CHAPTER 15

Systemic Lupus Erythematosus
A. Clinical and Laboratory Features

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- Systemic lupus erythematosus (SLE) is a common autoimmune disorder occurring predominantly in women during reproductive years and having strong minority representation.
- The hallmark of SLE is its diversity of presentation with accumulation of manifestations over time and undulating disease course.
- Essentially any organ system can be affected by SLE with constitutional symptoms, mucocutaneous, musculoskeletal, renal, and central nervous system (CNS) being most common.
- Presence of autoantibodies, the unifying manifestation of SLE, is useful for diagnosis and the pattern of autoantibodies may help to predict clinical manifestations. Anti–double-stranded DNA antibodies are useful, along with changes in complement levels, for predicting disease flares in some patients.
- Special attention during pregnancy may help to avoid disease flares and adverse fetal outcome.
- Many drugs can trigger a lupuslike illness associated with autoantibodies, but typically with fewer disease manifestations and temporal association with the offending agent.

In sharp distinction to organ-specific autoimmune diseases such as thyroiditis, diabetes, or myasthenia gravis, systemic lupus erythematosus (SLE) is a constellation of signs and symptoms classified as one nosologic entity. Indeed, it is the diversity of presentation, accumulation of manifestations over time, and undulating disease course that challenge the most astute of clinicians. With rare exception, the unifying laboratory abnormality is the presence of circulating antinuclear antibodies (ANA). Acknowledging the complexity of this disease, its broad differential diagnosis, and the need to develop better and more specific therapies, the American College of Rheumatology (ACR) has designated 11 diagnostic criteria (presented in Table 15A-1) (1,2). These criteria reflect the major clinical features of the disease (mucocutaneous, articular, serosal, renal, neurologic) and incorporate the associated laboratory findings (hematologic and immunologic). The presence of four or more criteria is required for diagnosis. They need not necessarily present simultaneously: a single criterion such as arthritis or thrombocytopenia may recur over months or years before the diagnosis can be confirmed by the appearance of additional features. While there is incomplete agreement among rheumatologists as to whether these criteria need to be strictly applied in a practice setting, or reserved only for formal academic studies, they do facilitate a methodologic approach to evaluate a patient.

As one reviews the clinical descriptions, it will become apparent that not only is just about every bodily part potentially targeted by lupus, but in each organ different structural components can be involved with varying frequencies, as exemplified in evaluating a large Canadian cohort (Figure 15A-1) (3). In addition, nonspecific constitutional features of SLE, some of which dominate the clinical picture, are fatigue, fever, and weight loss. Demographic characteristics, such as overwhelming female predominance (approximately 9:1), typical onset during the reproductive years, and strong minority representation, are helpful clues to diagnosis. Factors to consider that might precipitate the onset or exacerbation of systemic disease or isolated organ involvement include recent sun exposure, emotional stress, infection, certain drugs, such as sulfonamides, and surgery.

Happily, over 90% of SLE patients survive at least 2 years after diagnosis compared to about 50% three decades ago (4). Recent data support an 80% to 90% survival at 10 years (5). A bimodal mortality curve is prevalent in SLE (6,7). Patients who die within 5 years of diagnosis usually have active disease requiring high

TABLE 15A-1. THE REVISED CRITERIA FOR THE DIAGNOSIS OF SYSTEMIC LUPUS ERYTHEMATOSUS[a]

CRITERION	DEFINITION
1. Malar rash	Fixed erythema, flat or raised, over the malar eminence, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
6. Serositis	(a) Pleuritis; convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion OR (b) Pericarditis; documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	(a) Persistent proteinuria $>$ 500 mg per day or $>$ 3+ if quantitation not performed OR (b) Cellular casts: may be red cell, hemoglobin, granular, tubular or mixed
8. Neurologic disorder	(a) Seizures: in the absence of offending drugs or known metabolic derangement; e.g., uremia, ketoacidosis, or electrolyte imbalance OR (b) Psychosis: in the absence of offending drugs or known metabolic derangement; e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	(a) Hemolytic anemia: with reticulocytosis OR (b) Leukopenia: $<$ 4000/mm^3 total OR (c) Lymphopenia: $<$ 1500/mm^3 on two or more occasions OR (d) Thrombocytopenia: $<$ 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder[b]	(a) Anti-DNA: antibody to native DNA in abnormal titer OR (b) Anti-SM: presence of antibody to SM nuclear antigen OR (c) Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. ANA	Abnormal titer of ANA by immunofluorescence or equivalent assay at any point in time, in the absence of drugs known to be associated with drug-induced lupus syndrome

SOURCE: From Tan EM, Cohen AS, Fries JF, et al. (1), by permission of Arthritis Rheum.

[a]This classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person must have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation (1).

[b]The modifications to criterion number 10 were made in 1997 (2).

