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The Current Insights on Diagnostic Profile, Clinical Manifestations and Evidence Based Treatment for Prevention of Systemic Lupus Erythematosus (SLE)

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ABSTRACT

Systemic lupus erythematosus is a systemic autoimmune disease with multisystem involvement and is associated with significant morbidity and mortality. Genetic, immunological, endocrine, and environmental factors influence the loss of immunological tolerance against self-antigens leading to the formation of pathogenic autoantibodies that cause tissue damage through multiple mechanisms. The incidence of systemic lupus erythematosus varies globally, with a worldwide average of about 5.14 cases per 100,000 person-years, but regional and ethnic differences exist. Incidence is higher in women than men, and certain populations, such as African Americans, have a higher incidence compared to Caucasians. Diagnosis of SLE can be challenging, and while several classification criteria have been posed, their utility in the clinical setting is still a matter of debate. The SLE cannot be prevented, individuals can manage triggers and reduce flare-ups by protecting their skin from the sun, eating a healthy diet, managing stress, getting regular exercise, and avoiding smoking. Regular health checkups with a clinician is also crucial for monitoring health and addressing concerns that could contribute to flares. Management of SLE is dictated by organ system involvement. Systemic lupus erythematosus treatment involves a combination of medications to manage symptoms and reduce flares, tailored to the individual's specific needs. Common treatments include anti-inflammatory drugs for mild symptoms, antimalarial drugs like hydroxychloroquine for immune modulation, and corticosteroids for reducing inflammation.

Keywords: Systemic lupus erythematosus, autoantibodies, hydroxychloroquin, self-antigens, health checkups.

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C O N T E N T S

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multisystemic involvement. The condition has several phenotypes, with varying clinical presentations from mild mucocutaneous manifestations to multiorgan and severe central nervous system involvement. Several immunopathogenic pathways play a role in the development of SLE. Hargraves described the lupus erythematosus in 1948. Several pathogenic autoantibodies have since been identified. Despite recent advances in technology and understanding of the pathological basis and risk factors for SLE, the exact pathogenesis is still not well known. Diagnosis of SLE can be challenging, and while several classification criteria have been posed, their utility in the clinical setting is still a matter of debate. Management of SLE is dictated by organ system involvement[1-3].

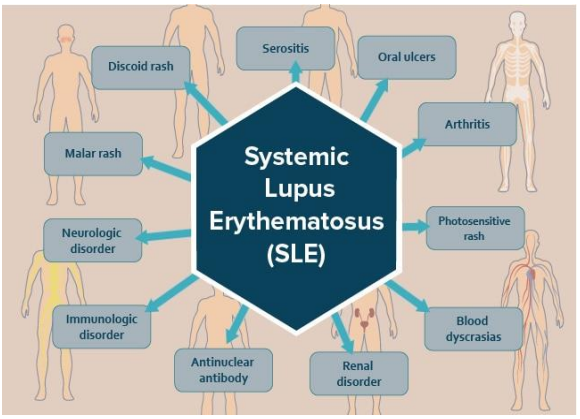

Fig 1: Systemic lupus erythematosus disease severity

Incidence

SLE disproportionately affects women of reproductive age and individuals of Asian, Black, Hispanic and Indigenous race/ethnicity. Yet, some of the most populous areas of the world with relatively young and diverse populations have limited recent epidemiological data available. We comprehensively reviewed global SLE epidemiology in 2021. This revealed marked variability in disease burden, with reported incidence ranging from 1.5 to 11.0 per 100000 person-years, and prevalence ranging from 13.0 to 7713.5 per 100000 individuals. Comparing incidence and prevalence amongst global regions was not feasible, given marked disparities in access to care across the world and inconsistent case ascertainment and study methodology, in addition to true variation related to population structure, genetics, socioeconomics and environmental influences. Several reports suggested an increase in SLE prevalence over time, perhaps related to diagnostic improvement and improved detection of early disease.

