

Systemic Lupus Erythematosus and Its Treatment

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Goals and Objectives

Goals:

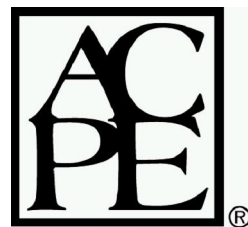
To provide the pharmacist with information regarding Systemic Lupus Erythematosus (SLE) and its treatment.

Objectives:

After reading this article, the pharmacist should be able to do the following:

1. Discuss the epidemiology of SLE.
2. Describe the major symptoms of SLE.
3. List the criteria associated with the diagnosis of SLE.
4. Discuss the drugs implicated as causing a lupus-like syndrome and know the differences between iatrogenic and idiopathic SLE.
5. Describe recommended drug therapy for minor and major SLE disease activity.
6. Counsel patients regarding long-term drug therapy of SLE.

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Universal Program Number 406-000-07-006-H01.
The expiration date for this program is 3/31/10.



Systemic lupus erythematosus (SLE) is a connective tissue disorder which can affect multiple systems, including the skin, joints, lungs, kidneys, heart, bone marrow, nervous system, and serous membranes. In addition, SLE is considered to be a classic autoimmune disease as well as an iatrogenic or drug-induced disease which has been caused or unmasked by more than thirty-five drugs.

Epidemiology of The Disease

Although the exact incidence of SLE is difficult to determine, it may be as high as one in 2,000 or as low as one in 25,000. However, improved diagnostic techniques indicate that the incidence appears to be much greater than one in 25,000.

Approximately 85% of SLE patients are women. Although the disease can occur at any age, most patients are between the ages of 10 and 50, with the greatest clustering between ages 15 and 35. Black and Asian individuals are affected more frequently than members of other races.

Systemic lupus erythematosus is a familial disease. Serologic features of SLE, such as positive antinuclear antibodies, are often detected in asymptomatic family members, and there is a prevalence of other rheumatic diseases among close relatives of patients with SLE. These factors suggest that SLE results from the production of multiple autoantibodies that are a genetically determined abnormality in immunologic regulation and cause tissue damage through a mechanism of immune complex deposition.

Iatrogenic SLE

Systemic lupus erythematosus is a classic iatrogenic disease. As mentioned previously, approximately 35 pharmacologic agents have been implicated as causing a lupus-like syndrome, but only a few of them cause the disorder with significant frequency.

The most common and well-studied drugs implicated in causing SLE are procainamide and hydralazine. As many as 25% of patients who receive procainamide develop some features of the disease. The percentage associated with hydralazine is more varied and somewhat lower. In addition, there appears to be a dose-related phenomenon with the use of hydralazine because in most instances, only daily doses of 150 mg or more are associated with the occurrence of a lupus-like syndrome.

Isoniazid has been implicated in causing SLE, but this is very rare. Representatives from various drug classes, such as anticonvulsants, antihypertensives, tetracyclines, and phenothiazines, have been implicated in causing an SLE-like syndrome.

Several features distinguish drug-induced SLE from the spontaneously occurring disease:

1. The female/male ratio is 3:2
2. The Renal and Central Nervous System (CNS) symptoms revert to normal when the drugs are not ordinarily present.
3. Most of the clinical features and laboratory abnormalities revert to normal when the drug is discontinued.
4. Most of the patients are caucasian and older than the average SLE patient.

Diagnosis Criteria

The diagnosis of SLE should be suspected in patients having a multi-system disease with positive serologic features. Differential diagnosis should exclude diseases that may be present in a similar manner, such as rheumatoid arthritis, scleroderma, chronic active hepatitis, acute drug reactions, polyarthritis, and drug-induced SLE.

Because SLE is a disease with multiple-organ involvement associated with a complexity of symptoms, the American Rheumatism Association has proposed a set of diagnostic criteria (Table 1). The original criteria were proposed in the early 1970s and were based on the "4 of 14" rule, i.e., if a patient has 4 of the 14 criteria, SLE should be suspected. In 1982, these were revised and refined to 11 criteria. The presence of 4 or more of the 11 current criteria, either serially or simultaneously, indicates that the diagnosis of SLE can be made with reasonable probability. These criteria are associated with various body systems (i.e., renal, hematologic, gastrointestinal).