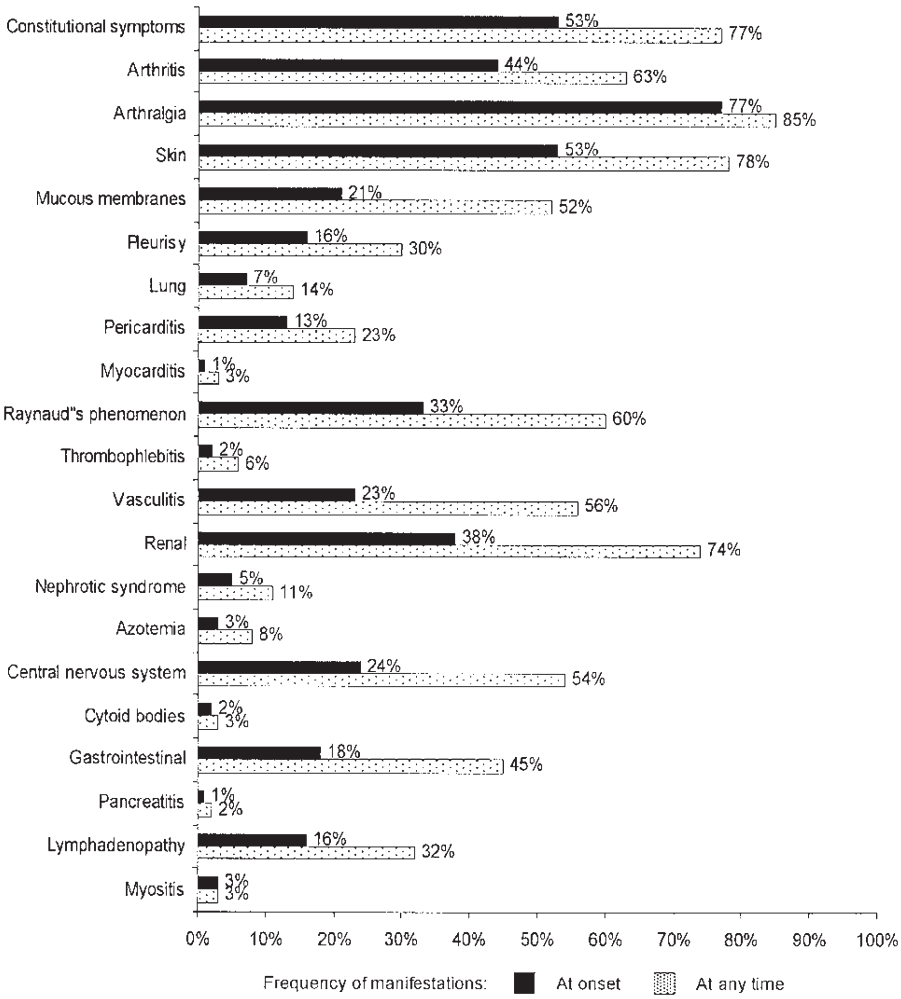


FIGURE 15A-1

Frequency of manifestations at onset and at any time during the course of systemic lupus erythematosus, in a large Canadian cohort (3). The frequency at onset is based on 376 patients diagnosed at Lupus Clinic (University of Toronto), and frequency at point is for 750 patients registered prior to July 1995. Estimates of the frequency of each manifestation differ in some studies; therefore, in the body of the text of this chapter, frequencies are reported that may be at variance with the above cohort. The reader is referred to two major books on systemic lupus erythematosus (50,51).

doses of corticosteroids, intense immunosuppression, and concomitant infections. In contrast, late deaths are often the result of cardiovascular disease. This latter point has received major attention at both the bench and bedside. While SLE is not considered curable, patients can enjoy periods of extended remission with virtually no clinical activity and even the disappearance of antinuclear antibodies.