We reported that infection and cardiovascular disease were leading causes of death in SLE patients, with overall mortality still two to three times higher than that of the general population and higher still in certain racial/ethnic groups. There was little data from many low- to middle-income countries (LMIC) in Africa, the Caribbean, Latin America, the Middle East, and parts of Asia and Europe[4-9].

Table 1: SLE classification

Table 1. SLE Classification Criteria Comparison				
		ACR 1997	SLICC 2012	ACR/EULAR Draft 2017
	SLE Classification Criteria	Satisfy 4 of 11 criteria	Satisfy 4 of the criteria with at least one clinical criterion and one immunologic criterion OR Biopsy-proven LN with positive ANA or anti-ds DNA antibodies	Score at least 10 points with ANA of at least 1:80 on HEp-2 cells or equivalent
				Criterion
Clinical Criteria	Cutaneous	1. Malar rash 2. Photosensitivity 3. Discoid rash 4. Oral/nasopharyngeal ulceration	1. Acute cutaneous lupus (including malar and photosensitive lupus rash) OR Subacute cutaneous lupus	Acute cutaneous lupus
			2. Chronic cutaneous lupus	Subacute cutaneous lupus OR Discoid lupus
			3. Oral or nasal ulcers	Oral ulcers
			4. Nonscarring alopecia	Nonscarring alopecia
	Joints	5. Nonerosive arthritis • tenderness, swelling, or effusion with ≥2 peripheral joints	5. Synovitis • swelling or effusion with ≥2 joints OR tenderness in ≥2 joints with ≥30 minutes of morning stiffness	Synovitis • tenderness in ≥2 joints with ≥30 min of morning stiffness
	Serositis	6A. Pleuritis OR 6B. Pericarditis	Serositis (pleurisy, pleural 6 effusions, pleural rub, pericardial pain, pericardial effusion, pericardial rub, pericarditis)	Pleural OR Pericardial effusion
				Acute Pericarditis
	Renal	7A. Persistent proteinuria • >0.5 mg/24 h or >3+ dipstick OR 7B. Cellular casts	7A. Urine protein-to -creatinine ratio (or 24 h urine protein) • >0.5 g/24 h OR 7B. Red blood cell casts	Proteinuria • >0.5 mg/24 h
				Class II or V LN
				Class III or IV LN
	Neurologic	8A. Seizures OR 8B. Psychosis	8A. Seizures OR 8B. Psychosis OR 8C. Mononeuritis multiplex OR 8D. Myelitis OR 8E. Peripheral/cranial neuropathy OR 8F. Acute confusional state	Seizure
				Psychosis
				Delirium
	Hematologic	9A. Hemolytic anemia OR 9B. Leukopenia • <4,000/mm³ on ≥2 occasions OR 9C. Lymphopenia • <1,500/mm³ on 2 occasions OR 9D. Thrombocytopenia • <100,000/mm³	9. Hemolytic anemia	Autoimmune hemolysis
			10A. Leukopenia OR • <4,000/mm3 once 10B. Lymphopenia • <1,000/mm3 once	Leukopenia
			11. Thrombocytopenia • 100,000/m3 once	Thrombocytopenia
	Constitutional			Fever

2. Pathophysiology

The pathogenesis of SLE is complex, and the understanding of SLE pathogenesis is constantly evolving. A break in the tolerance in genetically susceptible individuals on exposure to environmental factors leads to the activation of autoimmunity. Cell damage caused by infectious and other environmental factors exposes the immune system to self-antigens leading to activation of T and B cells, which become self-sustained by a chronic self-aimed immune response[10-15]. Cytokine release, complement activation, and autoantibody production lead to organ damage.

Both innate and adaptive immune systems play a role in the pathogenesis of SLE. The innate immune system activation is either Toll-like receptor (TLR) dependent or independent. The cell membrane-bound TLRs (TLR 2, 4, 6) are activated on exposure to the extracellular DNA and RNA from dying cells, which leads to downstream activation of the interferon regulatory family (IRF-3), NF-κB, and MAP-kinases, which serve as transcription factors for the production of proinflammatory mediators such as IFN-b. The endosomal TLRs (TLR 7, 9) are activated by single-stranded RNA, demethylated DNA, leading to interferon-alpha production, RNA binding autoantibodies such as antibodies against Ro La, Sm, and RNP.