Clinical Features

The clinical presentation of SLE may be variable. The disease may have a sudden onset with high fever and multi-system involvement, or it may be chronic with remissions and exacerbations. It may also be a benign condition with minimal arthralgias, arthritis, and immunologic abnormalities. Most individuals with SLE symptoms seek medical attention because of musculoskeletal or cutaneous manifestations.

The most common musculoskeletal manifestations are polyarthralgias and/or polyarthritis, which occur in 75% of the patients. The small joints of the hands, wrists, and knees are most frequently involved, and the disease is usually symmetrical. In most patients, the arthritis is nondeforming and joint function is usually preserved.

Approximately 80% of SLE patients experience cutaneous reactions. These may be highly specific, such as discoid lupus (discolored areas on the face and scalp

which eventually develop into scales that fall off and leave scars) or nonspecific, such as urticaria or purpura. Another common cutaneous problem is the butterfly rash, a malar rash across the nose and adjacent areas of the cheek in the pattern of a butterfly. This lesion, which occurs in about half the patients, usually leaves no scarring. About 30% of the patients with SLE report a history of photosensitivity, develop oral mucosal ulcerations, and have vasculitic skin lesions on the hands and toes. Alopecia is also an important manifestation and occurs in over half the patients.

Pericarditis is the most common cardiac manifestation of SLE, and occurs in approximately 30% of cases. Other cardiovascular manifestations include myocarditis, endocarditis, coronary artery disease and arrhythmias.

The pleural effusions that occur in approximately 35% of SLE patients are usually small to moderate, and can be bilateral. Pleuritic pain without effusion is also common. Another pulmonary problem associated with SLE is acute pneumonitis. Episodes may be self-limited or patients may develop chronic infiltrates.

The incidence of serious renal disease in SLE is about 50%. However, virtually all SLE patients have some evidence of renal involvement. Nephritis is a prominent feature of SLE and an important cause of morbidity and mortality. Most patients with active renal disease demonstrate evidence of multi-system involvement. Proteinuria and hematuria are very common renal abnormalities. Diffuse proliferative glomerulonephritis is the most serious form of renal problem in SLE. Virtually all glomeruli are affected and the prognosis is variable.

There are many neurological and psychiatric manifestations associated with SLE, and nervous system involvement occurs in 25% to 65% of patients.

Psychiatric problems, which may vary from mild mood changes to overt problems, are very common. They may be attributed to the disease itself, coinciding with periods of activity. Grand mal seizures occur in about 15% of SLE patients and may be severe. Other types of seizures (i.e., petit mal, Jacksonian epilepsy) also occur. There is no characteristic pathological lesion associated with SLE involving the CNS, but CNS involvement correlates with highly active disease and a worse prognosis.

Abdominal pain is a frequent complaint of SLE patients. It may be secondary to drug therapy or associated with other signs of active disease.

Laboratory Assessment

A variety of abnormal laboratory findings are detected in patients with SLE. Although it is present in the serum at some time in greater than two thirds of patients, the LE cell is only relatively specific, because it is also seen in

rheumatoid arthritis, drug-induced SLE, and other collagen disorders. The LE cell is a polymorphonuclear leukocyte that contains different structures within the cytoplasm. Antinuclear antibody, which is less specific, may be detected in about 95% of cases. Its titer often varies with disease activity. Elevated levels of antibodies to double-stranded DNA and depressed serum complement (findings suggestive of disease activity) return toward normal during disease remission. Hypergammaglobulinemia, a positive Coombs test reaction, and rheumatoid factor may be found in the serum. Biologically false-positive serologic tests for syphilis occur in about 20% of patients.

There is often a mild normocytic, normochromic anemia and occasionally autoimmune hemolytic anemia. The sedimentation rate is usually elevated when the disease is active. Leukopenia and lymphopenia are common. In addition, Thrombocytopenia may occasionally be severe, resulting in purpura.

