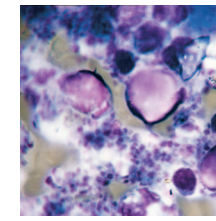
Lupus: An Overview of the Disease And Management Options



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ABSTRACT

Lupus is a chronic inflammatory autoimmune disease with a wide range of clinical presentations resulting from its effect on multiple organ systems. There are four main types of lupus: neonatal, discoid, drug-induced, and systemic lupus erythematosus (SLE), the type that affects the majority of patients. Patients with lupus experience a loss of self-tolerance as a result of abnormal immunological function and the production of autoantibodies, which lead to the formation of immune complexes that may adversely affect healthy tissue.

Although the precise etiologic mechanism is unknown, genetic, hormonal, and environmental factors, as well as immune abnormalities, have been identified. Associations between lupus onset and age, sex, geography, and race have also been established. Management of this disease should be individualized and should include both pharmacological and nonpharmacological modalities for symptom relief and resolution as well as improved quality of life.

INTRODUCTION

Lupus is associated with multisystemic inflammation resulting from abnormal immunological function. Patients experience periodic flares of varying severity or instances in which no observable signs or symptoms are present. The four main types of lupus are neonatal and pediatric lupus erythematosus (NLE); discoid lupus erythematosus (DLE); drug-induced lupus (DIL); and systemic lupus erythematosus (SLE).

1. As a rare form of lupus observed in newborns, NLE is thought to result from maternal autoantibodies passing through the placenta. However, of those pediatric patients who have positive maternal autoantibodies, only about 1% develop NLE. Common clinical presentations involve the heart, liver, and skin. Significant morbidity and mortality, along with cardiac manifestations, have been noted; however, in most NLE patients with other organ involvement (e.g. skin, liver, and blood), signs and symptoms sometimes resolve spontaneously within 4 to 6 months.[1]

2. DLE is manifested as a chronic scarring and atrophic photosensitive dermatosis, which may progress to SLE or may occur in patients with SLE. The cause is thought to be genetic, with the highest prevalence in women, African-Americans, and persons between 20 and 40 years of age. The diagnosis is frequently made by biopsy of a rash on the scalp, face, neck, or arms. Chemical and physical sunblocks, topical corticosteroids, or antimalarial agents are commonly used to prevent disease flares and to manage the clinical manifestations associated with DLE.[2]

3. DIL occurs after exposure to a medication, causing an autoimmune response. Various organ systems may be affected, but clinical manifestations usually subside upon discontinuation of the responsible agent. DIL is discussed on page 242.[3]

4. SLE is the most common type of lupus and is therefore the focus of this review. SLE is commonly referred to simply as "lupus," but it is differentiated from other types by its multiorgan system effects. SLE is diagnosed in approximately 20 to 150 persons per 100,000 and is typically seen in females of childbearing age; however, it may affect male or female patients at any age.[4–6] SLE is more commonly observed in African-Americans, Asians, Hispanics, and Native Americans.[7,8]

Arriving at the correct diagnosis of lupus is a challenge, considering the multitude of clinical presentations observed. The disease can affect the kidneys, lungs, skin, nervous system, and musculoskeletal system as well as other organs of the body. If SLE is suspected, patients' subjective complaints, as well as laboratory abnormalities and demographic characteristics, may help to pinpoint the diagnosis.

In recent decades, mortality rates attributed to SLE have declined as a result of earlier disease detection and advances in treatment. The average 10-year survival rate now exceeds 90%; three decades ago, the 10-year average survival rate was 76%.[9–11] The most common causes of death are related to early active SLE include SLE-induced and immunosuppressant-induced infectious complications. A common cause of late mortality related to SLE is an accelerated atherosclerosis that is associated with either the disease or the treatment.[9]

PATHOPHYSIOLOGY

SLE is a chronic disease that affects various organ systems, primarily as a consequence of the formation and deposition of autoantibodies and immune complexes, leading to eventual organ damage. Hyperactive B cells, resulting from T-cell and antigen stimulation, increase the production of these antibodies against antigens that are exposed on the surface of apoptotic cells.[12]

