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Systemic Lupus Erythematosus: An Review

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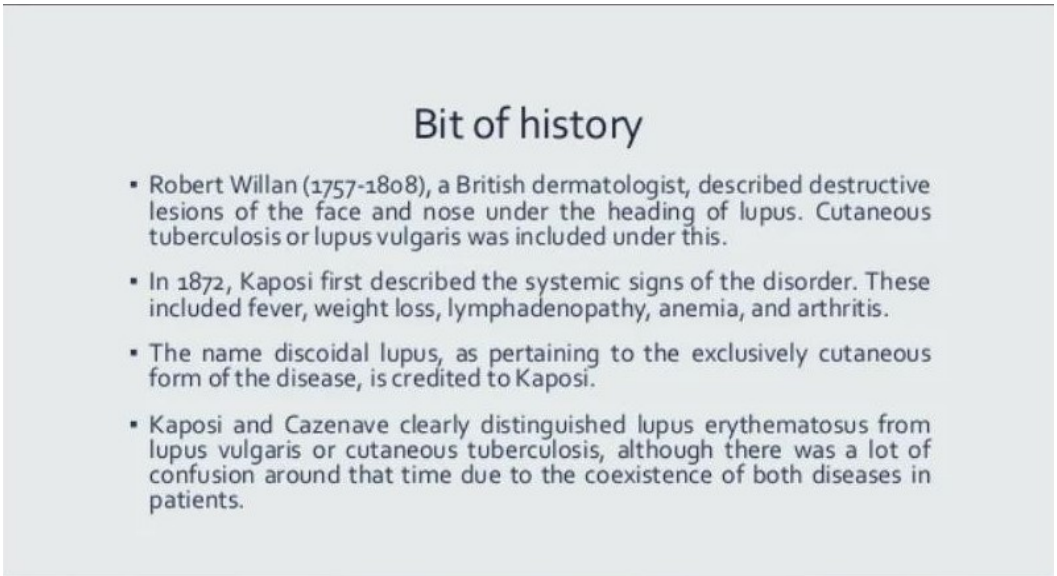
ABSTRACT:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with varied natural history and multisystemic involvement. The pathogenesis is multifactorial and complex precipitating the formation of autoantibodies. One of the main factors in SLE is the interaction between environmental triggers and genetic factors. Genome-wide association study technology has led to the identification of more than 80 loci which produce key proteins that lead to small pathophysiological changes and are associated with SLE. There has been an improvement in the management of the disease with newly standardized scores that have been validated in assessing disease activity and quality of life, and have helped in clinical care as well as research. The last five decades have seen a marked improvement in the prognosis of SLE, thanks to better general care and the development of newer immunosuppressive drugs, more specifically biological agents.

Introduction

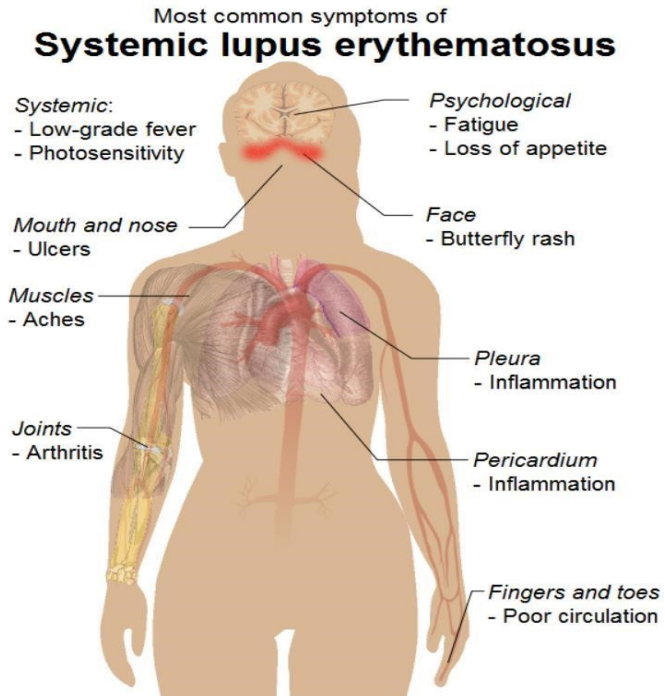
The Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multisystem involvement. The condition has several phenotypes, with varying clinical presentations from mild mucocutaneous manifestations to multiorgan and severe central nervous system involvement. Several immunopathogenic pathways play a role in the development of SLE. Hargraves described the lupus erythematosus (LE cell) 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. Despite several agents shown to be efficacious in treating SLE, the disease still poses significant morbidity and mortality risk in patients.

History



Etiology

SLE is a multisystemic disease with an unknown etiology. However, several genetic, immunological, endocrine, and environmental factors play a role in the etiopathogenesis of SLE.Familial segregation and high concordance rates in identical twins suggest a strong genetic contribution in SLE, although there is no obvious inheritance pattern. Concordant rates for identical twins have been reported as high as 50%. Over 100 gene loci with polymorphisms (or, rarely, copy numbers or mutations) have been identified to be associated with polygenic SLE (majority of cases), and more than 30 genes causing monogenic forms of SLE or SLE-like



Phenotype have been identified. These genes are associated with activation of the immune system in response to foreign antigens, self-antigen generation, and activation of innate and adaptive immune systems. Some gene mutations that are rare but are considered very high risk for the development of SLE include deficiencies of early complement components C1q, C1r, C1s (>90% risk), C4 (50%), C2 (20%), and TREX1. Some of the other genes associated include HLA-DRB1, HLA-DR2, HLA-DR3, HLA-DRX, TNFAIP3, STAT-4, STAT-1, TLR-7, IRAK1/MECP2, IRF5TNPO3, ITGAM, etc. The most common genetic predisposition is located at the major histocompatibility (MHC) locus. The MHC contains genes for antigen-presenting molecules (class I human leukocyte antigens [HLA-A, -B, and -C] and class II HLA molecules [HLA-DR, -DQ, and -DP]).In addition, women are at ten times more risk of developing SLE than men, and the risk of SLE is 14 times more in Klinefelter syndrome (47, XXY). This suggests an association with genes on the X-chromosome. However, despite several studies, the exact genes have not been identified.Female sex and hormonal influence are significant risk factors for SLE.

