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DIAGNOSIS AND CLINICAL MONITORING OF SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect any organ or tissue in the body.

In disease development and activity, genetic predisposition, environmental triggers, and the hormonal milieu al interact.

Clinical manifestations and organ involvement patterns are highly variable, reflecting the complex mosaic of di srupted molecular pathways that culminate in the SLE clinical phenotype.

The pathogenesis of SLE is complicated by the presence of autoantibodies and immunocomplexes, activation of the complement system, dysregulation of several cytokines, including type I interferons, and disruption of nuclei c acid clearance after cell death.

Immunomodulators and immunosuppression have altered the natural progression of SLE.Furthermore, morbidi ty and mortality in SLE are caused not only by direct immune-
mediated tissue damage but also by SLE and treatment-
related complications such as accelerated coronary artery disease and increased infection risk.In this section, we discuss the diagnostic approach, as well as the etiopathogenetic rationale and clinical evidence for SLE management.

This includes 1) lifestyle changes such as avoiding UV light; 2) prevention of co-morbidities such as coronary artery disease, osteoporosis, infections, and drug toxicity; 3) use of immunomodulatory (such as hydroxychloroquine and vitamin D), and 4) immunosuppressants and targeted therapy. We also go over new upcoming agents and regimens that are currently being tested.

Keywords: Lupus erythematosus, diagnosis, treatment.

INTRODUCTION

The classic autoimmune disease is systemic lupus erythematosus (SLE).

Sustaining autoimmune process results from a complex interaction of impaired apoptotic clearance, upregulatio n of the innate and adaptive immune systems, complement activation, immune complexes, and tissue inflammat ion.

Multiple pathogenic mechanisms are likely to converge on the clinical phenotypes known as SLE.

In fact, while SLE can affect many organs and tissues, the pattern of clinical manifestations and autoimmune ph enomena varies between patients and even changes over time.

As a result, diagnosis is frequently difficult or delayed, requiring keen clinical expertise to combine clinical and immunological findings.We examine classification criteria as well as current and future treatments from a mechanistic and evidence-based standpoint.

Epidemiology

Lupus is a disease that affects women of childbearing age all over the world.

The female to male ratio in women aged 15 to 44 years can reach 13:1, while it is only 2:1 in children and the el derly.

While it occurs in all ethnic groups, it is more common in non-Caucasians.

While people of African descent have a higher prevalence in Europe and the United States, SLE is uncommon i n Africa.

It is more common in African-Americans in the United States, who also have poorer outcomes. In fact, African-American women are roughly three times more likely than Caucasian Americans to have lupus and die from it. According to the Centers for Disease Control and Prevention, there are approximately 322,000 cases of probable or definite SLE, with African Americans, American Indians, and Alaska Natives having a higher prevalence.

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Pathogenesis Overview

The interaction of genetic predisposition, environmental precipitants, and immunological and hormonal factors i s required for the clinical onset of SLE.

Immune tolerance to selfantigens is lost in such a permissive environment, along with proinflammatory stimuli such as type 1 interferons and other cytokines.

Autoimmunity then develops as a result of a complex interplay between defective clearance of apoptotic waste a nd immune complexes, as well as neutrophil extracellular traps, nucleic acid sensing, disrupted lymphocyte biol ogy, and interferon pathways.50% monozygotic twin concordance and increased risk in families point to genetic susceptibility.

Many genes have been linked to a proclivity to develop lupus, typically encoding immune components such as HLA, IRF5, ITGAM, STAT4, BLK, and CTLA4, among others.

Lupus has been linked to a variety of environmental factors. UV light (the most well-known), drugs/supplements (echinacea, trimethoprim/sulfamethoxazole), smoking, infections (particularly the Epstein-Barr virus, silica, and mercury are all potential sources of harm. Additionally, stress has been linked to a 50% increase in the risk of developing lupus.

There is evidence that both the innate and adaptive arms of the immune system are disrupted in lupus. system linked in feedback loop T cells are defective, and their aberration in lupus is significant.

