin affinity [16].

Topical retinoids

Tazaroten 0.05% gel or tretinoin 0.025-0.05% gel/cream could be used in hypertrophic DLE lesions [5, 16].

Imiquimod

Imiquimod 5% cream could be used 2-3 days per week in DLE lesions [16].

Physical treatment

Cryotherapy, dermabrasion and laser treatments could be used in chronic persistent DLE lesions; however, as new lesion appearance and flaring could be caused due to the Koebner phenomenon, it could be experimented on selected patients [16].

Phototherapy

UV radiation is a well-known triggering factor for cutaneous lesions and could cause flaring of the systemic symptoms. In order to improve the tolerance development in SCLE cases responding to low dose UVA1 treatment and in photosensitive CLE lesions, UVB-hardening treatment could be attempted [16].

Systemic treatment options

Systemic treatment indication exist in the conditions where skin lesions are widespread, causing shape distortion, leaving scars or demonstrating resistance to topical treatments; and, in the presence of extracutaneous symptoms such as arthritis [16].

First line treatment options

Antimalarials

Antimalarial medications (hydroxychlorine, chloroquine, quinacrine) are accepted as the first line treatment options. Especially hydroxychloroquine sulphate with 200- 400 mg/day (<6.5 mg/kg) dose, is the primarily preferred medication. Although effect is seen after 4-8 weeks on average, it is beneficial for both skin and joint signs [5]. Mostly hydroxychloroquine is used as 200-400 mg/day per oral. Generally they help decreasing the steroid dose in cases with SLE. At the same time, anti-thrombotic and antilipidemic effects are present. Antimalarial medications could be used for long term in SLE treatment.

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Regular ophthalmology examination at every 6-12 months is advised because of the renal toxicity side effect.3 Chloroquine could be used at the dose of 250-500 mg/day but compared to hydroxychloroquine, ocular toxicity is more prominent. Nausea, vomiting, diarrhea and weight loss are the important antimalarial side effects. Skin pigmentation changes, peripheral neuropathy, myopathy, cardiomyopathy, haematological toxicity, psychosis and epileptic attacks are the other side effects [5].

Steroid treatment

It is the choice of treatment in almost all cases of SLE. Steroid treatment in various doses could be used depending on strength of the disease and the organs affected. However, side effects of steroids could be apparent in patients who require high dose steroid treatment. For this reason, good follow up of the steroid-using patients and prescribing the minimum efficient dose of steroid for the shortest time is vital [3]. Low dose systemic steroid is partially effective in DLE and SCLE lesions. It could be effective in acute lesions related to photosensitivity, malar rash and vasculitic lesions [5]. Long term steroid treatments could cause a great number of problems such as infections, osteoporosis, osteonecrosis, glucose and lipid metabolism malfunction, hypertension, early atherosclerosis and hypothalamus-pituitary- adrenal gland axis suppression.

Second line treatment options

Methotrexate (MTX)

It is the second line treatment option for the antimalarial-resistant CLE patients. It could be used in localized SCLE and DLE cases and in conditions where antimalarials could not be tolerated. It could be used weekly at 7,5-25 mg (0.2 mg/kg) dose through oral, intravenous or subcutaneous administration route [2]. Folic acid supplementation 5 days per week, except the day of MTX administration and the day after, should be provided [17]. Lately, it is reported that methotrexate is successfully used in resistant arthritis cases [18].

Retinoids

Synthetic retinoids (isotretinoin and acitretin) are the second line treatment options for the CLE cases that antimalarials are insufficient. They could be used especially in subacute cutaneous lupus where hyperkeratosis is obvious and resistant discoid lupus [2, 5]. Acitretin could be used at 0.2-1 mg/kg/day dose and isotretinoin could be used at 0.5-1 mg/kg/day dose. As both retinoids have a teratogenic character, efficient contraception must be performed during and after the treatment, 1 month post-treatment for isotretinoin and 2 years post-treatment for acitretin [17].