- **Epidemiology**

Varying prevalence and incidence rates of SLE have been reported, with differences mainly attributed to the population differences. The Georgia and Michigan lupus registries reported prevalence of 72.1 to 74.4 per 100,000 persons and incidence rates of 5.6 per 100,000 person-years in primarily Caucasian and African-American populations. African-Americans have the highest rates, which are higher among Asian and Hispanic populations than Caucasians. The disease tends to have an earlier age of onset and is more severe in African-Americans.SLE predominantly affects women of childbearing age, with a female to male ratio of 9 to 1. The risk, however, decreases after menopause in women, although still is twice as compared to men. Studies have indicated that although rare, lupus in men tends to be more severe. In addition, men tend to have more frequent skin manifestations, cytopenias, renal disease, serositis, neurologic involvement, thrombosis, cardiovascular disease, hypertension, and vasculitis than women.

- **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. 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 and demethylated DNA, leading to interferon-alpha production and RNA binding autoantibodies such as antibodies against Ro La, Sm, and RNP.

- **Histopathology**

Tissue pathology in SLE can demonstrate a variety of aberrant immunologic mechanisms, including immune complex formation, autoantibody formation, and immunologically mediated tissue injury.LE body or hematoxylin body is a hallmark of SLE pathology. It is a homogeneous globular mass of nuclear material that stains bluish-purple with hematoxylin. It can be observed in the lungs, kidneys, spleen, heart, lymph nodes, and serous and synovial membranes. They contain immunoglobulins and DNA, and phagocytes' engulfment of the LE body leads to the formation of the classic LE-cell.Pathology from skin lesions in SLE demonstrates immune complex formation leading to tissue damage, vascular and perivascular inflammation, and chronic mononuclear cell infiltration. Acute lesions demonstrate fibrinoid necrosis at the dermo-epidermal junction and the dermis, along with liquefactive degeneration of the epidermis and perivascular inflammatory cell infiltration with a T-cell predominance

- **Case Study**

A 20-year-old African American female with no prior medical history presented to the hospital with worsening fatigue, dyspnoea on exertion, and palpitations of over 1 month occurrence. The patient reported difficulty climbing more than 1 flight of stairs due to shortness of breath. She also noted slightly heavier than usual menstrual periods. She denied any history of anaemia, easy bruising or bleeding, yellowing of skin, rashes, or prior blood transfusions. Review of systems was positive for fever several weeks before presentation but otherwise negative. The patient was not on any medications, had no prior surgeries, and had no known allergies. The patient denied using alcohol, tobacco, or any illicit substances. On physical examination, her blood pressure was 116/79 mmHg, heart rate was 114 beats per minute, respiratory rate was 18 breaths per minute, temperature was 36.9°C (98.4°F), weight was 91.8 kg, height was 163 cm, and body mass index was 34.55 kg/m^2. The patient was alert, oriented, and in no acute distress. The rest of the clinical examination was insignificant except for tachycardia on cardiovascular examination and pale conjunctiva on eye examination.Laboratory data on admission included haemoglobin of 5.2 g/ld., haematocrit 14.1%, red blood cell (RBC) count 1.74×10^6 mall, platelet count 404×10^3, white blood cell count 6.2×10^3, and reticulocyte count 0.1%. Lactate dehydrogenase (LDH) was elevated at 235 unit/L, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphate were all within normal limits

Manifestations

- ***Mucocutaneous Manifestations***

More than 80% of patients with SLE suffer from mucocutaneous involvement, one of the most well-known and identified clinical features. SLE skin lesions may be lupus specific, while several nonspecific lesions are also seen. Lupus-specific lesions include (1). Acute cutaneous lupus erythematosus (ACLE) includes localized, malar, and generalized, (2) Subacute cutaneous lupus erythematosus (SCLE) includes annular and papulosquamous, and (3) Chronic cutaneous lupus erythematosus (CCLE) includes classic discoid lupus erythematosus (DLE), hypertrophic/verrucous, lupus panniculitis/profundus, lupus tumidus, chilblains lupus, mucosal discoid lupus, and lichenoid discoid lupus.

- ***Musculoskeletal Manifestations***

Approximately 80 to 90% of patients with SLE suffer from musculoskeletal involvement at some point during their disease course and may range from mild arthralgias to deforming arthritis. Lupus arthritis is typically a non-erosive, symmetrical inflammatory polyarthritis affecting predominantly the small joints of the hands, knees, and wrists, although any joint can be involved. Jaccoud arthropathy results from the joint capsule and ligament laxity, leading to non-erosive deformities of the hands, including ulnar deviation and subluxation of the metacarpophalangeal joints that may mimic rheumatoid arthritis. Usually, these deformities are reducible, although rarely, they may become fixed. Avascular necrosis (with or without steroid use) can occur in up to 10% of patients with SLE and is usually bilateral and involves the hip joints.

- **Hematologic and reticuloendothelial manifestations:**

Anemia is present in more than 50 % of patients with SLE and most commonly is anemia of chronic disease. Other causes of anemia in SLE may include iron deficiency anemia, coomb's positive autoimmune hemolytic anemia, red blood cell aplasia, and microangiopathic hemolytic anemia, which may be associated with antiphospholipid antibody syndrome. Leukopenia secondary to neutropenia or lymphopenia is also very frequent and severe. Thrombocytopenia can be mild or severe and may be associated with antiphospholipid antibody syndrome and autoantibodies against platelets, glycoprotein IIb/IIIa, or thrombopoietin receptor. Pancytopenia is not infrequent and may occasionally be associated with myelofibrosis. Soft non-tender lymphadenopathy is common in SLE, although rare cases of histiocytic necrotizing lymphadenitis have been reported (KikuchiFujimoto disease). Splenomegaly is common in SLE, while splenic atrophy and asplenism have been reported.

- ***Neuropsychiatric Manifestations***

Both central (CNS) and peripheral (PNS) nervous systems may be involved in SLE in addition to several psychiatric manifestations, although the diagnosis can be difficult. The most common CNS manifestation is intractable headaches, reported in more than 50% of cases. Focal or generalized seizures may be seen, and are associated with disease activity, although they carry a favorable prognosis. Other CNS manifestations include aseptic meningitis, demyelinating syndrome including optic neuritis and myelitis, movement disorders such as chorea and cognitive dysfunction. Patients with SLE are also at high risk for ischemic strokes.