The TLR-independent pathway is activated by intracytoplasmic RNA sensors (RIG-1, MDA-5) and DNA sensors (IFI16, DAI) and leads to activation of IRF3 and NF-κB. Both self DNA/RNA and foreign DNA/RNA, such as from viruses, can lead to this activation. NETosis has recently gained attention in the pathogenesis of SLE. On activation by various factors such as cytokines, activated platelets, and vascular endothelial cells, neutrophils systematically release their nuclear aggregates in the extracellular environment. These nuclear aggregates can then promote Interferon-alpha production by the dendritic cells, mediate thrombosis and vascular damage and serve as self-antigens for T-lymphocytes[16-25].

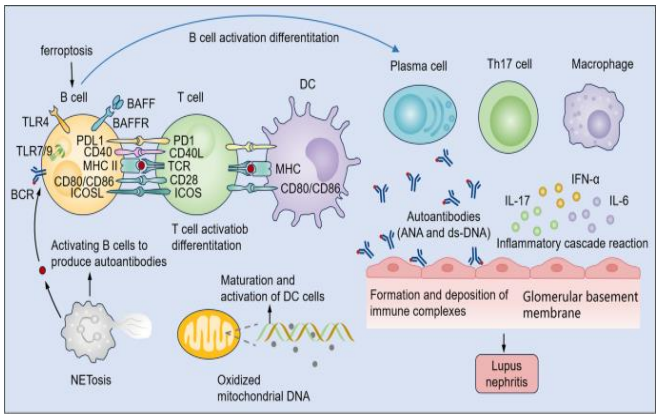

Fig 2: Pathophysiology

T-lymphocytes and B-lymphocytes play a significant role in the pathogenesis of SLE. Apoptotic and damaged cell-derived antigens are presented to T-cells by antigen-presenting cells. T-cells in SLE display a distorted gene expression leading to the production of several cytokines. These T-cells produce less IL-2, which leads to altered regulatory T-cell production. Increased IL-6, IL-10, IL-12, and IL-23 increase mononuclear cell production while increased IL-17 and IL-21 lead to increased T-cel production[26-33]. Increased Interfern-γ leads to defective T-cell production. T-cells lead to the activation of autoreactive B-cells by CD40L and cytokine production, leading to autoantibody production, a hallmark of SLE. Toll-like receptors on interaction with DNA and RNA lead to activation of these B-cells, and the nucleic acid and protein-containing intranuclear complexes are the most prominent antigens leading to B-cel activation. These autoantibodies are pathogenic and cause organ damage by immune complex deposition, complement, and neutrophil activation, altering cell function leading to apoptosis and cytokine production.

Symptoms

No two cases of lupus are exactly alike. Signs and symptoms may come on suddenly or develop slowly, may be mild or severe, and may be temporary or permanent. Most people with lupus have mild disease characterized by episodes called flares when signs and symptoms get worse for a while, then improve or even disappear completely for a time.

The most common signs and symptoms include[34-40]:

- Fatigue
- Fever
- Joint pain, stiffness and swelling
- Butterfly-shaped rash on the face that covers the cheeks and bridge of the nose or rashes elsewhere on the body
- Skin lesions that appear or worsen with sun exposure
- Fingers and toes that turn white or blue when exposed to cold or during stressful periods
- Shortness of breath
- Chest pain
- Dry eyes
- Headaches, confusion and memory loss