The antigens causing T-cell and B-cell stimulation in patients with SLE can be attributed to the inappropriate disposal of apoptotic cells. During the process of cellular death, pieces of cellular material form on the surface of the dying cell. Antigens that are normally absent on the surface of the cellular material,

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but instead are embedded within, are now present on the cell surface. Nucleosomes and anionic phospholipids are examples of antigens that have been identified in patients with SLE, and they have the potential to trigger an immune response.[12,13] It is believed that the removal of these apoptotic cells is compromised because of the impaired functioning of phagocytic cells, resulting in suboptimal disposal of dying cells and antigen recognition in patients with SLE.[14]

SLE is thought to develop when a T-lymphocyte to an antigen-presenting cell (APC) is introduced. The T-cell receptor binds to the major histocompatibility complex (MHC) portion of the APC, which may lead to cytokine release, inflammation, and B-cell stimulation.[12] Stimulation of B-cell division and the production of immunoglobulin G (IgG) autoantibodies that can cause tissue damage also occur in SLE.[12,15–19] Unlike the situation in healthy adults, autoantigen-specific T cells and B cells may also interact and produce harmful autoantibodies.[12,20]

Many of the autoantibodies identified in SLE—the antinuclear antibodies (ANAs)—target nuclear components of cells. The detection of ANAs in patients with SLE is essential to the diagnosis. Patients may have positive results for more than one ANA.[19] The ANAs that have been tested most extensively, with involvement confirmed in SLE, are the anti–double-stranded (ds) DNA antibodies.[21] These antibodies, which are linked to SLE-induced kidney and skin disease, are highly specific for SLE and are present in a significant number of patients.[12] ANAs also interact with single-stranded (ss) DNA as well as with RNA. Other examples of ANAs are the anti-Ro and anti-La antibodies that, when detected during pregnancy, have been linked to fetal heart damage as well as the anti-Smith (Sm) antibodies, which are a marker of kidney disease.[22–24]

A second grouping of autoantibodies targets the phospholipid moiety of the prothrombin activator complex as well as cardiolipin. These antiphospholipid antibodies can lead to abnormal clotting as well as loss of pregnancy.[25]

In summary, the presence of hyperactive B cells leading to the production of autoantibodies, in conjunction with the impaired removal of apoptotic cellular material, results in the formation of immune complexes. In the microvasculature, these complexes induce inflammatory reactions, causing the tissue inflammation and damage associated with SLE.

ETIOLOGY

The etiologic mechanism of SLE remains unknown, but multiple associations have been identified as a result of decades of research. Genetic, hormonal, immunological, and environmental factors all play a role in the development of SLE.

Studies focusing on a potential connection between genetics and SLE have shown a genetic predisposition within families. First-degree relatives of patients with SLE are significantly more likely to have the disease compared with the rest of the population. A study focusing on children of mothers with SLE documented that 27% of 195 children tested positive for ANAs.[26] Multiple studies addressing the incidence of SLE in identical and fraternal twins have demonstrated a strong relationship, especially with identical twins. One study revealed concordance rates of 14% to 57% in identical twins sharing the same trait; a second study showed an incidence rate of 24% to 58%.[27–29] In another study of non-identical twins, concordance rates of 3% to 10% were documented.[29]

The investigation of a genetic influence on SLE has led to the discovery of a number of gene variants linked to SLE expression. Typically, a combination of these genetic variants leads to the clinical manifestations of SLE. For example, the complement component C1q eliminates necrotic cellular waste (apoptotic material) in healthy individuals. In patients with SLE, a possible deficiency of the C1q component can lead to disease expression. A second example of genetic variance is a possible deficiency of the C4 complement, a component identified in the elimination of self-reactive B cells. When the overall genetic picture of a patient with SLE is taken into account, the additive effects of these genetic variances significantly increase the risk of SLE progression.[30]

The effect of hormones on the rate of occurrence and the severity of SLE has been of particular interest to researchers. The mechanism by which hormones affect SLE prevalence remains unknown. One hypothesis focuses on the roles of estrogens, progesterone, testosterone, dehydroepiandrosterone (DHEA), and prolactin in immune system responsiveness.