Liver function tests are often mildly abnormal. Abnormal urine sediment is often found in association with renal lesions. Red blood cells and mild proteinuria are frequent during exacerbation of the disease, but usually decrease with remission. The presence of profuse proteinuria indicates serious renal involvement.

Coagulation abnormalities occur, and are usually associated with the presence of an inhibitor of clotting factors or the so-called lupus anticoagulant. In SLE, this inhibitor affects both the intrinsic and extrinsic pathways of coagulation, and may also be present in other conditions. In some patients, this lupus anticoagulant may be associated with a tendency for thrombotic events, and its presence has been correlated with the false-positive serologic test for syphilis.

Although individual laboratory parameters are not specifically indicative of SLE, multiple positive findings supporting the criteria for the disease provide a strong diagnostic tool.

General Treatment

Treatment is considered after diagnosis and assessment of SLE activity. Regardless of the severity of the disease, the following general therapeutic measures are applicable.

Patient and family education associated with the chronic nature of SLE, its remissions and exacerbations, is very valuable. The patient should be reassured that a relatively normal life (i.e., job, marriage) is usually possible. Patients in remission should be counseled to watch for early signs and symptoms of SLE, and be acutely aware of the presence of infections. They must understand that active SLE may necessitate additional and/or different

medications as well as adequate rest. Patients should also be advised to avoid exposure to sunlight, particularly if they have a history of photosensitivity.

Because SLE is primarily a disease of young women, pregnancy will frequently be a major concern. In general, pregnancy should be avoided during exacerbations of SLE. The disease can occur during pregnancy and the risk of spontaneous abortion is increased, but normal births occur most frequently.

Drug Therapy

There is no specific cure for SLE, but conservative drug therapy is used for minor disease activity. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and indomethacin, can abate fever, joint stiffness, and pain. These drugs are thought to produce their effects by decreasing prostaglandin synthesis. In addition, the NSAIDs may also inhibit rheumatoid factor production. Gastrointestinal intolerance, hepatotoxicity, CNS disturbances, and renal impairment are the major adverse effects associated with these drugs.

Topical steroids are most often used to treat rashes encountered with SLE. In some instances hydroxychloroquine, an antimalarial agent, is valuable. It can also provide relief of musculoskeletal complaints, but regular doses of 200 mg daily or less should be used because of the potential for serious retinal changes associated with the use of hydroxychloroquine. If patients are unresponsive to these therapeutic measures or if additional symptoms occur, then such oral corticosteroids as prednisone in a daily dose of less than 20 mg can be added to the therapeutic regimen. Retinoids, such as isotretinoin (dose of 1 mg/Kg/day), have been used successfully to treat cutaneous manifestations.

A normochromic, normocytic anemia is seen in many SLE patients and its severity correlates well with disease activity. Because this is an anemia of a chronic disease, it is usually unresponsive to treatment with vitamins and mineral supplements. The anemia normally improves; however, as the disease process is brought under control.

The objectives in treating major disease activity are to take aggressive action against potentially life-threatening problems, and to restore organ function. A variety of complex problems affecting multiple systems, including the renal, hematologic, cardiovascular, and CNS, can be encountered with SLE.

Many SLE patients have a positive Coombs test, but less than 5% have significant hemolysis. If the patient has a Coombs positive hemolytic anemia, prednisone should be used to bring the hemolysis under control, then tapered

to the lowest dose that will keep the hemolysis suppressed.

Thrombocytopenia is a frequent result of systemic lupus erythematosus, and thrombocytopenia purpura may be the presenting symptom of SLE. Thrombocytopenia usually responds to prednisone.

Severe or refractory cases of pleuritis with large recurrent effusions often require 20 to 40 mg of prednisone daily. Acute lupus pneumonitis may require 60 to 100 mg of prednisone per day. In a few cases, parenteral steroid therapy may be needed to control symptoms. Patients who are slow to respond to steroids can be started on azathioprine in a dose of 2 mg/Kg/day.

The most frequent cardiac complication associated with SLE is pericarditis. Salicylates are used for mild pain in daily doses of 3.6 to 4.8 grams. If the pain is not relieved, then indomethacin or prednisone can be used.