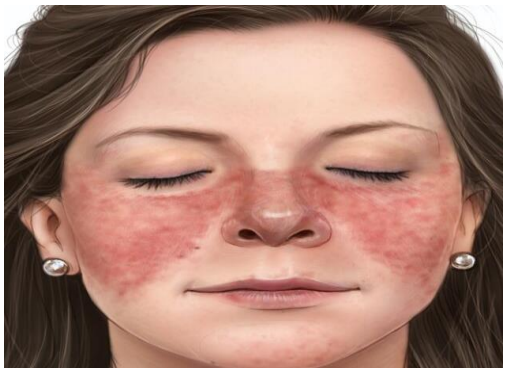

Fig 3: Lupus facial rashes

3. Risk factors

Factors that may increase your risk of lupus include:

- Your sex. Lupus is more common in women.
- Age. Although lupus affects people of all ages, it's most often diagnosed between the ages of 15 and 45.
- Race. Lupus is more common in African Americans, Hispanics and Asian Americans.
- Complications
- Inflammation caused by lupus can affect many areas of your body, including your:
- Kidneys. Lupus can cause serious kidney damage, and kidney failure is one of the leading causes of death among people with lupus.
- Brain and central nervous system. If your brain is affected by lupus, you may experience headaches, dizziness, behavior changes, vision problems, and even strokes or seizures. Many people with lupus experience memory problems and may have difficulty expressing their thoughts.
- Blood and blood vessels. Lupus may lead to blood problems, including a reduced number of healthy red blood cells (anemia) and an increased risk of bleeding or blood clotting. It can also cause inflammation of the blood vessels.
- Lungs. Having lupus increases your chances of developing an inflammation of the chest cavity lining, which can make breathing painful. Bleeding into lungs and pneumonia also are possible[41].
- Heart. Lupus can cause inflammation of your heart muscle, your arteries or heart membrane. The risk of cardiovascular disease and heart attacks increases greatly as well.

Causes

- As an autoimmune disease, lupus occurs when your immune system attacks healthy tissue in your body. It's likely that lupus results from a combination of your genetics and your environment.
- It appears that people with an inherited predisposition for lupus may develop the disease when they come into contact with something in the environment that can trigger lupus. The cause of lupus in most cases, however, is unknown. Some potential triggers include:

- Sunlight. Exposure to the sun may bring on lupus skin lesions or trigger an internal response in susceptible people.
- Infections. Having an infection can initiate lupus or cause a relapse in some people.
- Medications. Lupus can be triggered by certain types of blood pressure medications, anti-seizure medications and antibiotics[32-37].

4. Complications

- Inflammation caused by lupus can affect many areas of your body, including your:
- Kidneys. Lupus can cause serious kidney damage, and kidney failure is one of the leading causes of death among people with lupus.
- Brain and central nervous system. If your brain is affected by lupus, you may experience headaches, dizziness, behavior changes, vision problems, and even strokes or seizures. Many people with lupus experience memory problems and may have difficulty expressing their thoughts.
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- Heart. Lupus can cause inflammation of your heart muscle, your arteries or heart membrane. The risk of cardiovascular disease and heart attacks increases greatly as well.

Other types of complications

Infection. People with lupus are more vulnerable to infection because both the disease and its treatments can weaken the immune system. Cancer. Having lupus appears to increase your risk of cancer; however, the risk is small. Bone tissue death. This occurs when the blood supply to a bone declines, often leading to tiny breaks in the bone and eventually to the bone's collapse.

5. Clinical Diagnosis

Complete blood count. This test measures the number of red blood cells, white blood cells and platelets as well as the amount of hemoglobin, a protein in red blood cells. Results may indicate you have anemia, which commonly occurs in lupus. A low white blood cell or platelet count may occur in lupus as well. Erythrocyte sedimentation rate. This blood test determines the rate at which red blood cells settle to the bottom of a tube in an hour. A faster than normal rate may indicate a systemic disease, such as lupus. The sedimentation rate isn't specific for any one disease. It may be elevated if you have lupus, an infection, another inflammatory condition or cancer. Kidney and liver assessment. Blood tests can assess how well your kidneys and liver are functioning. Lupus can affect these organs.

Urinalysis. An examination of a sample of your urine may show an increased protein level or red blood cells in the urine, which may occur if lupus has affected your kidneys.