Hyper activation of the BLYS or BAFF pathway, The discovery of a cell-independent B cell survival pathway resulted in the development of a new biologic therapy. As will be explainedlaterfurthermore, the discovery of a strong type 1 interferon "signature" in lupus confirmed the import ance of the innate immune system.

Dendritic cells play an important role in the clearance and sensing of nucleic acids and immune complexes, whi ch are known autoantigens in lupus.Endogenous and exogenous nucleic acids, in fact, are a major antigenic stim ulus in lupus. Autoantibodies against nucleic acid-
bound antigens are one of the disease's hallmarks. Apoptosis and neutrophil extracellular traps (NETs) are the p rimary sources of such antigens.

Excess and impaired NET degradation are linked to lupus severity, lupus nephritis, anti-
dsDNA antibodies, and complement consumption.

These findings emphasized the critical role of hypersensitivity to an inability to manage nucleic acids from dyin g cells as well as immunocomplexes, resulting in the development of a "waste disposal" theory.

Diagnosis

Several sets of categorization for manifestations have been developed over time for epidemiological and scientif ic work.

Some, such as the SLICC classification criteria, which are more sensitive and thus particularly useful in early di agnosis, can, however, be included as a diagnostic framework to confirm clinical decision-making.

Classification Criteria

For more than three decades, the 1982 ACR criteria, revised in 1997, have been widely used.

The 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria were evidencebased, included a "stand alone" criterion of lupus nephritis, and required at least one clinical (acute cutaneous lupus, chronic cutan eous lupus, oral or nasal ulcers, synovitis, serositis, proteinuria or red blood cell casts, neurologic manifestations , hemolytic anemia, leukopenia or lymph for a total of four (hypocomplementemia, direct Coombs test, and hypocomplementemia),

Clinical Diagnosis

This section discusses key organ manifestations, as well as some recent developments, that are important in lup us diagnosis. There is more information and reviews of each clinical manifestation of lupus available elsewhere.

Cutaneous Lupus

In SLE, skin involvement occurs in nearly 90% of patients and includes lupus-specific manifestations such as discoid lupus, subacute cutaneous lupus, and chronic cutaneous lupus (discoid lupus, lupus profundus, chilblain lupus, and lupus tumidus). Alopecia, vasculitis, livedo reticularis, periungual telangiectasias, and Raynaud's phenomenon are examples of non-lupus manifestations. The histology of most forms of cutaneous lupus is

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similar, with interface dermatitis, perivascular and periadnexial inflammation, and immunoglobulin and complement deposition at the dermo-epidermal junction. A biopsy is frequently required in the diagnosis of cutaneous lupus. In lupus, a true photosensitive rash is raised, delayed, and. It usually happens a few days after long-lasting.

Ultraviolet light exposure tends to last for more than 3 weeks and may be associated with systemic symptoms such as arthralgia or fatigue

Musculoskeletal Involvement
In over 90% of SLE cases, arthralgia and genuine synovitis are present. Most frequently, it manifests as symmetric polyarthritis affecting the knee, proximal interphalangeal, and metacarpophalangeal joints.

Monoarthritis should trigger an investigation into potential secondary causes. If sensitive imaging is not used, erosions are uncommon and are linked to anti-cyclic citrullinated peptide antibodies. By using ultrasound and MRI, it was discovered that periarticular involvement, which includes the tendons and joint capsule, is more prevalent than previously thought. This involvement can result in Jaccoud's arthropathy, a condition that can cause reducible abnormalities. Articular ultrasonography and magnetic resonance imaging may be used to measure the severity of the disease and help distinguish between fibromyalgia-related tenderness and active inflammatory disease.

Renal Disease
Renal involvement is present in about 50% of patients with lupus with a predilection for certain ethnic groups such as African-Americans (70%). Early detection and treatment are paramount since lupus nephritis is a major cause of morbidity and mortality in SLE and delayed diagnosis is a risk factor for end-stage renal disease.