- ***Renal Manifestations***

Lupus nephritis is a well-known and common complication of SLE. The involvement may range from mild subnephrotic proteinuria to diffuse

progressive glomerulonephritis leading to chronic kidney damage. Lupus nephritis usually occurs early in the course of SLE. New-onset hypertension, hematuria, proteinuria, lower extremity edema, and elevation in creatinine shall raise suspicion for lupus nephritis. A biopsy is crucial in staging lupus nephritis and ruling out other causes. The six classes of lupus nephritis are mentioned in the histopathology section of this article. The biopsy findings dictate the treatment of lupus nephritis.

- ***Pulmonary Manifestations***

  Pleuritis is the most common pulmonary manifestation and may not always be associated with pleural effusion. Other pulmonary manifestations include exudative pleural effusions, acute lupus pneumonitis with bilateral pulmonary infiltrates, an interstitial lung disease which may be nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP), diffuse alveolar hemorrhage associated with capillaritis, pulmonary arterial hypertension, pulmonary embolism (with or without antiphospholipid antibody syndrome) and shrinking lung syndrome.

- ***Cardiovascular Manifestations***

  SLE may involve any layer of the heart, including the pericardium, myocardium, endocardium, and even the coronary arteries. Pericarditis associated with exudative pericardial effusions is the most common cardiac manifestation. Cardiac tamponade is rare. Myocarditis is rare and is associated with anti-Ro (SSA) antibodies. Hydroxychloroquine-associated cardiomyopathy shall be ruled out, and this may occasionally require an endomyocardial biopsy. Valvular abnormalities, including Libman-Sacks endocarditis involving the mitral valve, are common and may be associated with antiphospholipid antibody syndrome.

- ***Gastrointestinal Manifestations***

  Any part of the gastrointestinal tract may be involved in SLE. These manifestations include esophageal dysmotility (especially the upper one-third of the esophagus), mesenteric vasculitis, lupus enteritis, peritonitis and ascites, protein-losing enteropathy, pancreatitis, and lupoid hepatitis. Further, patients with SLE and antiphospholipid antibody syndrome can develop BuddChiari syndrome, mesenteric vessel thrombosis, and hepatic veno-occlusive disease.

- ***Pregnancy Complications***

  SLE patients with positive antiphospholipid antibodies are at a high risk of spontaneous abortions and fetal loss, pre-eclampsia, and maternal thrombosis. Anti-Ro (SSA) and Anti-La (SSB) antibodies can cross the placenta leading to fetal heart block and neonatal lupus presenting with a photosensitive rash, cytopenias, and transaminitis. The risk is 2% with the first pregnancy but increases to 20% if there is a history of neonatal lupus in a past pregnancy. SLE usually flares in pregnancy, especially if the disease was uncontrolled in the six months preceding pregnancy. Lupus nephritis can be challenging to differentiate from pre-eclampsia, although several clinical and laboratory features (low complements, positive Anti-Ds-DNA antibody, normal serum uric acid level, and active urinary sediment) may help.

- ***Other Manifestations***

  Eye involvement is common, and keratoconjunctivitis sicca is frequently seen in SLE in the presence or absence of secondary Sjogren syndrome. Other ocular manifestations are retinal vasculitis, optic neuritis, uveitis, scleritis, peripheral ulcerative keratitis, and episcleritis. Patients with SLE are also more susceptible to drug-induced ocular damage, including steroid-induced glaucoma or cataract and hydroxychloroquine-induced maculopathy.

➢ **Prognosis**

Despite the advancements in therapeutic options of SLE and a better understanding of the disease process, SLE patients suffer from significant morbidity and carry a high mortality. Survival rates are 85 to 90% during the first ten years. Leading causes of mortality include cardiovascular disease, infections, and renal disease. Early diagnosis with therapy to prevent organ damage, monitoring and screening patients for cardiovascular disease and infections with early intervention may improve these outcomes.

➢ **Complications**

Complications in patients with SLE may occur either due to organ damage by the disease or due to the adverse effects of the medications.

Disease process-related complications include but are not limited to accelerated atherosclerosis with a several-fold higher risk of coronary artery disease even in the younger population, end-stage renal disease, and neurological deficits, including blindness secondary to neuropsychiatric manifestations. Patients with severe cutaneous lupus, especially discoid lupus, can suffer permanent skin damage and alopecia..

Medication-induced complications are common and require close monitoring. Long-term corticosteroid use in SLE patients frequently leads to under-diagnosed and under-treated osteoporosis, leading to osteoporotic fractures. Other complications of long-term use of corticosteroid therapy include avascular necrosis, glaucoma, cataract, weight gain, and poor control of Diabetes mellitus. High-dose corticosteroid use can also be associated with opportunistic infections and acute psychosis. Long-term use of hydroxychloroquine may rarely result in maculopathy and retinopathy that is irreversible, and close ophthalmology examinations are recommended

➢ **Evaluation**

The diagnosis of SLE can be challenging, and no single clinical feature or lab abnormality can confirm SLE diagnosis. Instead, SLE is diagnosed based on the constellation of signs, symptoms, and appropriate laboratory workup. Imaging and histopathology may play a crucial role as well.

Several autoantibodies have been described in SLE, with varying sensitivity and specificity. While some autoantibodies may be associated with a certain clinical subset of SLE, others may serve as a marker of disease activity.

Antinuclear antibodies (ANA) are the hallmark of the disease and shall be the initial test performed. Immunofluorescence assay is considered the gold standard test for ANA. Although other detection methods such as enzyme-linked immunosorbent assay (ELISA) and multiplex assays are widely available, they lack sensitivity. A positive ANA is seen in more than 97% of cases of SLE. However, it can also be seen in several other disorders and a significant proportion of the healthy population, and have a specificity of only 20%. Hence, a positive ANA does not confirm SLE diagnosis, but a negative ANA makes it significantly less likely. ANA negative SLE has been rarely described, although it is primarily due to methodical error. Those cases have either a positive ANA on immunofluorescence or a positive Anti-Ro (SSA) antibody.

Management

- **principles**

The goals of treatment in lupus are 1) maintain lowest degree of activity using immunomodulators, immunosuppression as appropriate and avoiding known triggers, 2) prevent organ damage from active lupus, 3) reduce comorbidities secondary to lupus and its treatment, especially accelerated atherosclerosis, the major cause of death, and 4) address fatigue and pain, which often are not associated with active lupus. Early initiation of treatment as well as partnership with the patient towards these shared goals is essential. This translates into avoidance of known triggers of flares, the need for sun protection, maximization of immunomodulators (hydroxychloroquine and vitamin D, including monitoring for adherence), avoidance of maintenance prednisone >6mg daily, and control of active disease with immunosuppression or biologics when required. Here, we review the rationale for current and future treatments.

