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REVIEW ARTICLE

SYSTEMIC LUPUS ERYTHEMATOSUS – AN IMMUNOLOGICAL DISORDER: CLINICAL PRESENTATIONS AND THERAPEUTIC OPTIONS

AFZAL, N., SHEHZAD, F. AND RASHEED, S.
Department of Immunology, University of Health Sciences, Lahore – Pakistan

ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by production of numerous autoantibodies and damage to multiple organs and systems. SLE most often affects heart, joints, skin, lungs, blood vessels, liver, and kidneys. SLE is seen in young women of childbearing age (20 – 40 years) but it may occur at any age. Like other autoimmune disorders etiology of SLE is unknown, but it includes many components such as genetic, environmental, hormonal, drugs, etc. Immune responses against endogenous nuclear antigens are characteristic of SLE. SLE is diagnosed on the basis of classification criteria established by the American College of Rheumatology (ACR). The conventional treatment of SLE includes non-steroidal anti-inflammatory drugs (NSAIDS), anti-malarial agents, corticosteroids and other immunosuppressive medications. New treatment options for SLE include Belimumab, Mycophenolate mofetil, intravenous immunoglobulins, Rituximab, Atacicept etc. Main purpose of addition of new treatment modalities is prevention of complications of conventional treatment and to look for better therapeutic options.

Keywords: Systemic lupus erythematosus, immunological disorder, clinical manifestations, therapy.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is prototypic multi organ autoimmune disorder (Miah *et al,* 2008). The word lupus means wolf in Latin, as the destructive injuries of the disease resemble bites of this animal. The history of lupus can be divided into three periods: the classical period which includes description of cutaneous disorder, neoclassical period which shows description of systemic or disseminated manifestations of lupus, and the modern period which shows discovery of LE cell in 1948 (Blotzer *et al,* 1983). SLE shows a broad spectrum of clinical presentations involving almost all organs and tissues (Miah et al, 2008). Due to the heterogeneity of disease, SLE is proposed as a syndrome and not a single disease (Bertsias *et al,* 2008).

Epidemiology

The incidence of SLE in the USA ranges from 2.0 to 7.6 cases per 100,000 persons per year (Bongu *et al,* 2002). Prevalence of lupus is estimated to be as high as 51 per 100,000 people in the USA (Bertsias *et al,* 2008). The highest prevalence of SLE is reported in Brazil with 20 to 150 cases per 100,000 populations (George *et al,* 2011). Estimated incidence of SLE ranges from 2 to 8 per 100,000 per year in North America, South America, and Europe (Bertsias *et al,* 2008). The incidence of SLE has almost tripled worldwide in the last 4 decades and is increasing as the disease is recogized more readily and the survival rate has increased (George *et al,* 2011).

SLE is more common in people of African – Caribbean and Asian origin than in white population (Rahman *et al,* 2008). The overall prevalence of SLE in UK is approximately 28 per 100,000, and it is about 200 per 100,000 in African – Caribbean patients (Johnson *et al,* 1995). Sixty five percent of SLE patients have disease onset between 16 – 55 years, 20% before the age of 16, and 15% over the age of 55 (Bertsias *et al,* 2008). SLE affects all age groups but young women of childbearing age (20 – 40 years) are affected more commonly. The overall female: male ratio is 9:1. In pediatric population and in those who develop lupus over the age of 50 years, female to male ratio is 4:1 (Teresa *et al,* 2011).

Etiology

Etiology of SLE includes many components such as genetic, environmental, hormonal, drugs etc (Helen *et al,* 1999).

Genetic factors

During the last few years, by using hundreds of thousands of single nucleotide polymorphism (SNP) markers, understanding of genes involved in the pathogenesis of SLE has increased (Bertsias *et al,* 2008). Most of the SNPs associated with SLE fall within non-coding DNA regions of immune response – related genes (Harley *et al,* 1998). Certain SNPs linked to SLE have

Corresponding Author: Dr. Nadeem Afzal, Associate Prof. of Immunology
Department of Immunology, University of Health Sciences, Lahore – Pakistan
E-mail: immunology@uhs.edu.pk

been identified for genes whose products may contribute to abnormal T-cell function in SLE. A large scale replication study confirmed some of these associations and identified $TNIP_1$, PRDM1, $JAZF_1$, $UHRF_1BP_1$, and IL_{10} as risk loci for SLE (Gateva *et al,* 2009).