Renal disease is suspected when there is proteinuria. However, lupus nephritis (class III, IV, and V) can be present in 25% of SLE patients without clinical signs of renal disease.

Urine protein levels above 500 mg/24h are associated with histopathological lupus nephritis and should prompt a renal biopsy.

Central Nervous System Disease
SLE has been linked to a wide range of neuropsychiatric symptoms. Only a few of them, however, is more specific for SLE and useful for diagnosis. These include seizures, psychosis, and hallucinations.

Multiple mononeuritis, myelitis, peripheral or cranial neuropathy, and acute confusional state. Importantly, other known causes must be ruled out.

In addition to clinical evaluation, magnetic resonance imaging (MRI) and cerebral spinal fluid analysis are important diagnostic tools. Central nervous system MRI is helpful to detect chronic microvascular changes, infarcts, hemorrhages, cortical atrophy, edema, abscesses, and transverse and longitudinal myelitis.

Cognitive impairment affects up to 80% of SLE patients.To detect cognitive impairment and/or functional disorders, formal psychometric testing and a psychiatric evaluation may be useful. Surprisingly, mild to moderate cognitive impairment is present in the majority of patients and is better at the time of diagnosis and does not worsen during follow-up. The most important correlate of cognitive impairment is depression.

MANAGEMENT

Principles
The goals of lupus treatment are to

1) Maintain the lowest level of activity possible with immunomodulators, immunosuppression as needed, and avoidance of known triggers,
2) Prevent organ damage from active lupus,
3) Reduceco-morbidities secondary to lupus and its treatment, particularly accelerated atherosclerosis, the leading cause of death, and
4) Address fatigue and pain, which are frequently unrelated to active lupus. Early treatment initiation, as well as collaboration with the patient toward these shared goals, are critical. This translates into avoiding known flare triggers, the need for sun protection, optimizing immunomodulators (hydroxychloroquine and vitamin D, including adherence monitoring), avoiding maintenance prednisone >6mg daily, and controlling the active disease with immunosuppression or biologics when necessary. In this section, we will go over the reasoning behind it.

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Immunomodulators
Immunomodulators can improve immune regulation in SLE without increasing the risk of infection or cancer.

Hydroxychloroquine—Hydroxychloroquine modulates the immune response pleiotropically by inhibiting B cell receptor and TLR signalling as well as intracellular TLR-3 and-7 activation, which is essential in nucleic acid sensing. It raises lysosomal pH, interfering with MHC-antigen binding and thus autoantigen processing, as well as cytokine secretion. By interfering with the STING pathway, hydroxychloroquine has an anti-type 1 interferon effect.

Hydroxychloroquine is the cornerstone of lupus treatment. Unless there is a clear contraindication, it should be used in all patients. It is the only medication that has been shown to improve survival in lupus patients. It has been shown to reduce lupus flares, and prevent organ damage, including cardiovascular events, the triple mycophenolate response in lupus nephritis, seizures, and the risk of developing neuropsychiatric lupus. Hydroxychloroquine alleviates skin symptoms and arthritis. Hydroxychloroquine improves lipidslowers insulin resistance and the risk of thrombosis and improves bone density.

Vitamin D—for its immunomodulatory and anti-fibrotic effects, vitamin D should be supplemented in all SLE patients with insufficiency or deficiency. The vitamin D3 receptor (VDR) mediates vitamin D immunomodulatory properties in a variety of immune cell lineages, including monocytes, dendritic cells, and activated T cells, as well as in the skin, vasculature, and other tissues. Vitamin D has an anti-inflammatory and anti-proliferative effect in vitro by promoting Th1 (TNF-, IL-2, IFN-) to Th2 (IL-4, IL-5, IL-10, GATA3) polarization as well as Th17 (IL12, IL23, IL-6, 17) to Treg (IL-10, TGF-, FoxP3, CTLA4) polarisation [132]. It has an impact on the development and function of NKT.