Antinuclear antibody (ANA) test. A positive test for the presence of these antibodies produced by your immune system indicates a stimulated immune system. While most people with lupus have a positive antinuclear antibody (ANA) test, most people with a positive ANA do not have lupus. If you test positive for ANA , your doctor may advise more-specific antibody testing.

Chest X-ray. An image of your chest may reveal abnormal shadows that suggest fluid or inflammation in your lungs.

Echocardiogram. This test uses sound waves to produce real-time images of your beating heart. It can check for problems with your valves and other portions of your heart.

Biopsy

Lupus can harm your kidneys in many different ways, and treatments can vary, depending on the type of damage that occurs. In some cases, it's necessary to test a small sample of kidney tissue to determine what the best treatment might be. The sample can be obtained with a needle or through a small incision.

Prevention: Sun protection:

Avoid excessive sun exposure and use sunscreen with a high SPF, along with protective clothing like hats and long sleeves.

Healthy diet:

Eat a balanced diet with fruits, vegetables, and whole grains. Your doctor may also recommend certain supplements or dietary restrictions based on other health issues.

Exercise:

Stay physically active with regular, moderate exercise to promote overall well-being and maintain strong bones.

Avoid smoking:

Smoking increases the risk of cardiovascular disease and can worsen lupus effects on the heart and blood vessels.

Stress management:

Manage stress through relaxation techniques like meditation, yoga, or tai chi, and ensure you get enough rest.

6. Treatment and Management

Treatment in SLE aims to prevent organ damage and achieve remission. The choice of treatment is dictated by the organ system/systems involved and the severity of involvement and ranges from minimal treatment (NSAIDs, antimalarials) to intensive treatment (cytotoxic drugs, corticosteroids). Patient education, physical and lifestyle measures, and emotional support play a central role in managing SLE. Patients with SLE shall be well educated on the disease pathology, potential organ involvement, including brochures, and the importance of medication and monitoring compliance. Stress reduction techniques, good sleep hygiene, exercises, and emotional support shall be encouraged. Smoking can worsen SLE symptoms, and patients should be educated about the importance of smoking cessation. Dietary recommendations shall include avoiding alfalfa sprouts and echinacea and including a diet rich in vitamin D. Photoprotection is vital. All patients with

SLE shall avoid direct sun exposure by timing their activities appropriately, light-weight loose-fitting dark clothing covering the maximum portion of the body, and using broad-spectrum (UV-A and UV-B) sunscreens with a sun protection factor (SPF) of 30 or more.

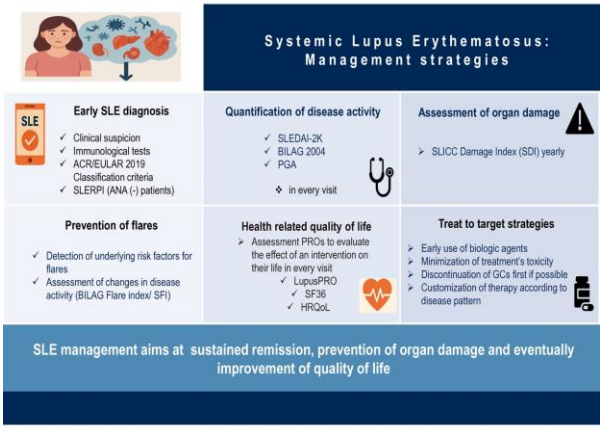

Fig 4: Systemic Lupus Erythematosus Management Strategies

Management

Cutaneous manifestations: Mild cutaneous manifestations can usually be treated with topical corticosteroids or topical calcineurin inhibitors such tacrolimus. Hydroxychloroquine is the drug of choice for most cutaneous manifestations and is very efficacious. Quinacrine can be used if intolerance or adverse effects of hydroxychloroquine. Methotrexate can be used if no response to hydroxychloroquine. For severe or resistant disease, systemic corticosteroids, mycophenolate mofetil (dual-benefit with underlying lupus nephritis), and belimumab can be considered. Other alternatives include thalidomide, cyclophosphamide, dapsone, azathioprine, and rituximab.