SLE may be associated with the deficiency of a single gene, e.g., complement components C_1q and C_4 (Moser *et al,* 2009, Tsokos *et al,* 2000) but the disease more commonly results from the combined effects of variants in a large number of genes (Roozendaal *et al,* 2007), whereas lack of C1q leads to deficient elimination of necrotic material (Manderson *et al,* 2004).

Hormonal factors

Through unknown mechanisms, in women hormones contribute to the increased prevalence of SLE (Duarte *et al,* 2011). The X chromosome may contribute independently from hormones in the severity of SLE. In experiments carried out in castrated female and male mice that have been genetically manipulated to express XX, XO (female), XY, or XXY (male) combinations, it was observed that the presence of two X chromosomes was associated with increased severity of SLE (Smith – Bouvier *et al,* 2008). Increase in estrogen or prolactin can lead to autoimmunity with an increase in mature high – affinity auto-reactive B cells (Bertsias *et al,* 2008).

Men and women suffering from SLE have different metabolisms of estrogen and androgen. For example, women with SLE metabolize estrogen to 16a – hydroxyestrone which is a more potent form as compared to 2 – hydroxyestrone which is produced by non SLE women and therefore they may have increased risk of miscarriage and irregular menstruation cycles (McAlindon *et al,* 2000).

Environmental factors

Environmental triggers of SLE include ultraviolet light, demethylating drugs, and infections. Sunlight is the most obvious environmental factor that may exacerbate SLE (Bertsias*et al,* 2008).

Epstein – Barr virus (EBV) has been identified as a possible factor in the development of lupus. EBV may reside in and interact with B cells and promotes interferon α (IFNα) production by plasmacytoid dendritic cells (pDCs), suggesting that elevated IFNα in lupus may be at least in part due to aberrantly controlled chronic viral infection (MH *et al,* 2009).

Drugs

Up to 10% of SLE patients may actually have drug induced lupus (DIL), and approximately 80 percent of drugs have been implicated in causing DIL. Hydralazine, Procainamide and isoniazid inhibit DNA methylation and can induce manifestations of lupus in healthy persons (Ballestar *et al,* 2006). All of these medications undergo acetylation as part of their metabolism; therefore patients who are slow acetylators tend to have more problems with DIL compared with those who have normal or fast acetylation (Teresa *et al,* 2011). Another potential cause of DIL involves hapten-like reactions where the drug or its metabolites bind to proteins rendering them foreign to the body (Teresa *et al,* 2011).

Pathogenesis

Immune responses against endogenous nuclear antigens are characteristic of SLE. Auto-antigens released