Vitamin D deficiency is common in SLE patients. Some VDR polymorphisms have been linked to lower serum vitamin D levels as well as SLE. Vitamin D deficiency is associated with increased disease activity and fatigue in lupus patients, as well as an increased risk of thrombosis, including antiphospholipid antibodies. Importantly, as demonstrated in an observational cohort and a randomized controlled study, vitamin D supplementation is associated with decreased proteinuria, higher complement levels, and improvement in overall disease activity in SLE. Aim for a 25(OH) vitamin D level of 40 ng/ml with supplementation. Supplementing with vitamin D is safe and should be done indefinitely. Vitamin D levels should be checked on a regular basis to determineDHEA.

Dehydroeipandrosterone—DHEA is an adrenal hormone that is regulated by ACTH. It is an important peripheral precursor of both estrogens and androgens. conversion Women with lupus have lower levels of androgens and higher levels of estrogen.independent of corticosteroid use, estradiol, lower DHEA, and DHEA-S (its metabolite). Furthermore, DHEA supplementation has been linked to the regulation of pro-inflammatory cytokines (IL-2, IL-1, IL-6, TNF-a) and may inhibit antibody production in mice.

Many of the numerous randomized clinical trials in women with SLE revealed a modest benefit. Improvement in disease activity, as well as improvements in cytokine profile and bone density DHEA, should not be used in postmenopausal women because it may cause breast cancer.increases the risk of hormone-sensitive malignancies. There is no evidence to support DHEA use in men.

Corticosteroids
Corticosteroids have an impact on all aspects of the immune system. High-dose or "pulsed" corticosteroids are essential for rapidly abating the autoimmune response in life-threatening manifestations such as nephritis, vasculitis, and central nervous system disorders.

Lupus, myocarditis, and alveolitis are a few examples. For example, in lupus nephritis, pulsedPreviously, therapy (250-1000mg IV daily for three days) was recommended in addition to there is no agreement on whether to use cyclophosphamide or mycophenolate for induction. Routine maintenance. The "rituxilup" protocol demonstrated that lupus nephritis can cause kidney damage.Remission can be achieved without the use of oral corticosteroids by using rituximab andMycophenolate suggests that corticosteroids may not be required to control even severe asthma. Lupus manifestations Only 25 mg of voclosporin were used in a recent phase 2 clinical trial.Prednisone was prescribed.Oral corticosteroids should be avoided as much as possible.

Prednisone is responsible for 80% of organ damage in lupus patients after diagnosis. Dosages of even 10 to 20 mg per day raise the risk of cardiovascular events.and any higher dose6 mg causes 50% more organ damage later in life.

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Cytotoxic-immunosuppressants

Cyclophosphamide - A highly toxic alkylating agent that depletes T and B cells and inhibits antibody production. It was previously more widely used to induce and maintain lupus nephritis and other severe lupus manifestations such as central nervous system lupus. However, less toxic immunosuppressive medications such as mycophenolate, calcineurin inhibitors, and azathioprine for nephritis and rituximab for severe central nervous system lupus have largely replaced them. Cyclophosphamide has been linked to premature ovarian failure, hemorrhagic cystitis, an increased risk of bladder and other malignancies, leukopenia, and an increased risk of infection.

Azathioprine - Azathioprineis an analogue of purine. In vivo, it is converted to 6-mercaptopurine, then to thioinosinic acid and 6-thioguanine, which are incorporated into DNA and RNA and inhibit their synthesis. Aside from its antimetabolite role, azathioprine may have a tolerogenic effect in T cells by inhibiting CD28-mediated signal 2 in T cells.

Azathioprine has been widely used to treat renal and extrarenal lupus. In two small randomized trials, azathioprine was shown to reduce mortality, flare rate, and corticosteroid use in patients with severe renal or central nervous system disease compared to corticosteroids alone. Given its inferiority to cyclophosphamide, its use in lupus nephritis induction waned in the following decades.