Estrogen has been linked to the stimulation of T and B cells, macrophages, and cytokines.[31,32] Estradiol in mice has an inhibitory effect on apoptosis, allowing the survival of B cells that produce high-affinity anti-DNA antibodies.[33] DHEA, an androgen that is a precursor to testosterone, has immunosuppressive properties. In patients with SLE, DHEA levels may be suboptimal.[34] Progesterone also affects autoantibody production, and elevated prolactin levels have been associated with SLE flares.[35–37]

Immunological involvement in SLE focuses on a patient's loss of "self-tolerance." The process of phagocytosis is compromised in SLE patients, leading to the inappropriate removal of apoptotic cells and immune complexes. The hallmark of SLE is the formation of autoantibodies that go on to form immune complexes (in combination with antigens), leading to inflammation and tissue damage.

Environmental factors include certain viruses and ultraviolet (UV) light. UV light stimulates keratinocytes, leading to B-cell stimulation and antibody production; it may also stimulate T-cell activity, resulting in additional autoantibody production.[13,38,39] Epstein–Barr virus (EBV) has also been linked to the onset of SLE in children. Patients with SLE have higher titers of antibodies to EBV.[40] Smoking, silica, and some hair products (e.g., dyes) may also be possible triggers of lupus.

EPIDEMIOLOGY

The incidence of SLE varies among ethnic groups and by geographic location, sex, and age. The reported prevalence of SLE in the general population is approximately 20 to 150 cases per 100,000 persons.[4–6]

Geography

A report submitted by the National Arthritis Data Working Group estimated that SLA affects 250,000 Americans.[41] The prevalence of SLE in the U.S. demonstrates a distinct elevation among Asian, Afro-American, Afro-Caribbean, and Hispanic-Americans compared with Americans of Eastern European descent.[42,43] For example, the prevalence of SLE among

Caucasian patients in Rochester, Minn., is approximately 40 cases per 100,000 persons, compared with Hispanic patients in Nogales, Arizona, where the rate is 100 cases per 100,000 persons.[44,45]

Black persons in Africa have a much lower incidence of SLE than African-Americans in the U.S.[46] The incidence of SLE in various populations (e.g., urban versus rural areas) is also a topic in need of further investigation. Epidemiologic data utilizing lupus registries point to the need for larger, population-based studies with a large patient base. Such data are currently lacking because of potential obstacles, such as differing case definitions, small-source populations, and varying demographic group targets.[47]

Sex and Age

SLE is more common in women, particularly those of childbearing age. This increased incidence may be attributed to hormones, namely estrogen, as studies have shown women who had an early menarche or who used oral contraceptives or hormonal therapies had an increased risk of SLE.[48,49] The lower risk in men is similar to that in prepubertal or postmenopausal women. Klinefelter's syndrome, which features an extra X chromosome in males, is linked to an elevated incidence of SLE, thereby providing further support for the association between SLE and a possible hormonal pathogenesis.[50]

CLINICAL PRESENTATION

The presentation of SLE can be complex, considering the number of organ systems that can be affected by the disease. Patients experience flare-ups to varying degrees as well as periods of disease remission. Although certain signs and symptoms are common in SLE, every patient presents with a unique set of identifiers. General signs and symptoms observed in SLE include fever, fatigue, and weight loss. The skin, musculoskeletal system, and pulmonary system are primarily affected.[6,7]

SLE patients who report symptoms involving the skin most commonly have a red rash on the nose and cheeks following exposure to the sun. This "butterfly" rash is identified in a significant number of SLE patients at some point during the disease course. Patients experiencing photosensitivity reactions also report skin rashes on other areas of the body that were exposed to the sun. Other symptoms associated with skin manifestations include alopecia, Reynaud's phenomenon, and sores in the mouth or nose. Musculoskeletal involvement includes arthralgias, myalgias, and/or arthritis. Arthritis can affect any minor or major joints, commonly presenting as painful, stiff joints accompanied by either occasional or persistent inflammation.[11,12]

Patients with pulmonary symptoms report painful breathing, coughing, and shortness of breath. Pleural effusion and pulmonary hypertension have also been reported.[51]