Musculoskeletal manifestations: Hydroxychloroquine is the initial drug of choice for lupus arthritis. If no response, methotrexate or leflunomide can be considered. Belimumab and rituximab can be considered in refractory cases. Hematological manifestations: Drug-induced cytopenias shall be excluded. Mild cytopenias usually require no treatment. For moderate to severe cytopenias, corticosteroids are the mainstay of treatment, and azathioprine or cyclosporine-A can be used as a steroid-sparing agent. Severe refractory cytopenias may require intravenous pulse dose steroids, mycophenolate mofetil, rituximab, cyclophosphamide, plasmapheresis, recombinant G-CSF, or splenectomy.

Cardiopulmonary manifestations: Serositis usually responds to NSAIDs or moderate to high-dose oral corticosteroids. Hydroxychloroquine and methotrexate can be considered as steroid-sparing agents. Acute lupus pneumonitis requires high-dose IV pulse corticosteroids, while plasmaphereses and/or cyclophosphamide may be needed if diffuse alveolar hemorrhage is present. Interstitial lung disease can be managed by low to moderate-dose corticosteroids with immunosuppressive agents such as azathioprine or mycophenolate mofetil. Pulmonary arterial hypertension requires vasodilator therapy, while thrombotic complications such as pulmonary embolism require anticoagulation. Therefore, high-dose corticosteroids are necessary to manage myocarditis and coronary arteritis.

CNS manifestations: Accurate diagnosis and ruling out other potential causes is critical before initiating treatment for neuropsychiatric manifestations of SLE. High-dose corticosteroids with immunosuppressive agents such as cyclophosphamide, azathioprine, or rituximab are used for inflammation-related neuropsychiatric manifestations such as optic neuritis, aseptic meningitis, demyelinating disease, etc. Lifelong warfarin is indicated in cases of thromboembolic CNS events associated with antiphospholipid antibody syndrome. High-dose corticosteroids can be used for cognitive impairment, although there is no robust data on this.

Renal manifestations: Lupus nephritis (LN) shall be confirmed with a biopsy, which confirms the diagnosis, rules out other causes and helps to classify the disease. Class I and II LN should be treated with renin-angiotensin-aldosterone system blockade. Immunosuppression with high-dose corticosteroids followed by azathioprine is indicated only if proteinuria is more than 1 gram/day. Membranous LN (class V) shall also be treated with renin-angiotensin-aldosterone system blockade. If proteinuria of more than 1 gram/day is present (which is frequent in Class V LN), induction therapy with high-dose corticosteroids and azathioprine or tacrolimus/cyclosporine/mycophenolate mofetil/IV cyclophosphamide (moderate-to-severe disease) followed by maintenance therapy with azathioprine, mycophenolate mofetil, cyclosporine or tacrolimus should be used.

Corticosteroids shall be gradually tapered during maintenance therapy. Proliferative LN (class III/IV) requires more aggressive therapy. Induction therapy is with IV pulse dose methylprednisolone followed by high-dose oral steroids combined with mycophenolate mofetil, IV cyclophosphamide, or azathioprine. Maintenance therapy with mycophenolate mofetil should be continued (azathioprine can be used if MMF is not tolerated) for at least three years. IV pulse cyclophosphamide for one year can be considered maintenance therapy for severe disease. Lupus nephritis patients need very close monitoring of their renal function and proteinuria in addition to other SLE disease activity markers. Flares and incomplete remission are common. Renal replacement therapy and transplant may be needed in some patients.

