SYSTEMIC LUPUS ERYTHEMATOSUS

Introduction: There is perhaps no rheumatic disease that evokes so much fear and confusion among both patients and health care providers as SLE. Difficult to diagnose, evaluate, and manage, SLE is an illness that may result in a wide variety of complications, ranging from bothersome arthritis, rash, and fatigue to life-threatening involvement of major organ systems such as the kidneys and brain.

SLE affects 1 in 2,000 individuals in Caucasian populations but is more common in other ethnic groups, such as Afro-Americans and Asians. Women are affected 8-10 times more commonly than men, and the onset of symptoms is typically during active child-bearing years, resulting in a substantial impact on quality of life. While survival rates have steadily improved over the past several decades, 5% of patients with SLE die within 5 years of being diagnosed, while nearly 10% die in the first 10 years from time of diagnosis.

While the cause of SLE is unknown, it is believed that a combination of genetic factors and exposure to either infectious triggers or chemical agents is necessary to initiate the disease. While first-degree relatives of SLE patients have an approximate 5% chance of developing the same illness, an identical twin of an SLE patient has a nearly 50% chance.

We consider SLE to be an *autoimmune* disease. This means that the body's immune system, which is ordinarily designed to recognize and destroy everything that is foreign to the body (such as infections) while leaving the various organs of the body alone, inexplicably begins attacking different parts of the body and causing inflammation. This results in the manifestations of SLE in the skin, joints, and potentially just about any location.

Features of SLE: While it is difficult to summarize the vast array of complications seen in SLE, the most common features are arthritis, rash, and general symptoms such as fatigue and intermittent fever. The arthritis is usually involving the small joints of the hands and/or feet or occasionally the knees, ankles, or elbows. While often troublesome, the arthritis of SLE does not typically cause joint destruction such as what we can see in rheumatoid arthritis (RA). The rash is typically triggered by exposure to sunlight and occurs most frequently in sun-exposed areas. Blistering or scarring may

complicate skin lesions of SLE in severe cases. When deep layers of the skin are involved, this may be called a *discoid* rash.

Other manifestations of SLE include inflammation around the lining of the heart and lungs (*pleuritis* and *pericarditis*, respectively), lowering of blood cell counts (white or red blood cells, platelets), mouth ulcers, an increased tendency to form blood clots, inflammation of the kidneys (*nephritis*), and inflammation of the brain (*cerebritis*) causing seizures or changes in mental functioning. Even after reviewing this list of complications, it can be said that any part of the body is "fair game" for SLE. Of all of the manifestations of SLE, nephritis seems to have the biggest impact in overall outcomes and survival, particularly if the kidneys fail to function and dialysis is required.

Another important late complication of SLE is *atherosclerosis* (hardening of the arteries). Just as in RA, patients with SLE have an increased risk of heart attacks and strokes, which seems to be related to the effects of inflammation on the lining of the blood vessels. Specifically, women in their 40's with SLE have approximately *40 to 50* times the risk for heart disease as women of the same age in the general population. For this reason, other risk factors for heart disease, such as smoking, high cholesterol levels, high blood pressure, and diabetes should be addressed and minimized if possible.

Diagnosis: Even in the hands of experienced physicians, the diagnosis of SLE is often very challenging. Most of the common symptoms patients with SLE exhibit may mimic a number of other illnesses. Making the diagnosis is not as simple as performing a blood test; it involves a comprehensive approach to each patient and incorporating symptoms, physical findings, and laboratory abnormalities into the final analysis. For this reason, it may require several visits to either confirm or rule out the diagnosis, but this investment of time is critical to avoid either over-diagnosing or under-diagnosing SLE.

Laboratory findings are helpful in confirming the presence of SLE, but are not sufficient to do so in the absence of typical symptoms or findings on physical examination. The anti-nuclear antibody (ANA) is positive in about 99% of patients with SLE, and depending on the presence or absence of other features, a negative test can rule out SLE. A positive test, however, does not mean that one has "tested positive for lupus." Up to 10% of the general population may express a positive ANA, and by some estimates just over 10% of individuals who show a positive ANA when a physician is suspicious enough to order the test actually have SLE.