SLE also affects the cardiovascular, gastrointestinal, renal, and hematological systems, as well as the central nervous system (CNS). Cardiovascular effects often include pericarditis, myocarditis, endocarditis, and coronary artery disease.[52,53] It has been theorized that certain drugs used to treat SLE (e.g., immunosuppressants and corticosteroids) are risk factors for coronary artery disease in SLE patients along with the traditional risk factors observed in the general population.[52]

Signs of gastrointestinal involvement include nausea, vomiting, and abdominal pain. Hematological changes reported in SLE include anemia as well as leukopenia or thrombocytopenia.[54] The presence of antiphospholipid antibodies in patients with SLE can lead to thrombosis and fetal loss.[55]

SLE patients with CNS manifestations may experience headaches, depression, anxiety, seizures, stroke, or cognitive impairment. Renal involvement in SLE typically results in diminished kidney function, which may result in elevated serum creatinine levels and proteinuria. Patients with renal involvement have a poorer prognosis, with likely progression to end-stage renal disease, which can be life-threatening. Approximately 50% of lupus patients develop nephritis, which is a major cause of morbidity and mortality. Autoantibodies appear to be involved in the formation of immune complexes, which may be deposited in the kidneys, leading to renal infiltration by T cells, macrophages, and other cells.[56,57]

DIAGNOSIS

The diagnosis of SLE is based on observed signs and symptoms, laboratory testing, and diagnostic testing tailored to each patient. The *1997 Update of the 1982 American College of Rheumatology (ACR) Revised Criteria for Classification of Systemic Lupus Erythematosus* is a valuable resource in the assessment of patients when SLE is suspected.[58] If a patient displays four or more of the 11 criteria (either simultaneously or at different time points), the diagnosis of SLE can be made with 95% specificity and 85% sensitivity.[58] However, a study conducted in 2003, which compared ACR criteria with modified weighted criteria, demonstrated a higher sensitivity in favor of the weighted criteria (sensitivity, 90.3% vs. 86.5%; specificity, 60.4% vs. 71.9%).[59]

Considering that almost all patients with SLE are ANA-positive, ANA testing is essential in the diagnosis of SLE.[60] A positive ANA result is sometimes reported in disorders other than SLE (e.g., rheumatoid arthritis), but lower titers are commonly observed with rheumatoid arthritis than with SLE. Anti-dsDNA and anti-Smith (Sm) are two specific autoantibodies that are highly diagnostic for SLE.[61–63]

In addition to autoantibody testing, other commonly performed diagnostic laboratory analyses include a complete blood count (CBC) with differential, a complete metabolic profile, and a urinalysis to determine the creatinine clearance and the presence of proteinuria or active sediment. The testing of complement levels (C3 and C4) as potential markers during SLE flares is also useful and is being studied further.[64]

Diagnostic testing may be individualized to address signs and symptoms affecting each patient. Radiography can be used to assess joint involvement; renal ultrasound, kidney size and impairment; chest radiography, pulmonary involvement; and electrocardiography, chest pain.

Drug-Induced Lupus

Each year, approximately 15,000 to 30,000 cases of lupus are induced by a pharmaceutical product.[3,65,66] Certain medications, when administered to susceptible patients, may initiate or exacerbate SLE or may independently lead to drug-induced lupus (DIL). Procainamide (e.g., Pronestyl, Bristol-Myers

Squibb) and hydralazine (e.g., Apresoline, Novartis), although not frequently used today, have been commonly associated with DIL.[67,68] Penicillamine (e.g., Cuprimine, Merck), minocycline (Minocin Wyeth/Pfizer), isoniazid (formerly Nydrazid, no longer available in the U.S.), methyldopa (e.g., Aldomet, Merck), and anti–tumor necrosis factor (anti-TNF) agents have also been linked to DIL. Unlike that of idiopathic SLE, the incidence of DIL is similar among men and women; the disease primarily affects patients of advanced age.[3,63]

The exact cause of DIL is unknown, but genetics are believed to be involved. Patients who are slow acetylators, particularly those taking procainamide or hydralazine, have a higher risk of developing DIL.[61,69,70]