- **Immunomodulators**

Immunomodulators can favorably regulate the immune system in SLE without increasing the risk of infection or malignancy.

- **Hydroxychloroquine**

Hydroxychloroquine pleiotropically modulates the immune response by inhibition of B cell receptor and TLR signaling as well as intracellular TLR-3 and-7 activation, fundamental in nucleic acid sensing . It increases the lysosomal pH interfering with MHC-antigen binding, thus processing of autoantigens, as well as secretions of cytokines . Hydroxychloroquine exerts an anti-type 1 interferon effect by interfering with the STING pathway .
Hydroxychloroquine is the cornerstone of medical therapy in lupus. It should be used in every patient unless there is a clear contraindication. It is the only medication shown to increase survival in lupus patients . It has been shown to reduce lupus flares , prevent organ damage including cardiovascular events , triple mycophenolate response in lupus nephritis , prevent seizures and reduces the risk of developing neuropsychiatric lupus .

- **Vitamin D**

Vitamin D should be supplemented in all SLE patients with insufficiency or deficiency, for its immunomodulatory and anti-fibrotic effects. Vitamin D immunomodulatory properties are mediated by the vitamin D3 receptor (VDR) in multiple immune cells lineages including
monocytes, dendritic cells, and activated T cells as well as in the skin, vasculature and other tissues . In vitro, vitamin D exerts an anti-inflammatory and anti-proliferative effect by promoting a Th1 (TNF-α, IL-2, IFN-γ) to Th2 (IL-4, IL-5, IL-10, GATA3) polarization as well as Th17 (IL12, IL23, IL-6, 17) to Treg (IL-10, TGF-β, FoxP3, CTLA4) state . It affects the development and function of NKT cells . In addition, vitamin D may act as an anti-fibrotic agent. Vitamin D deficiency is associated with increased risk of multiorgan fibrosis including, among others, the kidneys and the lungs . Importantly, patients with lupus nephritis refractory to mycophenolate have increased expression of profibrotic pathways in the affected kidneys suggesting that renal tissue could be rescued by targeting such pathways.

- **Dehydroeipandrosterone (DHEA)**

DHEA is an adrenal hormone regulated by ACTH . It is an important precursor of both estrogens and androgens via peripheral conversion . Women with lupus tend to have lower levels of androgens, higher estradiol, lower DHEA and DHEA-S (its metabolite), independently of corticosteroid use . In addition, DHEA supplementation has been associated with regulation of proinflammatory cytokines (IL-2, IL-1, IL-6, TNF-a) and may reduce antibody production in mice Many of the several randomized clinical trials in women with SLE showed a modest improvement in disease activity along with improvement in cytokine profile and bone density . DHEA should not be used in postmenopausal women since it may increase the risk of hormone sensitive malignancies. There is no evidence to support DHEA use in men

- **Corticosteroids**

Corticosteroids affect all components of the immune system [155]. High dose or “pulsed” corticosteroids are important to rapidly ablate the autoimmune response in life or organ threatening manifestations such as some cases of nephritis, vasculitis, central nervous system lupus, myocarditis, or alveolitis, among others. In lupus nephritis for example, pulsed therapy (250– 1000mg IV daily for 3 days) was previously recommended along with cyclophosphamide or mycophenolate for induction, but there is no consensus on an oral maintenance regimen . The “rituxilup” protocol showed that lupus nephritis remission can be induced without any oral corticosteroids using rituximab and mycophenolate suggesting that corticosteroids might not be necessary to control even severe lupus manifestations . Oral corticosteroids should be avoided as much as possible. In lupus patients, 80% of organ damage after diagnosis is directly or indirectly attributable to prednisone . Doses of even 10 to 20 mgs daily increase the risk of cardiovascular events and any dose above 6 mg increases later organ damage by 50% .
Intramuscular triamcinolone, or a brief 1-week methylprednisolone dose pack, is effective for management of most mild to moderate flares. Results from the FLOAT trial showed that a single intramuscular triamcinolone 100 mg injection is a faster acting and effective alternative to oral maintenance corticosteroids . As it is released slowly, its effect lasts for about 1 month and has equipotency of approximately 2 mg of prednisone daily.

Cytotoxic-Immunosuppressants

- **Cyclophosphamide**

Cyclophosphamide is a highly toxic alkylating agent that depletes T and B cells and suppresses antibody production . It was more widely used in the past for the induction and maintenance of lupus nephritis and other severe lupus manifestations such as central nervous system lupus . However, it has now been largely replaced by less toxic immunosuppressive medications such as mycophenolate, calcineurin inhibitors, and azathioprine for nephritis

and rituximab for severe central nervous system lupus

- **Azathioprine**

Azathioprine is a purine analogue. It is converted *in vivo* to 6-mercaptopurine followed by thioinosinic acid and 6-thioguanine which are incorporated into DNA and RNA, inhibiting their synthesis. Besides its antimetabolite role, azathioprine may have a tolerogenic effect by inhibiting CD28-mediated signal 2 in T cells . Azathioprine has been commonly used in renal and extrarenal lupus since the late 1960s. In two small randomized studies, azathioprine compared to corticosteroids alone was shown to reduce mortality, rate of flares and corticosteroid use, including patients with severe renal or central nervoussystem disease . In the following decades, its use in induction in lupus nephritis waned given its inferiority to cyclophosphamide . Azathioprine was inferior to mycophenolate in the ALMS trials and equal in the MAINTAIN trial .In extrarenal lupus, azathioprine is widely used as a corticosteroid sparing agent . However, a recent non-blinded randomized controlled study showed that mycophenolate was superior to azathioprine to control disease activity and prevent flares (renal and extrarenal) while maintaining a similar side effect profile . Azathioprine remains an excellent choice to control renal and extrarenal disease during pregnancy as the metabolite 6-MMP is not generated in the fetus with DNA synthesis, repair, and replication by irreversibly binding to dihydrofolate reductase, thus reducing purine synthesis. However, the mechanism of its anti-inflammatory effects goes beyond arresting the cell cycle by folate depletion and is not completely understood . For instance, co-administration of folate does not impair its efficacy, while mitigating side effects. Low-dose methotrexate has pleiotropic effects involving increased anti-inflammatory adenosine signaling, apoptosis of activated lymphocytes, reduction of circulating pro-inflammatory T-cells, reduction of adhesion molecules on endothelial and synovial cells, reactive oxygen species, and others .