Other antibody tests, such as anti-Smith, anti-RNP, anti-Ro/SSA, anti-La/SSB, or anti-dsDNA are more specific, and when present are much more supportive of a diagnosis of SLE. Of these antibodies, anti-dsDNA seems to be the best marker for disease activity, particularly in those patients with nephritis. Proteins of the immune system known as *complement* may be consumed with active inflammation in SLE patients and also can be

good markers for active disease. The findings of anti-cardiolipin antibodies or a "lupus anticoagulant" are often present in those who demonstrate an increased risk for blood clots.

Routine lab studies, such as blood counts, blood chemistries, and urine tests are also useful in diagnosing SLE as well as screening for complications of the disease. Patients with nephritis do not typically experience pain over the kidneys or other specific symptoms other than fever or active disease in other locations, so urine tests are particularly useful in picking up this complication at an early stage.

To assist doctors in making the diagnosis of SLE, criteria have been devised. These criteria are not perfect and do not account for every feature that a given patient may exhibit, but they at least serve as a useful guideline. The criteria include:

1. Mouth or nasal ulcerations, observed by a doctor
2. Rash present over the cheeks (malar or "butterfly" rash)
3. Rash triggered or worsened by sun exposure (photosensitive rash)
4. Discoid rash
5. Arthritis of 2 or more different joints
6. Inflammation of the lining of the heart or lungs (pericarditis or pleuritis)
7. Nephritis
8. Cerebritis
9. Abnormalities of blood cells (low white blood cells, red blood cells, or platelets)
10. Abnormal Anti-Nuclear Antibody (ANA)
11. Other abnormal immunologic tests (Anti-Smith, Anti-dsDNA, Anti-Cardiolipin, Lupus Anticoagulant, or false + syphilis test)

4 of 11 of these criteria are required for a diagnosis of SLE.

Treatment: Because SLE is a disease that can behave very differently in any given patient, therapy must be individualized. The challenge lies in screening for and detecting complications of the disease and prescribing the appropriate medications to adequately suppress SLE activity while minimizing side effects. For serious disease manifestations that may be either damaging to various organs or life-threatening, the potential hazards of aggressive therapy are generally worth the risk. On the other hand, SLE that involves only skin and joints is usually most appropriately treated with safer long-term maintenance therapies (*see Medications section*).

One frustration that physicians and patients alike face is that while many therapies are available for treating SLE, no new drugs have been FDA-approved in > 40 years. If faced with the prospect of using only formally "approved" drugs, we would be left with only aspirin, corticosteroids, and hydroxychloroquine, a scenario none of us would find acceptable.

Antimalarial drugs such as hydroxychloroquine (HCQ, trade name Plaquenil) are the mainstay of therapy for SLE, typically used as the chief therapy for those patients who lack serious organ system involvement but increasingly recommended for most if not all SLE patients due to recent information that suggest a favorable effect on survival. Benefits are typically seen in 1-2 months for clearing of rashes but arthritis symptoms may require 3-6 months of therapy before maximum relief is seen. The effect of anti-malarial therapy on fatigue and other manifestations of SLE are variable. One study showed that patients on HCQ who were previously stable and discontinued their medication experienced worsening of disease activity compared to those who stayed on their medication. Newer data suggests that HCQ may reduce the risk of cardiovascular complications in SLE as well, and this may be where this drug has its positive effect on survival. The only significant side effect of HCQ is a 1 in 1,000 risk of damage to the retina in the area where color vision is located, which is typically minimized when detected early by regular screening through an eye doctor.

Sunscreens, avoidance of ultraviolet (UV) light, and protective clothing are recommended, particularly for those who have active skin manifestations of SLE. Any UV light, even many fluorescent lights, can trigger a disease flare. Therefore, avoidance of concentrated exposure to such light is advisable, and special screens or shields are available to limit UV exposure from fluorescent bulbs at one's place of work. Sunscreens with SPF 15 or above usually provide protection from UV light as well and should be worn every day that significant light exposure is anticipated.