The presence of autoantibodies is a significant immunological finding in DIL. Antihistone antibodies, the predominant autoantibodies identified in DIL, are present in 95% of patients.[71] Anti–dsDNA antibodies have been identified in patients taking interferon-alpha or anti–TNF-related drugs, and antineutrophil cytoplasmic antibodies have been associated with necrotizing vasculitis in patients with DIL.[72]

Procainamide and hydralazine are the two agents most often implicated in the development of DIL. Most patients test positive for ANAs if they were taking procainamide for more than 2 years,[67] especially true in patients with the slow acetylator phenotype.[68] It is estimated that symptoms develop in up to one-third of patients who take procainamide after 1 year of therapy.[39,73] The risk of DIL from hydralazine becomes a special concern in patients receiving increased doses (more than 200 mg daily), in female patients, in slow acetylators, and in patients with certain genetic mutations.[73–77]

Patients with DIL commonly present with fever, fatigue, myalgia, arthralgia, pericarditis, and pleuritis. A diagnosis of DIL is made if a patient has taken a drug thought to have caused DIL, has no prior history of idiopathic SLE, has a combination of the symptoms listed, and has a positive ANA test result.[69,78,79]

The remedy for DIL is to discontinue taking the offending agent. Nonsteroidal anti-inflammatory drugs (NSAIDs) help to relieve musculoskeletal symptoms. Antimalarials and corticosteroids may be given if the symptoms of DIL are considered to be very serious. Following discontinuation of the suspected drug, patients should experience improvement within days to weeks, although some cases of DIL may take a year or longer for the disease manifestations to resolve completely.[80]

MANAGEMENT

The approach to the treatment of signs and symptoms of lupus depends on the type and the severity of disease. General recommendations for all patients include sun protection, proper diet and nutrition, exercise, smoking cessation, appropriate immunizations, and management of comorbid conditions.

In patients with mild-to-moderate lupus, NSAIDs, antimalarial agents, and corticosteroids are commonly used to treat signs and symptoms. As the disease progresses and clinical manifestations worsen, high-dose corticosteroids and immunosuppressive agents are used to help control disease progression. A list of drugs commonly used to treat SLE is presented in Table 1.[81,82]

NSAIDs

NSAIDs may be used to alleviate musculoskeletal pain, swelling, and aches. These drugs possess pain-reducing, anti-inflammatory, and anticoagulant properties, which are beneficial in treating common lupus-associated manifestations; however, the potential for side effects (see Table 1) must be considered before clinicians prescribe NSAIDs for a patient with lupus.[81,82]

Antimalarial Medications

Some antimalarial agents have proved effective in treating the various signs and symptoms of lupus and preventing subsequent flares. Although the exact mechanism is unclear (see Table 1), antimalarials may interfere with T-cell activation and inhibit cytokine activity. These agents may also inhibit intracellular toll-like receptors, which recognize and bind foreign materials, thereby contributing to activation of the immune system.[83] Hydroxychloroquine (e.g., Plaquenil, Sanofi) is the most commonly studied and used drug in its class, but it has the potential to cause serious visual and muscle disturbances.

Steroids

Corticosteroids mimic naturally occurring hormones excreted by the adrenal gland and help regulate blood pressure and immune function. These agents decrease the swelling and pain associated with inflammation, which can occur in a lupus flare. Because of their serious long-term side effects (see Table 1), corticosteroids should be used at the lowest possible dose and only for periods necessary to control an active exacerbation of lupus.[81,82]

Immunosuppressive Agents

Immunosuppressants are primarily used in more severe cases of lupus when high-dose corticosteroids or antimalarial treatments have failed to control the signs and symptoms of disease. They are also used when it is necessary to induce and maintain remission and to reduce flares or relapses. Immunosuppressants may be given with high-dose corticosteroids to control flares, to achieve a lower dose of each medication, or to reduce the occurrence of adverse events. The most commonly used agents in this class are cyclophosphamide (Cytoxan, Bristol-Myers Squibb) and azathioprine (Azasan, Salix; Imuran, GlaxoSmithKline). Mycophenolate (CellCept, Genentech/Roche) has also been used for lupus-related kidney problems. Side effects of this drug class are listed in Table 1.[81,82]