Methotrexate-Methotrexate is an antimetabolite that inhibits DNA synthesis, repair, and replication by binding irreversibly to dihydrofolate reductase, reducing purine synthesis. However, the mechanism of its anti-inflammatory effects extends beyond cell cycle arrest caused by folate deficiency and is not fully understood.

Co-administration of folate, for example, has no effect on efficacy while reducing side effects. Low-dose methotrexate has pleiotropic effects, including increased anti-inflammatory activity at low dosesinflammatory adenosine signalling, activated lymphocyte apoptosis, decrease in circulating pro-inflammatory T-cells, decrease in adhesion molecules on endothelial and synovial cells, reactive oxygen species, and others. Inflammatory adenosine signaling activated lymphocyte apoptosis, decreased circulating pro-inflammatory T-cells, decrease endothelial and synovial cell adhesion molecules, reactive oxygen species, and others.

Methotrexate has been used to treat lupus since the 1960s. Evidence from three sources combinedMethotrexate reduced inflammation in small randomized trials and several observational studies. Disease activity, was corticosteroid-free, was effective for joint and skin disease, andAnti-dsDNA and complement levels were improved. Methotrexate had a minor effect. Arandomized controlled trial of steroid-sparing activity.

Mycophenolate-Mycophenolate depletes guano side nucleotides preferentially in theProliferation of T and B cells is inhibited. It inhibits lymphocyte and monocyte recruitment.tissue that is inflamed It inhibits inducible nitric oxide synthase, which may reduce nitric oxide production.Macrophages mediate oxidative tissue damage. Mycophenolate is effective for lupus nephritis induction and maintenance.

According to the ALMS trial (n=140), 22.5% of patients treated with mycophenolate improved.achieved complete renal remission after 24 weeks versus 5.8% in the cyclophosphamide group. The larger ALMS lupus nephritis induction trial revealed thatMycophenolate versus cyclophosphamide.

Currently being 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 a placebo or one of two dosages of anifrolumab . 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 favourable response. In addition, anifrolumab was associated with decreased anti-dsDNA titers and higher C3 levels. There was a mildly increased risk of viral infections, including influenza and herpes zoster. However, the first phase III trial (TULIP 1) did not reach its primary endpoint of decreasing the SRI-4. TULIP 2 is currently under way- s, compared to only 17.6% in the placebo group. The effect was stronger in patients who had the interferon signature at the start. Both skin and joint disease responded favorably. Furthermore, anifrolumab was linked to lower anti-dsDNA titers and higher C3 levels. There was a slight increase in the risk of viral infections, such as influenza.

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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 have been found in lupus nephritis biopsies. IL-17 is also produced by double-negative T cells. STAT3, which is activated by IL-23, is upregulated in lupus and encourages the production of IL-17 as well as differentiation toward Th17and Tfh have been linked to the overstimulation of B cells and are increased in SLE. Double negative T cell growth is facilitated by IL-23 and the generation of-2 may have a subliminal impact on the generation of Tregs.Ustekinumab, a monoclonal antibody targeting IL12 and IL-23 that is now licensed to treat psoriasis, psoriatic arthritis, and inflammatory bowel disease, can disrupt the IL-23/Th17 axis.102 SLE patients were randomly assigned (3:2) to receive ustekinumab or a placebo in a phase 2 trial. At 24 weeks, 60% of patients receiving ustekinumab achieved the primary goal, SLE responder index-4 (SRI-4), as opposed to 31% of patients receiving standard of treatment (p=0.0046). Skin and joint scores significantly improved, according to subgroup analysis. Ustekinumab increased C3 and decreased levels of anti-dsDNA.

Baricitinib: Through the JAK-STAT pathway, the Janus kinases (JAKs), a family of tyrosine kinases, mediate the intracellular signaling of a number of cytokines. One JAK inhibition may prevent the simultaneous blockage of the downstream effects of multiple cytokines. A group of cytokines may nevertheless signal through various JAKs, and various JAKs may facilitate signaling from various groups in this redundant system.