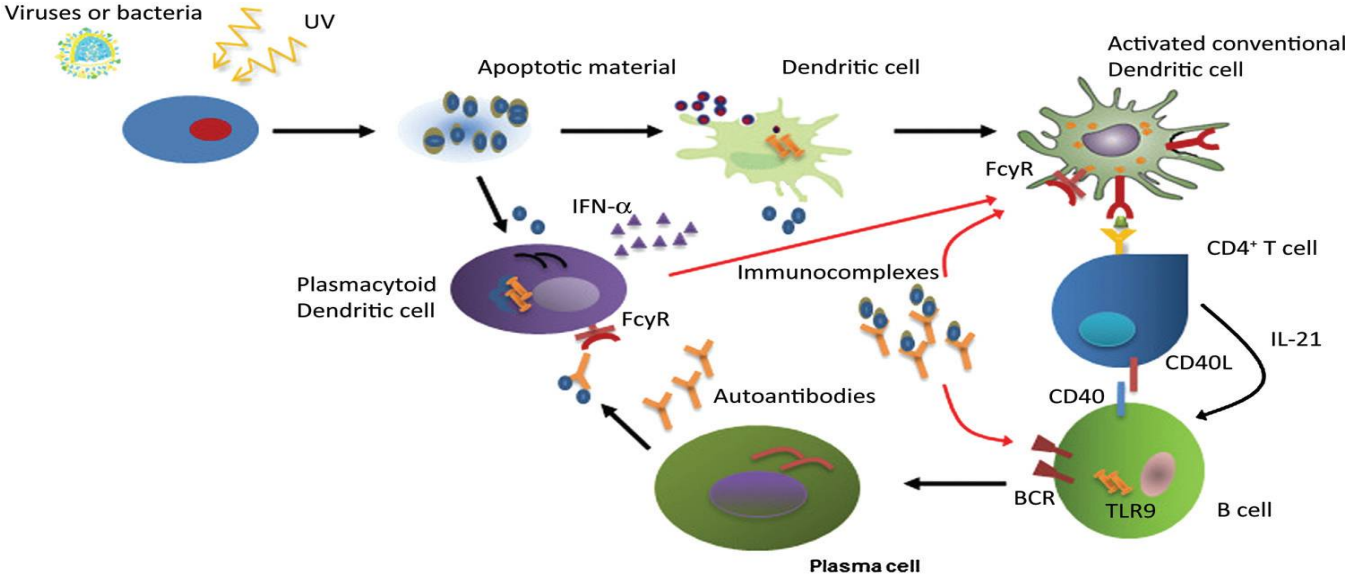

Fig. 1: *Pathogenesis of SLE (Adapted from Bertsias et al. EULAR recommendations for the management of SLE. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis. 2008; 67: 195–205).*

Table 1: *American College of Rheumatology (ACR) criteria for the classification of systemic lupus erythematosus.*

Criterion		*Definition*
1.	Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2.	Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3.	Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4.	Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5.	Non-erosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6.	Pleuritis or Pericarditis	Pleuritis – convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion. Or Pericarditis – documented by electrocardiogram or rub or evidence of pericardial effusion
7.	Renal Disorder	Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed. Or Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed
8.	Neurologic Disorder	Seizures – in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance. Or Psychosis – in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance.
9.	Hematologic Disorder	Hemolytic anemia – with reticulocytosis Or Leukopenia – < 4,000/mm^3 on ≥ 2 occasions Or Lyphopenia – < 1,500/ mm^3 on ≥ 2 occasions Or Thrombocytopenia – < 100,000 / mm^3 in the absence of offending drugs
10.	Immunologic Disorder	Anti-DNA: antibody to native DNA in abnormal titer. Or Anti-Sm: presence of antibody to Sm nuclear antigen Or Positive finding of antiphospholipid antibodies on: an abnormal serum level of IgG or IgM anticardiolipin antibodies, a positive test result for lupus anticoagulant using a standard method, or a false – positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11.	Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

For the purpose of identifying patients in clinical studies, a person must have SLE if any of the 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation. (Adapted from Tan EM, Cohen AS, Fries JF *et al*. The 1982 revised criteria for the classification of SLE. Arthritis Rheum 1982; 25: 1271-7)

by apoptotic cells are presented by dendritic cells to T cells leading to their activation. Activated T cells in turn help B cells to produce antibodies to these self – constituents by secreting cytokines such as interleukin 10 (IL_{10}) and IL_{23} and by cell surface molecules such as $CD_{40}L$ and $CTLA_4$. In addition to this antigen – driven T cell – dependent production of autoantibodies, recent data supported T cell – independent mechanisms of B cell stimulation via combined B cell antigen receptor (BCR) and TLR signaling (Bertsias *et al,* 2008).

The pathogenesis of SLE involves a multitude of cells and molecules that participate in apoptosis, innate and adaptive immune responses. Increased amounts of apoptosis – related endogenous nucleic acids stimulate production of IFNα and promote autoimmunity by breaking self – tolerance through activation of antigen presenting cells. Once initiated, immune reactants such as immune complexes amplify and sustain inflammatory response (Bertsias *et al,* 2008) (Fig. 1).

Diagnosis criteria

Diagnosis of SLE is based on classification criteria established by the American College of Rheumatology (ACR). It was developed in 1971, revised in 1982, and in 1997. The ACR classification criteria were developed for clinical studies of lupus to ensure that cases reported in the literature do have the disease. In clinical trials to label as SLE, a minimum of 4 out of 11 ACR criteria should be there. The 11 ACR criteria are divided into systems: cutaneous, musculosketetal, non-erosive arthritis, cardiopulmonary pleuritis or pericarditis, renal, neurological disorder with seizures or psychosis due to unknown causes, and laboratory parameters.[21] The ACR criteria (1997) are presented in Table 1.