The initial treatment of lupus nephritis is usually based on results of renal biopsy. If a patient is diagnosed as having diffuse proliferative glomerulonephritis, aggressive steroid therapy is required. Prednisone (60 mg/daily) is usually begun immediately, with continuous assessment of renal function to determine if the dose is effective. Once an appropriate prednisone dose is established for the patient, it should be maintained for 4 to 6 months. At this time, if there has not been an adequate response or if the glucocorticoid side effects are intolerable, then azathioprine (2 mg/Kg/day) or cyclophosphamide (2mg/Kg/day) is added. Another approach to treating lupus nephritis is the use of pulse steroids. Intravenous methylprednisolone (1 Gm/day) is administered for 3 days, and the regimen is repeated if the patient does not respond. Oral prednisone (20 to 40 mg/day) is given concurrently. Methotrexate and cyclosporine have also been used in treating lupus nephritis.

Serious CNS manifestations of systemic lupus erythematosus include seizure disorders or psychosis. These problems may be very difficult to control, requiring increasing doses of prednisone (80 to 200 mg/daily) to bring about remission. If it cannot be determined whether the psychosis is related to the SLE or is drug-induced (steroids, indomethacin), a rule of thumb is to increase the steroid dose if other aspects of the disease are active and taper it if the patient is otherwise doing well.

The drugs used to treat these serious problems produced many adverse effects. Steroids may contribute to or cause osteoporosis, cataracts, hypertension, acne, hirsutism, hyperglycemia, and infection. The antimetabolites (such as azathioprine) and alkylating agents (such as cyclophosphamide) may cause nausea, vomiting, rash,

alopecia, bone marrow suppression, and stomatitis. It is important that the therapeutic regimen be continuously evaluated in order to assess risks and benefits encountered.

Disease Course and Prognosis

The prognosis for SLE patients today appears to be considerable better than earlier reports implied. From both community settings and university centers, 10-year survival rates exceeding 90% are being reported. In most patients, the illness pursues a mild chronic course, occasionally interrupted by disease activity. With time, the number and intensity of exacerbations decrease and the probability of major insult to visceral structures declines.

After five years of disease, abnormal laboratory findings tend to revert to normal in many patients. However, there are some patients in whom the disease pursues a virulent course, leading to serious impairment of such vital structures as lungs, heart, brain, or kidneys, and the

disease may lead to death. Although such manifestations are more likely in the early phases of the illness, one must be alert to the possibility of their occurrence at any time.

The most frequent observed serious complication is progressive renal disease followed by CNS involvement. Another important cause of morbidity and mortality is infection, related in part to the use of corticosteroids. With careful management, however, the outlook for most patients with SLE is reasonably good.

Role of The Pharmacist

As with most chronic diseases, the patient is frequently responsible for much of his therapy between visits to the physician. The pharmacist often becomes the health professional most frequently involved in counseling the patient about compliance with the treatment program. Therefore, it is essential that the pharmacist be familiar with the multiple manifestations of SLE, the various therapeutic strategies, and the adverse effects of therapy in order to perform this important role effectively.

**Table 1
American Rheumatism Association Criteria For Diagnosis of SLE**

Malar rash
Discoid lupus erythematosus
Photosensitivity
Oral ulcers
Nonerosive arthritis
Serositis (pleuritis or pericarditis)
Renal Disorder (proteinuria or cellular casts)
Neurological Disorder (seizures or psychosis)
Hematologic dysfunction (i.e., leukopenia, hemolytic anemia, thrombocytopenia)
Immunologic Disorder (anti-DNA or anti-Sm antibodies, LE cells, or false-positive, serologic test for syphilis)
Positive antinuclear antibodies

**Table 2
Major Drugs Used in Treating SLE**

Generic Name	Brand Name Example
Cyclosporine	Sandimmune
Ibuprofen	Motrin
Indomethacin	Indocin
Aspirin	Ecotrin
Prednisone	Deltasone
Hydroxychloroquine	Plaquenil
Cyclophosphamide	Cytoxan
Azathioprine	Imuran
Methylprednisolone	Medrol
Isotretinoin	Accutane
Methotrexate	Rheumatrex