Monoclonal Antibodies

Belimumab

In March 2011, the FDA approved the first human monoclonal antibody for the treatment of lupus. Belimumab (Benlysta, Human Genome Sciences/GlaxoSmithKline) is the first agent in more than 50 years to be approved for patients with lupus. Belimumab inhibits the activation of B lymphocytes by interfering with a protein necessary for B-cell activity (BLyS). Previously known as LymphoStat-B, belimumab is recommended for patients with active SLE who are receiving standard therapy with NSAIDs, antimalarials, corticosteroids, and/or immunosuppressants. Common adverse effects are presented in Table 1.[84]

Table 1 Commonly Used Medications in the Treatment of Systemic Lupus Erythematosus

Drug Class	Mechanism of Action	Commonly Used Agents and Dosage	Potential Adverse Effects	Common Monitoring Parameters
NSAIDs (including salicylates)	Block prostaglandin synthesis through inhibition of cyclooxygenase enzymes, producing anti-inflammatory, analgesic, and antipyretic effects	Various agents and dosages	Gastrointestinal irritation and bleeding, renal toxicity, hepatic toxicity, hypertension	Nausea, vomiting, abdominal pain, dark/tarry stool; baseline and annual CBC, SCr, LFTs, urinalysis
Antimalarials	Unclear; may interfere with T-cell activation and inhibit cytokine activity; also thought to inhibit intracellular TLRs	Hydroxychloroquine PO 200–400 mg daily	Macular damage, muscle weakness	Funduscopy and visual field examination at baseline and every 6 to 12 months
Corticosteroids	Multiple effects on immune system (e.g., blocking cytokine activation and inhibiting interleukins, γ-interferon and tumor necrosis factor-α)	Prednisone PO 0.5–2 mg/kg per day Methylprednisolone IV 500–1,000 mg daily for 3 to 6 days (acute flare)	Weight gain, hypertension, hyperglycemia, hyperlipidemia, osteoporosis, cataracts, edema, hypokalemia, muscle weakness, growth suppression, increased risk of infection, glaucoma	Baseline blood pressure, bone density, glucose, potassium, lipid panel; glucose every 3 to 6 months; annual lipid panel and bone density
Immunosuppressants	Multiple suppressive effect on immune system (e.g., reduction of T-cell and B-cell proliferation; DNA and RNA disruption)	Cyclophosphamide PO 1–3 mg/kg per day or 0.5–1 g/m^2 IV monthly with or without a corticosteroid Azathioprine PO 1–3 mg/kg per day Mycophenolate PO 1–3 g daily	Myelosuppression, hepatotoxicity, renal dysfunction, infertility, increased risk of infection and cancer	Baseline and routine CBC, platelet count, SCr, LFTs, and urinalysis (depends on individual drug)
Monoclonal antibodies	Block binding of BLyS to receptors on B cells, inhibiting survival of B cells, and reducing B-cell differentiation into immunoglobulin-producing plasma cells	Belimumab IV 10 mg/kg (over a period of 1 hour), every 2 weeks for the first three doses, then every 4 weeks	Nausea, diarrhea, pyrexia, nasopharyngitis, insomnia, extremity pain, depression, migraine, gastroenteritis, infection (e.g., pneumonia, UTI, cellulitis, bronchitis)	Gastrointestinal complaints, infectious signs and symptoms, mood or behavioral changes, infusion reactions

BLyS = B-lymphocyte stimulator protein; CBC = complete blood count; DNA = deoxyribonucleic acid; IV = intravenous; LFTs = liver function tests; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = by mouth; RNA = ribonucleic acid; SCr = serum creatinine; TLRs = toll-like receptors; UTI = urinary tract infection.

Belimumab is also discussed in this month's Drug Forecast column, also by Dr. Hilas and colleagues, on page 212.