Disease activity index

Assessing disease activity in SLE is crucial to the physician as it forms the basis for treatment decisions. Disease activity needs to be distinguished from damage as this has important implications for the long term prognosis and the appropriate treatment (Bertsias *et al,* 2008).

SLE activity has three patterns: flare, chronic, and long quiescence. A flare or relapsing remission is an exacerbation that occurs suddenly and unpredictably; patients are usually in good health between flares. Factors that may trigger a disease flare-up include stress, excessive work, emotional crisis, sunlight, ultraviolet light, infection, injuries, surgery, pregnancy, abrupt discontinuation of medications, treatment noncompliance, medications, and immunizations (Miah *et al,* 2008). Serologic tests are not helpful in predicting flares because serologic activity of SLE may occur without clinical manifestations. Chronic cases of SLE have persistent activity such as chronic synovitis, chronic cytopenias, or active discoid lupus. This chronic activity may or may not require treatment. Patients with long quiescence have a long remission period before having additional flare-up (Gladman *et al,* 1999). Patients can also have comorbid conditions associated with SLE e.g., nephritis and neuropsychiatric involvement (Teresa *et al,* 2011).

Several validated global and organ-specific activity indices are widely used in the evaluation of SLE patients (Urowitz *et al,* 1998). These include European Consensus Lupus Activity Measure (ECLAM), British Isles Lupus Assessment Group Scale (BILAG), Lupus Activity Index (LAI), National Institutes of Health SLE Index Score (SIS), Systemic Lupus Activity Measure (SLAM), and SLED is a Disease Activity Index (SLEDAI). SLEDAI is more convenient for use in daily practice as shown in Table 2.

Table 2: *Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).*

Score	*Descriptor*	*Definition*
8	Seizure	Recent onset. Exclude metabolic, infectious, or drug – related causes
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Includes hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized or catatonic behavior. Exclude the presence of uremia and offending drugs
8	Organic brain syndrome	Altered mental function with impaired orientation or impaired memory or syndrome other intellectual function, with rapid onset and fluctuating clinical features. Includes a clouding of consciousness with a reduced capacity to focus and an inability to sustain attention on environment, and at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic, infectious, and drug – related causes.
8	Visual	Retinal changes from systemic lupus erythematosus: cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, optic neuritis (not due to hypertension, drugs, or infection).
8	Cranial nerve	New onset of a sensory or motor neuropathy involving a cranial nerve.
8	Lupus headache	Severe, persistent headache; may be migranous; unresponsive to narcotics.
8	Cerebrovascular accident	New syndrome. Exclude arteriosclerosis.

Score	*Descriptor*	*Definition*
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages. Vasculitis confirmed by biopsy or angiogram.
4	Arthritis	More than 2 joints with pain and signs of inflammation.
4	Myositis	Proximal muscle aching or weakness associated with elevated creatine phosphokinase / aldolase levels, electromyographic changes, or a biopsy showing myositis.
4	Casts	Heme, granular, or erythrocyte.
4	Hematuria	More than 5 erythrocytes per high power field. Exclude other causes (stone, infection).
4	Proteinuria	More than 0.5 grams of urinary protein excreted per 24h. New onset or recent increase of > 0.5g / 24h.
4	Pyuria	More than 5 leukocytes per high – power field. Exclude infection.
2	New malar rash	New onset or recurrence of an inflammatory type of rash.
2	Alopecia	New or recurrent. A patch of abnormal, diffuse hair loss.
2	Mucous membranes	New onset or recurrence of oral or nasal ulcerations.
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	Pericarditis	Pericardial pain with at least one of rub or effusion. Confirmation by electro- or echocardiography.
2	Low complement	A decrease in CH_{50}, C_3, or C_4 level (to less than the lower limit of the laboratory – determined normal range).
2	Increased DNA binding	More than 25% binding by Farr assay (to > the upper limit of the laboratory – determined normal range, e.g. 25%).
2	Fever	More than 38°C after the exclusion of infection.
2	Thrombocytopenia	Fewer than 100,000 platelets
2	Leukopenia	Leukocyte count of < 3000/mm^3 (not due to drugs)

Adapted from Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE (Arthritis Rheum. 1992; 35: 630-40).