- **Mycophenolate**

Mycophenolate preferentially depletes guanoside nucleotides in T and B cells inhibiting proliferation. It suppresses lymphocyte and monocyte recruitment to inflamed tissue. It inhibits inducible nitric oxide synthase which may curtail nitric oxide oxidative tissue damage mediated by macrophages . Mycophenolate is effective for induction and maintenance of lupus nephritis. The ALMS trial (n=140) showed that 22.5% of patients treated with mycophenolate achieved complete renal remission at 24 weeks compared to 5.8% in the cyclophosphamide group . The larger ALMS lupus nephritis induction trial showed similar efficacy of mycophenolate compared to cyclophosphamide. Mycophenolate had a better safety profile. This was confirmed by a recent Cochrane systematic review, although with low certainty evidence .

- **Calcineurin inhibitors**

Calcineurin inhibitors target T cells by blocking the inhibition of calcineurin . This prevents translocation of transcription factors such as nuclear factor of activated T-cells (NFAT) resulting in T cells inhibition with reduction of IL-1b, IFN-γ, IL-6 and IL-10. B cell activation is also impaired along with class switching and immunoglobulin production. Furthermore, calcineurin inhibitors affect the kidneys directly by stabilizing podocytes, reducing mesangial proliferation, and improving proteinuria . Calcineurin inhibitors are commonly used to prevent transplant rejection. In lupus, tacrolimus has been used, alone or in combination with mycophenolate, more extensively than cyclosporine given its better side effects profile . However, both have significant variability in plasma concentration and require monitoring. Multiple small RCTs showed that lupus nephritis induction with calcineurin inhibitors (cyclosporine or tacrolimus) is as effective as cyclophosphamide or mycophenolate . A recent metanalysis suggested a possible superiority of tacrolimus over cyclophosphamide . A larger trial comparing mycophenolate vs tacrolimus in 150 Chinese patients with active class III/IV showed similar complete response rates at 6 months (59% vs 62%, respectively) and side effects .They are recommended by EULAR .

Voclosporin is a new calcineurin inhibitor. It has greater pharmacological potency, faster elimination and less variability in blood concentration. It is non-inferior to tacrolimus in preventing kidney transplant rejection . The AURA phase IIb study randomized 265 patients with active lupus nephritis to receive voclosporin or placebo in addition to mycophenolate and corticosteroids . Both voclosporin doses showed higher complete remission rate than mycophenolate alone at 24 and 48 weeks (48 weeks complete remission 40%, 49%, and 24% in the high dose, low dose, and mycophenolate alone arm, respectively). Glomerular filtration rate decreased with voclosporin. There was an imbalance of death in the low dose voclosporin arm. A phase III trial (AURORA) is ongoing.

➢ ***Currently studied***

- **Anifrolumab**

Type 1 interferon signaling is mediated by the type I IFN-α/β/ω receptor (IFNAR). Anifrolumab is a monoclonal antibody blocking IFNAR. In a phase 2b trial, 305 lupus patients were randomized to receive placebo or one of two dosages of anifrolumab [235]. At 24 weeks, 34% and 29% of patients receiving anifrolumab (300mg and 1000mg every 4 weeks, respectively), while only 17.6% in the placebo group, achieved the primary outcome of SRI-4 response with sustained reduction of oral corticosteroids. The effect was greater in patients with the interferon signature at baseline. Both skin and joint disease showed a favorable response. In addition, anifrolumab was associated with decreased anti-dsDNA titers and higher C3 levels. There was a mild increased risk of viral infections, including influenza and herpes zoster. However, the first phase III trial (TULIP 1) did not reach its primary end point of decreasing the SRI-4 . TULIP 2 is currently under way.

- **Ustekinumab**

There is increased Th17 activity in lupus. Serum IL-17 and IL-23 levels are higher in SLE and correlate with disease activity . IL-17-producing cells are present in biopsies from lupus nephritis . Double negative T cells are also a source of IL-17. STAT3, which is downstream to IL-23 stimulation, is upregulated in lupus and promotes IL-17 production as well as differentiation toward Th17 and Tfh . Tfh are expanded in SLE and have been implicated in the overstimulation of B cells . IL-23 promotes the development of double negative T cells and impairs the production of IL-2 suggesting a possible indirect effect on the production of Tregs . The IL-23/Th17 axis can be disrupted by ustekinumab, a monoclonal antibody blocking IL12 and IL-23 currently approved to treat psoriasis, psoriatic arthritis and inflammatory bowel disease. In a phase 2 trial, 102 patients with SLE were

randomized (3:2) to ustekinumab vs placebo. At 24 weeks, 60% of ustekinumabtreated patients achieved the primary endpoint, SLE responder index4 (SRI-4) compared to 31% in the standard of care group (p=0.0046).

- **Baricitinib**

The Janus kinases (JAKs) are a family of tyrosine kinases mediating intracellular signaling of several cytokines via the JAK-STAT pathway. Inhibition of a single JAK may lead to blocking the downstream effect of several cytokines at the time. However, this is a redundant system in which a group of cytokines may signal through different JAKs and different JAKs mediate signaling from different groups. At present, baricitinib and tofacitinib are FDA approved for the treatment of rheumatoid arthritis. Baricitinib is a reversible inhibitor of JAK1 and JAK 2. These mediate signaling for type 1 interferons, IFN-γ, IL-6, IL-12, and IL-23 among others . An international, multicenter, double-blind, placebo-controlled phase 2 trial assessed the efficacy of baricitinib in patients with SLE. The primary outcome was the proportion of patients achieving resolution of rash or arthritis at 24 weeks, defined by SLEDAI-2K . Three-hundred and fourteen patients with inadequate control despite standard of care were included. The primary outcome was achieved in a statistically significant higher proportion of patients treated with baricitinib 4 mg daily, but not 2 mg daily, as compared to placebo (67% vs 58% vs 53%, respectively).