Dapsone

It could be used in lupus related vasculitic lesions, SCLE, bullous lupus, lupus panniculitis and oral ulcerations. It could be used in inflammatory lesions that are not hyperkeratotic, at 25-200 mg/day dose [5].

Mycophenolate mofetil

Good response is reported in some cases with cutaneous lesions unresponsive to antimalarials and other immunosuppressive agents [2]. It could be used in SLE with

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internal organ or severe kidney involvement, at the dose of 1-3 g/day. Possible side effects are myalgia, myelosuppression and gastrointestinal disturbance [3, 19].

Non-steroidal anti-inflammatory drugs (NSAIDs)

They are very efficient against joint and serous membrane involvement. They could be used for the treatment in different stages of the disease [3]. NSAID use requires special attention in SLE. Renal prostaglandin production decreases with the effect of NSAIDs, renal blood flow and glomeruli filtration rate decreases due to this. Serum creatinine levels should be closely monitored in patients using NSAIDs. Salt retention and rarely hyperkalemia or interstitial nephritis could develop in cases. Hepatic and gastrointestinal side effects due to NSAIDs happen more commonly in SLE [18].

Other immunosupressives

Steroids alone may not be sufficient for the treatment of cases with severe organ involvement such as nephritis, vasculitis, and musculoskeletal system involvement. In order to control the disease activity in SLE, immunosupressives are also used together with high dose steroids [18].

Cyclophosphamide

Cyclophosphamide is the immunosuppressive medication of choice in active SLE cases with severe organ involvement. The most important side effects are haemorrhagic cystitis, bladder and haematologic malignancy development and permanent gonadal insufficiency development. Full blood count, urine test, creatinine, AST, ALT measurements should be taken in the beginning followed by regular tests after dose change, such as full blood count initially every 1-2 weeks followed by 1-3 month intervals and urine test every 6-12 months [18].

Azathioprine

Azathioprine could be a better treatment option for decreasing the steroid dose or for continuation treatment after cyclophosphamide use. It could be beneficial in autoimmune hepatitis, nephritis, skin lesions and inflammatory arthritis. Generally it is more beneficial in slowly progressing clinical cases. Azathioprine dose is 1-3 mg/kg/day. Opportunistic infections (especially herpes zoster), ovarian insufficiency, myelosuppression, hepatotoxicity and secondary malignancy could develop in patients on chronic azathioprine treatment [18]. Because of this, full blood count, creatinine, AST, ALT levels should be measured in the beginning of the treatment and at every dose change, full blood count should be controlled initially every 1-2 weeks followed by 1-3 month intervals [19].

Cyclosporine A

It is reported that partial benefit is observed for the SLE patients with the dose of 2,5-5 mg/kg/day. Nephrotoxicity, malignancy risk and hypertension are the important side effects [17].

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Thalidomide

It could be used in cases with deeply localized lesions such as DLE and lupus panniculitis (Filho). Teratogenicity, neuropathy, thrombosis, amenorrhea and headache are the important side effects [5].

Danazol

Danazol that has antioestrogenic effects, is reported to be successful in antimalarial-resistant DLE patients and premenstrual flarings, at the dose of 100-400 mg/day [17].

Clofasimine

Successful results are reported in the control of cutaneous lesions with 100-200 mg/day dose [2].

Biological treatments

Rituximab

It has been used and demonstrated successful results in SLE resistant to conventional treatments, with starting dose of 15-40 mg/day, continued for 2 weeks with a dose of 375 mg/m2/week, combined with systemic prednisolone [20].

Infliximab

Although it is successful in arthritis and lupus nephritis treatments, it could trigger SCLE lesions [17].

Belimumab

It is approved by FDA for SLE treatment. This medication is a monoclonal antibody against BLyS, stimulating B lymphocytes, and has been found to be effective in cases with light-medium SLE activity. However, this medication is not accepted in daily practice yet [1, 2].

Etanercept

Has been used in SCLE lesions [17].

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