Clinical presentation

Clinical presentation of SLE can be nonspecific e.g. fever, malaise, arthralgias, myalgias, headache, and loss of appetite and weight. Fatigue, fever, arthralgia, and weight changes are the most common symptoms in new or in recurrent active SLE. Fatigue, is the most common constitutional symptom and it can be due to active SLE, medications, lifestyle habits, concomitant fibromyalgia or affective disorders. Fatigue due to active SLE generally occurs in concert with other clinical and laboratory markers. Fever, another common yet nonspecific symptom of SLE, may also result from many causes, the most common of which include active SLE, infection, and drug fever. The specific symptoms of SLE are photosensitivity, malar rash, oral ulcer, alopecia, serositis etc (D'Cruz *et al,* 2007).

Cutaneous involvement

Common skin manifestations include malar or butterfly rash, with sun-induced macules or papules occurring on the face, or generalized rash on the body, which may or may not be sun induced. Discoid lupus presents as a hyperkeratotic lesion associated with atrophy, scarring, and hypopigmentation (D'Cruz *et al,* 2007). Diffuse alopecia can generally occur when the disease is active and is usually reversible during remission. Patchy alopecia, on the other hand, may lead to scarring and can become permanent (Cervera *et al,* 2003).

Muscloskeletal features

Ninety percent of SLE patients have joint inflammat ion such as arthralgia, arthritis, tendinitis, or early morning stiffness that is generally in knees, wrists, and hands. Joint inflammation does not cause permanent damage. Men with SLE tend to have less arthritis, but serositis can be more predominant in men than in women (Amissah – Arthur *et al,* 2009).

Another common feature, occurring in 50% of SLE is mucosal ulceration; usually oral. Since methotrexate can also cause these ulcerations, it can be difficult to determine if the ulceration is induced by SLE or it is drug induced (Teresa *et al,* 2011).

Cardiovascular features
Cardiovascular and respiratory symptoms are also common and include chest pain on inspiration due to pleurisy or pericarditis. Cardiovascular disease (e.g. myocardial infarction) can be exacerbated in SLE but mostly these are secondary to accelerated atherosclerosis and other risks i.e. hypertension, hypercholesterolemia, hypertriglyceridemia, diabetes, and heart failure. The risk of hospitalization for an acute myocardial infarction was 2.27 times greater for lupus patients between aged 18 to 44 years than for non-lupus patients (Aranow *et al,* 2000).

Renal complications
Although it is almost common in SLE that there are deposits of immunoglobulin in the glomeruli, but only one half of the patients present with the features of clinical nephritis (Ben – Menachem *et al,* 2010). Lupus nephritis (LN) is a common and potentially devastating manifestation of SLE. In general, LN occurs in more than half of SLE patients. LN is primarily caused by the deposition of immune complexes. The classification of LN is based on renal biopsy. If possible, a biopsy should be obtained from patients who are suspected of renal impairment. Renal biopsy need not to be made routinely in patients with normal creatinine values and normal urine analysis (Petri *et al,* 2007).

Neuropsychiatric manifestations
Neurological manifestations of lupus are reported in 25 to 75% of patients and can involve all parts of the nervous system (D'Cruz *et al,* 2007). Incidence of elevated anti-phospholipid (APL) antibodies in patients with neurological symptoms is approximately two times higher than in those without neurological symptoms. Moreover, APL antibodies antedated neurological symptoms in 81% of patients (Ben – Menachem *et al,* 2010).

Pulmonary manifestations
Pulmonary manifestations of SLE may manifest acutely or indolently that include many complications such as serositis, which can affect both cardiac and pulmonary systems and cardiac and pulmonary serositis often coexist. Serositis can be due to pericardial or pulmonary effusions, pulmonary embolism, lupus pneumonitis, chronic lupus interstitial lung disease, complement – mediated pulmonary leukoaggregation, or infection may be related to lupus disease. Pleurisy with pleuritic chest pain with or without pleural effusion is the most common feature of acute pulmonary involvement in SLE. Shortness of breath or dyspnea may be due to many causes (Ben – Menachem *et al,* 2010).

Ocular manifestations
Ocular manifestations of lupus are reflection of systemic disease and therefore these manifestations should alert the clinicians for the presence of disease activity elsewhere as well. The most common ocular manifestation of SLE is kerato-conjunctivitis sicca (KCS) that occurs in approximately 25% of patients (Arevalo *et al,* 2002). Conjunctivitis, interstitial keratitis, episcleritis and diffuse or nodular scleritis are less common. The severity of episcleritis and scleritis may closely mirror the activity of systemic disease. Necrotizing scleritis is rare in patients with SLE. Retinal involvement in SLE is the second most common ocular manifestation after KCS (Peponis *et al,* 2006).