The FDA has currently approved baricitinib and tofacitinib for the treatment of rheumatoid arthritis. JAK1 and JAK2 are reversibly inhibited by the drug baricitinib.These mediate signaling for a variety of molecules, including type 1 interferons, IFN, IL-6, IL-12, and IL-23. a double-blind, multicentre, international study. A phase 2 placebo-controlled trial evaluated baricitinib's effectiveness in treating SLE patients. The primary outcome, as measured by SLEDAI-2K, was the percentage of patients whose rash or arthritis had cleared up by 24 weeks. There were 314 patients with insufficient control despite receiving conventional therapy. A statistically significant larger percentage of individuals receiving baricitinib 4 mg daily than those receiving placebo (67% vs. 58% vs. 53%, respectively) were successful in achieving the primary outcome.

Several of the Results were influenced by the way baricitinib affected arthritis because there was no discernible difference in skin ratings. Additionally, there were fewer flares in the 4 mg group when compared to the placebo group (33% vs. 51%). Compared to the 2 mg (2%) and placebo (1%), the 4 mg arm (6%) had more serious infections. In the 4 mg arm, one deep venous thrombosis (1%) was found.

Atacicept: is a TACI-Ig fusion protein that inhibits B cells by inhibiting APRIL and BLYS simultaneously. Atacicept demonstrated a dose-dependent reduction in circulating B cells and immunoglobulins in a phase 1b trial.306 patients were randomly assigned to receive weekly subcutaneous atacicept (75mg or 150mg) or placebo in the

ADDRESS II phase 2b trial. Atacicept was associated with a trend toward better SRI-4 response at 4 weeks when compared to placebo, particularly in people with high disease activity, serologically active disease, or both. For example, 62% of patients treated with atacicept in the serologically active group achieved SRI-4 at 24 weeks, compared to 24% in the placebo arm.

Lifestyle

Some lupus treatments are non-pharmacological. Patients should avoid sun exposure by wearing protective clothing and applying sunscreen with an SPF of at least 50 (as demonstrated in a randomized clinical trial. Fibromyalgia and "fibromyalgia-ness" (a proclivity to respond to illness and psychosocial stress with fatigue, an increase in symptoms, and widespread pain) are more common in SLE.Regular exercise, stretching, and relaxation can help with fibromyalgia fatigue, cognitive dysfunction, and pain.

Prevention of Co-Morbidities

Lupus increases all-cause mortality by 2.4 times. Cardiovascular events are the leading cause of death in lupus, followed by infections, and finally renal and respiratory complications. The risk of cardiovascular events is 2.66 times higher. To prevent premature death, aggressive management of traditional (smoking, obesity, diabetes, hypertension, dyslipidemia) and lupus (lupus activity, antiphospholipid antibodies, homocysteinemia, excessive corticosteroid use) modifiable cardiovascular risk factors is critical.

Homocysteinemia affects 15% of patientsand is associated with an increased risk of cardiovascular disease, renal injury, and fibrosis, as well as a higher prevalence of myocardial infarction and thrombosis in patients with antiphospholipid antibodies. In lupus patients, hyperhomocysteinemia is an independent risk factor for cardiovascular disease.Lupus infections are common, especially from encapsulated bacteria.

Future Perspectives and Personalized Medicines

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 phenotyping of disease phenotypes based on molecular and clinical features is critical for designing personalizedtreatment.

The Accelerated Medicine Partnership (AMP), for example, is an ongoing effort to identify the molecular pathways involved in lupus nephritis at the single-cell level.

CONCLUSION

A complicated area of clinical care is covered by published SLE guidelines, although the methodological consistency, recommendations, and scope differ drastically. For optimal care and health outcomes for SLE patients, collaborative and interdisciplinary efforts are required to create thorough, high-quality evidence-based guidelines.

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