Rituximab

As a genetically engineered chimeric monoclonal antibody directed against the CD20 antigen, rituximab (Rituxan, Genentech/Roche) has also shown potential in the treatment of SLE. It is believed that B cells responsible for the production of pathogenic autoantibodies, and other immune-mediated substances associated with lupus, are depleted by rituximab. During the past few years, a number of open-label and retrospective studies have reported promising results with rituximab (when taken with corticosteroids and other immunosuppressants in the management of both pediatric-onset and adult-onset lupus).

Benefits of rituximab have also been noted in patients with lupus nephritis, arthralgia, arthritis, serositis, cutaneous vasculitis, mucositis, rashes, fatigue, and neurological and refractory symptoms. Adverse events were generally mild. Mild-to-moderate infusion reactions were reported most often.[85,86]

A few randomized controlled studies have provided mixed

results regarding the efficacy and role of rituximab in the treatment of SLE. In a study by Terrier et al., clinical responses were reported in 71% of patients who received rituximab, demonstrating a significant benefit in refractory lupus (with or without concomitant immunosuppressive therapy). Cutaneous, articular, renal, and hematological improvements were noted most often, along with an acceptable tolerance profile.[87]

In a systematic review of 188 SLE patients treated with various regimens of rituximab, 91% showed a significant improvement in one or more systemic manifestations, particularly in patients with renal involvement (e.g., lupus nephritis). Adverse events were experienced by 23% of patients, and infections were reported most often.[88] However, two additional randomized, placebo-controlled studies, conducted since 2010, failed to demonstrate significant clinical improvements with rituximab in patients receiving concomitant steroid therapy.[89,90] Despite the favorable tolerability and safety profile of rituximab, further evaluation of this drug is required for patients with SLE.

Additional Treatment Options

Researchers have been particularly interested in the use of stem-cell transplantation to introduce healthy cells into the body in order to help rebuild the immune system. Both DHEA and rituximab have been studied in clinical trials and have provided improvements in patients' quality of life. DHEA is believed to help in the regulation of sex hormones, whereas rituximab decreases the number of B cells and may be most beneficial in patients who do not respond to the other traditionally used immunusuppressants.[85,86]

PREGNANCY

Women with SLE are at increased risk for serious medical and pregnancy complications, such as thrombosis, infection, thrombocytopenia, transfusion, pre-eclampsia, and death.[91,92] Because of the high risk of miscarriage, stillbirths, premature delivery, and exacerbation of SLE, it is recommended that women not become pregnant if they have active disease or significant organ involvement. Oral contraceptives must be given cautiously because high doses of estrogen can cause SLE exacerbations.[92] Pregnancy outcomes are improved if conception is delayed until SLE has been inactive for at least 6 months and if the patient's medications are adjusted in advance.

Baseline and monthly monitoring (e.g., laboratory tests, ultrasonography, fetal surveillance tests, maternal echocardiography, and antibody testing) should be performed for all pregnant lupus patients, because signs and symptoms of lupus flares may be similar to those typical of pregnancy.[92] Neonates should be carefully evaluated for placental transfer of maternal antibodies, which could lead to cutaneous or cardiac complications (e.g., congenital heart block and cardiomyopathy).[93]

If a woman is pregnant and has active SLE, corticosteroids may be prescribed with caution to manage the disease. Most steroids are Pregnancy Category C drugs. NSAIDs (Pregnancy Category C and D) have also been used, but to a lesser extent, and they should be avoided during early pregnancy and the last trimester.

If necessary, hydroxychloroquine may be used, but it is also a Pregnancy Category C drug. Therefore, therapy must be individualized and the drug's benefits and risks must be carefully considered. Immunosuppressive agents are contraindicated in pregnancy, except for azathioprine, a Pregnancy Category C drug.

In women with SLE and antiphospholipid antibodies, prophylaxis with aspirin, low-molecular-weight heparin, or both, is indicated for the prevention of fetal loss.[91,92]

CONCLUSION

Lupus continues to present many unanswered questions. Although no cure has been discovered for this autoimmune disease, many medications are available to help control flares, to maintain remission, and to manage symptoms. Pharmacists and other health care professionals can play a vital role in treatment by educating patients, monitoring their therapeutic regimens, and identifying preventable drug-associated adverse events. Current research is under way, with the hope that improved quality of life and increased survival can be achieved for the many patients affected by SLE each year.

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