Pregnancy manifestations:

Pregnancy shall be considered only if the disease was quiescent at the time and six months prior due to an increased risk of flares otherwise. Contraception, if needed, shall be used until then and shall be progesterone-only contraception. Hydroxychloroquine is considered safe in pregnancy, has been associated with a significant reduction in flares and disease activity, and shall be continued through pregnancy. Azathioprine and low-dose

corticosteroids can be used for mild manifestations. Other immunosuppressive agents, including methotrexate, leflunomide, mycophenolate mofetil, cyclophosphamide, are teratogenic and contraindicated in pregnancy. Rituximab and belimumab shall also be avoided during pregnancy. Patients with antiphospholipid antibody syndrome shall transition from warfarin to low-molecular-weight heparin and aspirin before pregnancy. For females with positive Anti-Ro or Anti-La antibodies with a history of neonatal lupus in a previous pregnancy, close fetal heart monitoring with weekly or alternate-weekly fetal echocardiography is recommended during the second trimester. First or second-degree heart block shall be promptly treated with dexamethasone, although prophylaxis with dexamethasone is not recommended. A complete heart block is irreversible and requires a permanent pacemaker in the infant. Hydroxychloroquine decreases the risk of fetal heart block.

Other management considerations: Hydroxychloroquine shall be used in all patients with SLE given its benefits beyond just managing active manifestations, including anti-thrombotic properties, and preventing flares. Patients on hydroxychloroquine will require regular ophthalmology exams to monitor for the rare but irreversible maculopathy associated with this drug. Corticosteroids are frequently used in SLE, with many patients unable to taper them completely. Long-term adverse effects of corticosteroids shall be considered and monitored, including osteoporosis, glaucoma, cataract, and avascular necrosis. Patients on high-dose corticosteroids will also need antibiotic prophylaxis to prevent infections. Most immunosuppressive agents used in SLE have several potential adverse effects ranging from cytopenias and hepatotoxicity with most to an increased risk of urinary bladder cancer with cyclophosphamide. These patients shall be appropriately and closely monitored for adverse effects of these agents.

Recently approved and emerging drugs

Anifrolumab (Saphnelo): A monoclonal antibody that blocks the type I interferon receptor. It is used for moderate-to-severe SLE and has shown effectiveness in reducing disease activity while potentially allowing for less steroid use.

Voclosporin (Lupkynis): An oral calcineurin inhibitor used to treat lupus nephritis (lupus kidney disease). It is a more potent and stable form of cyclosporine.

Belimumab (Benlysta): A monoclonal antibody that targets B-lymphocyte stimulator (BLyS). It has been shown to prevent future disease flares and is used to treat SLE.

Obinutuzumab: A monoclonal antibody that targets CD20 on B-cells. It has been investigated in clinical trials, such as the NOBILITY trial, for proliferative lupus nephritis.

Telitacicept: A novel drug that inhibits B-lymphocyte stimulator (BLyS). A phase 3 trial has shown its potential efficacy in treating SLE.

Investigational and experimental new drugs

- Cenerimod: A selective sphingosine-1-phosphate (S1P) receptor modulator that has shown promise in clinical trials.
- Litifilimab: An antibody being developed for lupus.
- CAR-T cell therapy: Genetically engineered T-cells are being explored to target and eliminate the specific B-cells that produce harmful antibodies in lupus.
- DS-7011a: A monoclonal antibody that targets toll-like receptor 7 (TLR7).

7. Conclusion

The higher burden of infections and malignancies in SLE, identifying strategies to abate these long-term outcomes in SLE is an important goal. The multidisciplinary care that involves generalist providers an opportunity to improve the provision of preventive steps in SLE. The activating the immune response, skewing the cytokine microenvironment, and impairing the debris clearance machinery; summarized current knowledge on SLE diagnosis by the disease onset, activity and comorbidities; identified risk factors predisposing SLE at the genetic, approaches can prevent SLE. For instance, glucocorticoid, primarily functions via modulating the cytokine microenvironment, also attenuates the immune response by inhibiting the maturation and activity of DCs, interfering with TCR signaling, and inducing B cell apoptosis as well as affecting the downstream pathways of B cell receptor signaling such as NF-κB. Hydroxychloroquine, known capable of alleviating SLE and largely by blocking TLR signaling, also modulates the cytokine distribution and homeostasis among Th1, Th2, Th17 and Treg cells.

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