Atacicept

- **Atacicept**

is a TACI-Ig fusion protein that inhibits B cells by dual inhibition of APRIL and BLyS. In a phase 1b trial, atacicept showed a dose dependent reduction in circulating B cells and immunoglobulins . In the ADDRESS II, a phase 2b trial, 306 patients were randomized to receive weekly subcutaneous atacicept (75mg or 150mg) or placebo . Atacicept was associated with a trend toward better SRI-4 response at 4 weeks compared to placebo, especially in individuals with high disease activity, serologically active disease, or both. For example, in the serologically active group, 62% of patients treated with atacicept achieved SRI-4 at 24 weeks compared to 24% in the placebo arm

- **Prevention of comorbidities**

Lupus confers a 2.4-fold increase in all-cause mortality. The number one cause of death in lupus is cardiovascular events, followed by infections, and finally by renal and respiratory complications of lupus . The risk of cardiovascular events is increased 2.66 fold . Therefore, aggressive management of traditional (smoking, obesity, diabetes mellitus, hypertension, dyslipidemia) and lupus (lupus activity, antiphospholipid antibodies, homocysteinemia, excessive corticosteroid use) modifiable cardiovascular risk factors is paramount to prevent earlydeath . Homocysteinemia is present in 15% of patients and has an independent association with cardiovascular risk renal injury and fibrosis , and is associated with higher prevalence of myocardial infarction and thrombosis in patients with antiphospholipid antibodies.Hyperhomocysteinemia is an independent risk factor for cardiovascular disease in patients with lupus . Infections are common in lupus, particularly from encapsulated bacteria . Typical organisms are the most common causal agents but opportunisticbacterial, mycobacterial, protozoal,fungal and viral infection are also increased . Pneumonia, especially from Streptococcus pneumoniae, is common in lupus and is associated with excess mortality .

- **New Treatment of Systemic Lupus Erythematosus**

Cellular approach

- **Killing the B Cell**

The B cell has been targeted in SLE since decades. Initially considered guilty only as autoAb producers, B cells were subsequently also recognized as efficient antigen-presenting cells and cytokine producers. Works from the Craft Lab disclosed that murine lupus could indeed develop in T cell deficient animals . In contrast, it was principally with the works of Chan et al. that a central, eminent, and indispensable pathogenetic role was assigned to the B cell in murine lupus models . In humans, critical functions of the B cell, such as the antigen-receptor initiated activation was revealed to be intrinsically abnormal (Liossis et al., work from the Tsokos Lab) .

- **Alternative Sequencing of Biologics in SLE**

Another study assessed the efficacy of switching RTX to other, alternative anti-CD20 agents in comparison to switching to belimumab in SLE patients who had a secondary failure to RTX . Secondary failure was reported in patients initially responding (and depleting B cells) that subsequently developed serious infusion reactions, or did not sustain B cell depletion, or failed to sustain a good clinical response. One hundred and twenty-five patients were treated with RTX and 14 of them had a secondary failure. Eight out of these14 patients were switched to belimumab and 6/14 patients were switched to an alternative humanized anti-CD20 agent. More specifically, ocrelizumab was substituted in 3 patients,ofatumumab was administered in 2 patients and obinutuzumab was substituted in 1 patient. In the belimumab group, a new or worsening British Isles Lupus Assessment Group (BILAG)-2004 grade A for lupus nephritis was noticed in 2 patients, whereas SLEDAI-2K scores yielded disappointing results .

- **Silencing (Instead of Killing) the B Cell**

Obexelimab is a mAb that targets the CD19 molecule expressed on the surface of B cells. However, obexelimab simultaneously binds the Fcγ receptor IIb (FcγRIIb) the only inhibitory Fcγ receptor that is also expressed on the surface of B cells. Therefore, obexelimab inhibits the activation of B cells without depleting them. In a phase II study, 104 patients were randomly assigned to receive obexelimab or placebo after achieving low disease activity by intramuscular (IM) steroids and after discontinuing previous immunosuppression. Maintenance of improvement was observed through day 225 in 42% of patients in the obexelimab group and in 28.6% of patients in the placebo group (p = 0.18). Nevertheless, patients in the obexelimab group showed a significantly longer time to loss-of-improvement (median: 230 vs. 131 days for patients in the placebo group, p = 0.025).

- **Targeting the T Cell**

T cells also play a critical role in the pathogenesis of SLE. Belatacept is a fusion protein consisting of the Fc segment of the human IgG1 immunoglobulin and the extracellular domain of CTLA-4. Therefore, belatacept is a costimulation blocker; by blocking the B7-CD28 interaction it selectively inhibits T-cell activation. A retrospective study evaluated the efficacy of belatacept administered in lupus nephritis of 6 patients following renal transplantation . Five patients had stable creatinine levels over the following 6 months after belatacept treatment, one patient returned to hemodialysis and another patient was re-listed for a kidney transplant. Mean SLEDAI-2K decreased from 13 to 7.6 in 3 patients.

- **Plasma Cells**

Daratumumab, a mAb approved for the treatment of multiple myeloma, is an IgG1k mAb directed against CD38 causing depletion of plasma cells. Long-lived plasma cells are residents in niches in the bone marrow or (perhaps more importantly) in inflamed tissue and they do not respond to immunosuppressants, including B-cell-targeting treatments. Two patients with severe manifestations of SLE received daratumumab at a dose of 16 mg/kg of body weight once a week for 4 weeks followed by maintenance treatment with I.V. belimumab . Daratumumab treatment resulted in remarkable clinical outcomes not only of severe manifestations such as lupus nephritis, autoimmune hemolytic anemia and autoimmune thrombocytopenia but also on less severe manifestations such as arthritis, skin rashes, pericarditis, cutaneous vasculitis, alopecia, and mucosal ulcers.

The cytokines Approach

- **Inhibition of BLyS**

From discovery in experimental animals to availability for everyday clinical practice, the story of BLyS/BAFF and anti-BLyS mAb is unprecedented . Following BLyS description, its role in human autoimmunity was sought; circulating levels of BLyS are elevated in patients with SLE as described by the group of Stohl, and therefore it was targeted therapeutically .

- **Blocking BLyS in Lupus Nephritis**

The potential effects of belimumab in lupus nephritis specifically were not known, because the large clinical trials leading to the approval of belimumab, the specific BLyS (B lymphocyte stimulator)-inhibitor, had excluded patients with severe lupus nephritis. Additionally, we previously reported two patients in which lupus nephritis manifested shortly after the initiation of belimumab treatment . Of notice, both these patients improved immediately by withdrawal of belimumab and before the initiation of standard therapy. Furthermore, a retrospective study recently reported that introducing belimumab into a standard treatment regimen of patients with lupus without nephritis resulted in development of lupus nephritis with an increased frequency compared to a control group of patients with lupus .