Hematologic manifestations
Patients with SLE have a complex array of abnormalities of immune system. Among other etiologies, history of multiple cytopenias such as leukopenia, lymphopenia, anemia, or thrombocytopenia may suggest SLE. Leukopenia and more specifically lymphopenia are common in SLE and along with this decreased complement levels may predispose people with SLE to frequent infections (Manole *et al,* 2011).

Treatment of SLE
Management of SLE often depends on disease severity and disease manifestations (Hahn et al, 2005). Duration of therapy is also highly variable and it depends upon the disease severity in an individual and is based on the patient's response (Chaichian *et al,* 2013).

Conventional therapy: Conventionally, patients of SLE are treated with non-steroidal anti-inflammatory, anti-malarial, glucocorticoids and immunosuppressive drugs including cyclophosphamide, azathioprine, methotrexate, and Mycophenolate mofetil. In addition to anti-inflammatory effects, inhibitors of cyclooxygenase promote the death of auto-reactive T cells. The anti-malarial agent hydroxychloroquine has therapeutic value and limited toxicity. It inhibits the function of toll – like receptors that contribute to autoimmunity (Karlsson *et al,* 2007). Every month or bimonthly at lower dose intravenous infusions of cyclophosphamide is effective for the treatment of LN, although there are serious potential side effects, including bone marrow suppression, infections, and gonadal suppression (Illei *et al,* 2001). Mycophenolate mofetil has considerable therapeutic value with few side effects (Radhakrishnan *et al,* 2010) but its long-term effects with respect to the preservation of kidney function are under trial (Boumpas *et al,* 2010).

New drugs and treatment options
The development of new modalities is important for

the prevention of complications of current treatment options and it is believed that they have better therapeutic outcomes (Chaichian *et al,* 2013). New potential drugs for SLE therapy are as follows.

Belimumab (Benlysta): Belimumab (human immunoglobulin (Ig) G_1 – gamma monoclonal antibody, is a selective inhibitor of soluble protein B lymphocyte stimulator (BLyS).The protein BLyS is essential for B cell maturation, proliferation, survival and antibody production. High serum levels of soluble BLyS are found in SLE and are associated with high autoantibody levels and active disease (Chaichian *et al,* 2013). Belimumab binds to soluble BLyS and inhibits its biological activity. Therefore, autoantibodies are not produced and do not damage tissues of the body (Navarra *et al,* 2011).

Mycophenolate mofetil (Cellcept): Mycophenolate mofetil (MMF) inhibits the action of an enzyme that is vital for the proliferation and maturation of white blood cells (Chaichian *et al,* 2013). LN which is one of the life – threatening complications of SLE is associated with kidney failure that needs treatment with dialysis. A common treatment employed for grade IV LN (diffuse proliferative glomerulonephritis) is a combination of corticosteroids and immunosuppressive drugs, mainly intravenous cyclophosphamide (CYC). This combination is used to achieve and maintain remission in disease activity. The administration of CYC is limited by significant toxic effects, including premature ovarian failure, sterility, infections, bladder toxicity and malignancies (Netta *et al,* 2014)**.**

Intravenous immunoglobulins (IVIG): IVIG is a biologic therapy of antibodies obtained from pooled human plasma donors. The mechanism is not entirely clear, but several mechanisms are suggested, including suppression of white blood cells, inhibition of immune system activation, and neutralization by antibodies causing damage to organs. IVIG treatment is effective for treating moderate to severe SLE and IVIG can be used as an adjuvant therapy (Netta *et al,* 2014)**.**

Rituximab (Mabthera): Rituximab is a chimeric monoclonal antibody that selectively depletes CD_{20} – positive B cells. Rituximab changes immune system activity, thus decreasing the degree of damage to vital organs including the kidneys. Rituximab is given to lupus patients that are resistant to standard therapy (Merrill *et al,* 2010).