Non-steroidal anti-inflammatory drugs (NSAIDs) may be used to treat joint symptoms or pleuritis/pericarditis but may be best avoided in patients with nephritis due to the potential for these medications to reduce blood flow to the kidneys. Also, NSAIDs increase the risk of ulcer formation, particularly in patients taking corticosteroids (*see below*). In patients at risk for stomach complications, COX-2 selective NSAIDs may minimize this problem.

Aspirin (ASA), while an FDA-approved drug for treating SLE, is now only used by most in low doses to prevent blood clots and cardiovascular disease in SLE patients. *Corticosteroids* such as prednisone are widely utilized to treat many symptoms and complications of SLE. While effective in the majority of patients, steroids must be used wisely to avoid side effects, including weight gain, elevation of blood sugar, cataracts, increased susceptibility to infection, and thinning of the bones leading to increased fracture risk, among others. For this reason, it is important to resist the urge to automatically treat each and every symptom in an SLE patient with steroids. Keeping this in mind, low-dose prednisone ($\leq$ 10 mg/day) may be used to treat joint symptoms, while high doses of steroids (oral or intravenous) are appropriate to rapidly treat serious disease manifestations while awaiting the effects of other medications that are typically started in this setting.

Methotrexate (MTX) may be used in SLE patient with more active arthritis that is resistant to HCQ and other therapies. Just as in patients with RA, MTX is given once weekly with folic acid daily to reduce side effects and generally begins taking effect in 1 to 3 months. While often very effective in treating inflammatory arthritis, MTX must be routinely monitored to screen for side effects, such as infections, lowered blood counts, and elevated liver enzymes.

Immunosuppressive drugs are typically reserved for serious manifestations of SLE, such as nephritis, cerebritis, or other involvement of major organ systems. Examples of such medications include cyclophosphamide (Cytoxan), azathioprine (Imuran), and cyclosporine (Neoral). These medications work by more powerfully suppressing the activity of the white blood cells causing inflammation and damage in SLE patients. Many physicians consider Cytoxan the treatment of choice for life-threatening SLE, particularly nephritis. This medication is often given in high doses intravenously ("pulses") on a monthly basis and has been shown to reduce mortality and kidney failure in serious lupus nephritis.

Novel agents used in the treatment of SLE include DHEA, mycophenolate mofetil (Cellcept), rituximab (Rituxan), belimumab (Benlysta), tocilizumab (Actemra), and abatacept (Orencia). DHEA is a hormone produced by the adrenal gland that may improve fatigue and/or mental functioning in SLE patients. Cellcept is rapidly gaining popularity for the treatment of nephritis, both as a maintenance therapy after initial treatment with Cytoxan, or in selected patients as an alternative to Cytoxan. In fact, some studies have shown Cellcept to be equivalent to Cytoxan in this setting.

Rituxan is an intravenous medication given in 4 once weekly infusions. While used to treat lymphoma and RA and currently not approved for SLE by the FDA, rituximab has shown some promise in treating certain SLE manifestations in recent case series of patients. Controlled studies, however, have shown inconsistent benefit, and it is likely that the role of this drug will be reserved for certain types of patients. Benlysta is a new intravenous medication that has demonstrated promising results in controlled studies and is soon expected to be FDA-approved for the treatment of SLE. This drug inhibits the activation of B-lymphocytes, the body's antibody producing white blood cells.

Actemra, an intravenous medication blocking the effect of a chemical known as interleukin 6, has recently been approved for use in RA but reduced disease activity, particularly arthritis, in a recent series of SLE patients. Orencia is an intravenous medication already approved for the treatment of RA that blocks signals between cells in the immune system and is being studied as an adjunct for treating lupus nephritis. Finally, an antibody against interferon, another substance involved in stimulating the immune system, is in early stages of development and has the potential to be a valuable addition to our therapeutic options. It is anticipated that these medications as well as

other “biologic response modifiers” will become useful options for treating SLE in coming years.

Because SLE patients may be seen by multiple physicians, it is of utmost importance that all doctors are in communication with one another and that decisions to alter therapy be known by all involved. Ideally, clarifying which doctor is responsible for treating different components of the disease prevents confusion. By working with experienced physicians and making decisions between doctor and patient together, SLE management can be tailored for maximum benefit to patients suffering from this complicated and challenging illness.