- **Inhibition of IFN Pathway**

The story behind IFN targeting in patients with SLE is not new. More than 40 years ago it was reported that interferon is increased in the sera of patients with lupus, in active more than in inactive . Even though this report was about immune interferon, more recently the interest in interferons was renewed and was re-focused on IFNα and perhaps more importantly on IFN signature, based on a pivotal study by the groups of Bennett et al. . Anifrolumab is a fully human mAb that binds to the type I interferon receptor, blocking the activity of type I interferons such as interferon-α and interferon-β. A phase 3, randomized, double-blind, placebo-controlled trial included 362 patients with SLE. They were randomized to receive anifrolumab (n = 180) or placebo (n = 182) . A BICLA response was achieved in 47.8% of the patients in the anifrolumab group and 31.5% of the patients in the placebo group at week 52. For patients with a high interferon gene signature, the percentages were 48% in the anifrolumab group and 30.7% in the placebo group. For patients with a low interferon gene signature, the percentages were almost similar to those with a high interferon signature (46.7 and 35.5%, respectively

- **Cytokines IL-12 and IL-23**

Ustekinumab is a human mAb that binds the p40 subunit of IL-12 and IL-23 rendering both of them unable to bind to their receptors. Pioneering studies by Zhang and Kyttaris from the Tsokos Lab provided evidence that the IL23/IL17 axis is central in the pathogenesis of lupus nephritis in the MRL/lpr murine model . Double negative T cells from such mice overproduce IL17 and MRL/lpr lymph node cells, but not normal murine lymph node cells treated with IL23, transfer nephritis in non-autoimmune and lymphocyte deficient mice. A multicenter, double-blind, phase 2, randomized, controlled trial included 102 patients with active SLE .

- **Low Doses of IL-2**

It has been suggested that low levels of IL-2 may result in disruption of immune tolerance. Lupus is a “low IL-2” disease and this is thought to play a role in the pathogenesis of the disease.

According to the results of a randomized, double-blind, placebo-controlled clinical trial, low-doses of IL-2 might be a beneficial and safe choice in the treatment of patients with SLE . More specifically, 60 SLE patients (including patients with lupus nephritis) received either IL-2 (n = 30) or placebo (n = 30) for 12 months. The SRI-4 response rates were 55.17% in the IL-2 group and 30% in the placebo group, at week 12..

- **Selective Inhibition Of Intracellular Biochemical Pathways**
- **Calcineurin**

Activation of the BCR and TCR in SLE is followed by an enhanced and more rapid ionized calcium influx into the cytoplasm. In T cells, Ca^{2+} activates eventually calcineurin; this effect is believed to be inhibited by calcineurin inhibitors. Voclosporin is a novel cyclosporine analog, the most potent and least toxic among all known calcineurin inhibitors. A phase 2 randomized, doubleblind, placebo-controlled trial included 265 patients with lupus nephritis . Two doses of voclosporin (23.7 or 39.5 mg, each twice daily) wereevaluated vs. placebo in combination with MMF and corticosteroids for

induction of remission in lupus nephritis. The primary endpoint was complete renal remission defined as a decrease in UPCR to ≤ 0.5 in 2 consecutive measurements and an eGFR >60 ml/min per 1.73 m^2or no decrease of ≥20% of baseline eGFR on 2 consecutive measurements at 24 weeks.

- **mTOR Inhibition**

Sirolimus is an immunosuppressive macrolide. It blocks activation of T cells and B cells through mTOR (mammalian target of rapamycin) inhibition, reducing thereby their sensitivity to IL-2. Activation of mTOR plays a role in lupus T cell signaling dysregulation. Such mTOR-mediated lupus T cells defects were described by Fernandez et al. from the Perl Lab . A prospective, openlabel, single-arm clinical trial sirolimus was administered in 40 patients with SLE for 12 months . Patients with severe or life-threatening manifestations of SLE, proteinuria (an UPCR higher than 0.5) and hematological abnormalities such as anemia, leukopenia and thrombopenia had been excluded. Eleven patients discontinued the study due to lack of compliance or lack of tolerance.

- **JAK-STAT Signaling**

The activation of the JAK-STAT pathway plays a role in the differentiation of pathogenic effector T cells and in the impairment of Treg cells. Baricitinib is an oral inhibitor of Janus kinase (JAK), blocking the subtypes JAK1 and JAK2. In a double-blind, multicenter, randomized, placebocontrolled, 24-week phase II study, 314 patients with active SLE involving skin or joints were randomly assigned to receive placebo (n = 105), baricitinib 2 mg/d (n = 105), or baricitinib 4 mg/d (n = 104) . At week 24, reductions of SLEDAI scores were observed in 67% of the patients in the baricitinib 4 mg/d group and in 58% of the patients in the baricitinib 2 mg/d group.

Baricitinib (4 mg/d), but not the lower dosage, appeared to be more effective in the management of patients with SLE that remains active despite standard treatment.

- **Ongoing Clinical Trials**

Apart from trials that were mentioned above, other ongoing clinical studies can be grouped as follows:

- **Fighting T Cells**

T cells are essential players in the autoimmune response of lupus patients. Dapirolizumab pegol is an anti-CD40L pegylated Fab fragment that blocks costimulatory interactions between T cells and antigen presenting cells expressing CD40. A phase 2b study of dapirolizumab pegol in patients with active SLE with an inadequate response to standard treatment has been carried out . The study did not meet its primary endpoint (achieving a dose-response at 24 weeks). SLEDAI and PGA did not differentiate treatment groups; changes of BICLA and SRI-4 scores were assigned to escape medicines given during the study. Itolizumab (EQ001) is a monoclonal antibody targeting the CD6 receptor on the surface of T cells. It blocks the binding of CD6 on its ALCAM (activated leukocyte cell adhesion molecule) ligand, inhibiting therefore immune responses mediated by T cells. Data were presented at the 2019 ACR/ARP Annual Meeting . CD6 and ALCAM positive cells were reportedly increased in patients with lupus nephritis and were associated with SLE activity. Increased excreted ALCAM levels were also measured in the urine of patients with active lupus nephritis. Itolizumab ameliorated renal disease in murine models, decreased the migration of T cells to inflamed tissues and also increased levels of IL-10. In addition, itolizumab resulted in suppression of T-cell development and proliferation. Based on animal model data, the manufacturer was granted a U.S. FDA fasttrack designation for itolizumab for the treatment of lupus nephritis. The EQUALIZE trial is designed to include 2 groups. The first group is composed of patients with SLE that will receive itolizumab subcutaneously every 2 weeks for 4 weeks, while the second group consists of patients with lupus nephritis to receive itolizumab or placebo for 12 weeks.