Atacicept: Atacicept is a soluble, fully human, recombinant fusion protein that inhibits both BLyS and a proliferation – inducing ligand (APRIL**)** unlike belimumab which selectively blocks BLyS activity (Ginzler*et al,* 2012)**.**

Abetimus: It is a synthetic toleragen molecule consisting of four double-stranded oligo-deoxy-ribo-nucleotides attached to non-immunogenic polyethylene glycol. It is an immune – modulating agent that induces tolerance in B cells directed against double-stranded DNA (dsDNA).The presumed mechanism of action is rapid decrease in anti-dsDNA antibody levels through clearance of drug-antibody complexes and development of tolerance among anti-dsDNA – specific B cells (Alarcón – Segovia *et al,* 2003).

Ocrelizumab: A humanized anti-CD_{20} monoclonal antibody, has also been evaluated in SLE (Chaichian *et al,* 2013).

Antibody against CD_{22}: B – cell depletion using CD_{22} as a target has been studied as a potential therapy in SLE. Epratuzumab is a humanized monoclonal antibody against CD22. Unlike anti-CD_{20} medications such as rituximab and ocrelizumab, epratuzumab affects B cell activity without fully depleting peripheral B cell stores (Wallace *et al,* 2010).

Abatacept: Abatacept binds to B_7 ($CD_{80/86}$) molecule on the surface of antigen – presenting cells and B lymphocytes to inhibit co-stimulation of T cells (Merrill *et al,* 2010).

Rapamycin: Mitochondrial abnormalities in T cells of SLE patients, leading to oxidative stress have also been the subject of clinical investigation. Rapamycin regulates mitochondrial transmembrane potential and calcium flow. It is safe and effective in reducing disease activity (Fernandez *et al,* 2006).

N-acetylcysteine: N-acetylcysteine is a precursor of glutathione that inhibits the mammalian target of rapamycin (mTOR) activity in T lymphocytes (Lai *et al,* 2012).

Spleen tyrosine kinase (Syk) and CD_{40} ligand blockade: Syk acts downstream of mTOR. R_{788} which is an orally bio available Syk inhibitor, has been effective in treating nephritis and skin disease in mouse models of lupus (Deng *et al,* 2010).

Oral quinoline-3-carboxamide (Laquinimod): Small molecules have also drawn interest as possible therapies in SLE. Laquinimod alters T helper cell response in favor of TH_2 over TH_1 cells, leading to suppression of pro-inflammatory cytokines and promotion of several anti-inflammatory cytokines (Chaichian *et al,* 2013).

Other drugs which are under clinical trials includes, Sifalimumab which is a fully human IgG_1K monoclonal antibody that binds strongly to IFN – alpha and inhibits IFN – alpha signaling through its receptor. Rontalizumab; a humanized IgG_1 monoclonal antibody inhibits IFN, Tocilizumab; humanized monoclonal antibody against IL_6 receptor, B-N_{10}; murine anti-IL_{10} monoclonal antibody, Infliximab; chimeric TNF – alpha inhibitor and Etanercept; soluble TNF – receptor fusion protein (Chaichian *et al,* 2013).

It is ***concluded*** that SLE is an autoimmune dise-

ase that predominantly affects women and typically has manifestations in multiple organs including skin, kidneys and CNS. Immune – system aberrations, genetic, hormonal, and environmental factors contribute in organ damage. Immune complexes, auto-antibodies, auto reactive lymphocytes, dendritic cells, and local factors are all involved in clinical manifestations of SLE. Biologic therapies and small – molecule drugs that can correct aberrant immune – cell function are being developed in the hope that they will be more effective and would have less toxic effects as compared to the current treatment options. The lack of consistency in disease activity indices due to various therapies employed in the clinical trials of SLE has made comparison of targeted therapies more challenging. Numerous B-cell, T-cell, and anti-cytokine targets have been studied (Chaichian *et al,* 2013). The new treatment options e.g rituximab, atacicept, abetimus etc. available for SLE patients have shown to improve disease activity parameters, increased disease free period and to have a steroid sparing effect. Therefore, they can be considered as an alternative treatment options in patients who cannot be treated with cytotoxic agents or in those who would like to avoid side effects of standard treatment. A number of these possible therapeutic targets e.g. rituximab, atacicept, abetimus etc have shown promise in early trials and it is likely that the approach to lupus management will undergo significant change in the coming years and it is hoped that further targeted therapies will meet success in the near future(Chaichian *et al,* 2013).

Author's contributions:
All the authors contributed equally to this work.

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