BTK inhibitors, JAK inhibitors, and other agents that are currently under investigation.

BTK inhibitors	JAK inhibitors	Miscellaneous
Fenebrutinib (GDC-0853) (63)	Upadacitinib (JAK1 inhibitor) (64)	Lenabasum (JBT-101) (endocannabinoid type 2 receptor agonist) (65)
Orelabrutinib (ICP-022) (66)	Tofacitinib (JAK1, JAK3, JAK2 inhibitor) (67)	Memantine (NMDA receptor antagonist) (68)
Branebrutinib (69)	PF-06700841 or Brepocitinib (JAK1, TYK2 inhibitor) (70)	EBV-specific cytotoxic T lymphocytes (71)
Elsubrutinib (64)	BMS-986165 or Deucravacitinib (TYK2 inhibitor) (72)	Mesenchymal stem cells in A) SLE (73) B) Lupus nephritis (74)
		Curcumin (75)

LY3471851 (NKTR-358) is a novel Treg cell stimulator through targeting the IL-2 receptor complex. It is designed to correct specifically this immune system abnormality, i.e., the deficiency in Treg in patients with lupus, and it does not affect the entire immune system. The primary outcome of a phase 2 study is the percentage of patients that will achieve a ≥4-point reduction in SLEDAI-2K Score at week 24 . Despite the non-encouraging results of previous attempts in T cell costimulation blockade in patients with SLE, a phase 2 study aims to assess the efficacy of abatacept in patients with SLE and the primary endpoint is the BICLA response at 6 months .

- **Targeting B Cells and Beyond**

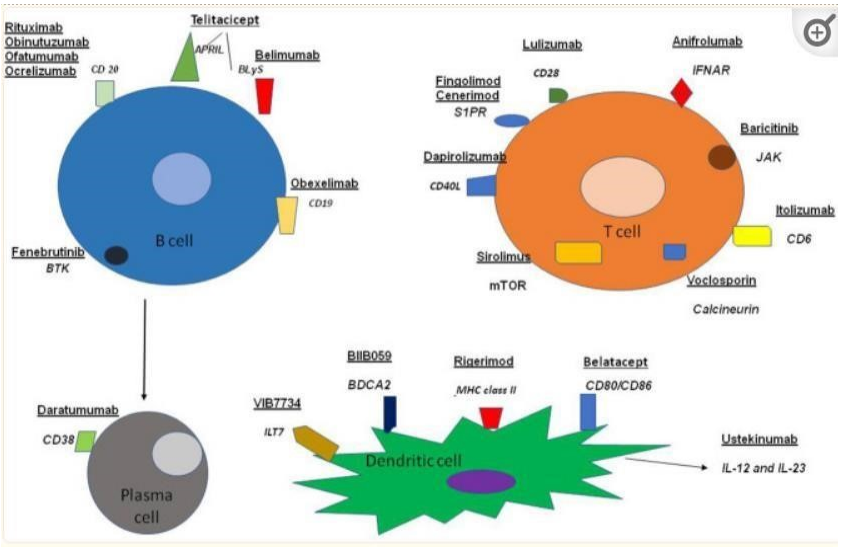
B cells are being targeted directly or indirectly in patients with lupus. RC18 is a recombinant human BLyS receptor antibody fusion protein and it is used in a phase III placebo-controlled study plus standard treatment with primary outcome an SRI response rate at week 52 . CC-220 is a cereblon modulator causing potent degradation of Ikaros and Aiolos leading to suppressed B cell proliferation and cytokine production. A phase 2, placebo-controlled study aims to evaluate efficacy and safety of CC-220 in patients with active SLE and the primary outcome is an SRI-4 at week 24. B cell and T cell collaboration is essential for the lupus autoimmune response. To this end, AMG 570, an ICOSL and BAFF bispecific inhibitory antibody, has been employed in a phase 2b study. The primary endpoint is the percentage of patients achieving an SRI-4 at week 52 . Based on the same concept, VAY736 or Ianalumab, a mAb that blocks the BAFF receptor and CFZ533 or iscalimab, a mAb that prevents CD40 pathway signaling are under investigation in a phase 2 study in patients with SLE with a primary outcome of an SRI-4 response at week 29 .

BTK inhibitors, JAK inhibitors, and some other agents with different targets are also currently under investigation and are summarized in

- ***Enhancing Healthcare Team Outcomes***

Lupus is a chronic inflammatory disorder with no cure. It can affect many organs and leads to poor quality of life without appropriate management. Premature death is common for a variety of causes. To reduce morbidity and mortality, an interprofessional team should educate and manage patients with SLE.

The primary care provider and nurse practitioner should educate the patient on avoiding triggers that cause flare-ups. In addition, the patient should be told to avoid UV light and minimize exposure to the sun. Appropriate garments, sunglasses, and a wide brim hat are recommended when going out. The dietitian should educate the patient on the importance of a low-fat diet to prevent hyperlipidemia. In addition, because patients with lupus are told to avoid the sun, vitamin D supplements are recommended. The physical therapist should educate the patient on the importance of exercise. The pharmacist should educate the patient on the importance of medication compliance and avoiding smoking. The nurse practitioner should counsel the patient on family planning and contraception. Many drugs used to treat are teratogenic, and thus, contraception is highly recommended.



Future Prospectives and Personalized medicine

The more granular understanding of the molecular basis of lupus pathogenesis has led to several new promising treatments that are undergoing late phase clinical testing. These recent phase 2 trials underlined how targeting a specific pathway may elicit dramatically different responses in patient subgroups. Precise characterization of disease phenotypes based on molecular and clinical features is crucial to design personalized treatment. The Accelerated Medicine Partnership (AMP), for example, is an ongoing effort to identify the molecular pathways, at the single cell level, involved in lupus nephritis. This may help to redefine the way we classify SLE and lupus nephritis and identify precise predictors of treatment response. We expect that the understanding of the heterogeneity of autoimmunity in lupus will lead to more effective and less toxic regimens in the future.

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