MORE COMMONLY INVOLVED ORGAN SYSTEMS

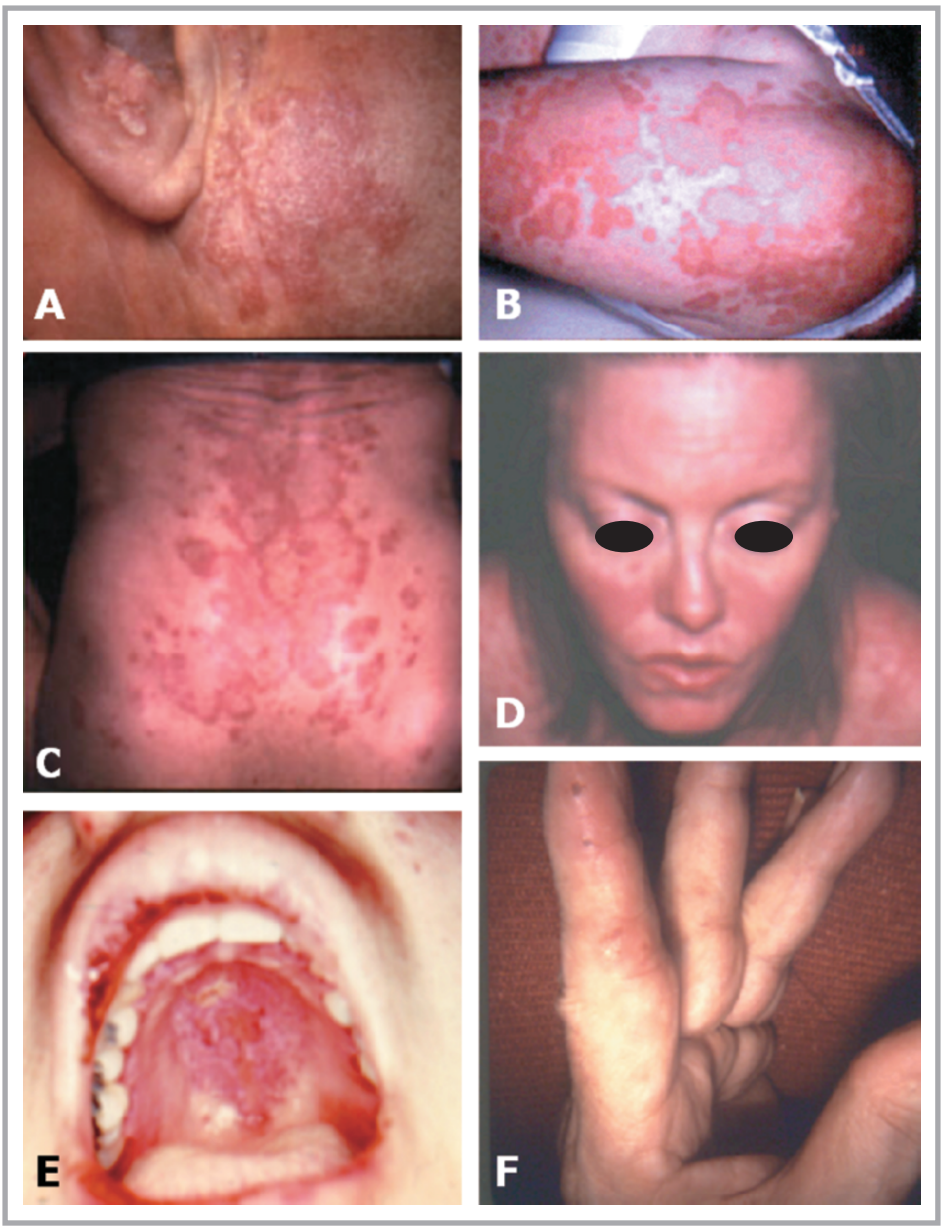
Mucocutaneous

Clearly, the cutaneous system is one of the most commonly affected, approaching 80% to 90%. In parallel with the myriad of signs and symptoms of SLE itself, the skin and mucous membranes can be involved in a variety of ways (8). Notably, 4 of the 11 formal criteria can be fulfilled in this system alone. SLE-specific skin lesions are classified into three types—chronic, subacute, and acute—based strictly on clinical appearance and duration, without considering the extracutaneous manifestations or laboratory features of the overall disease.

The most common form of chronic disease is discoid lupus [DLE; 15%–30%; Figure 15A-2(A)], which can occur as part of the systemic disease or exist in isolation in the absence of any autoantibodies (2%–10% will develop SLE). DLE lesions are discrete plaques, often erythematous, covered by scale that extends into dilated hair follicles. These lesions most typically occur on the face, scalp, in the pinnae, behind the ears, and neck. They can be seen in non–sun-exposed areas. The lesions can progress, with active indurated erythema at the periphery. Central atrophic scarring is very characteristic. Irreversible alopecia can result from follicular destruction. Albeit rare, prominent dermal mucin accumulation in the early course of DLE can result in the succulent, edematous lesions of tumid lupus. Lupus panniculitis-lupus profundus is a less common form of chronic disease. These lesions spare the epidermis and represent involvement of the deep dermis and subcutaneous fat. The lesions of lupus panniculitis are firm

FIGURE 15A-2

Cutaneous manifestations of systemic lupus erythematosus. (A) Discoid lesions are present on the face and in the pinnae. (B, C) Examples of the lesions of subacute cutaneous lupus erythematosus on the back and arm. (D) Classic malar rash. (E) Extensive acute perforating ulcer on the upper palate. (F) Erythematous lesions consistent with cutaneous vasculitis on the digits. (Photographs provided by Dr. Andrew Franks, Associate Professor of Clinical Dermatology, New York University School of Medicine.)



nodules generally without surface changes. In time, the overlying skin becomes attached to the subcutaneous nodular lesions and is drawn inward, resulting in deep depressions.

Subacute cutaneous lupus erythematosus (SCLE) lesions are seen in 7% to 27% of patients [Figure 15A-2(B,C)]. SCLE primarily affects Caucasian females. The lesions are typically symmetric, widespread, superficial, and nonscarring, and are most often present in sun-exposed areas, for example, the shoulders, extensor surfaces of the arms, upper chest, upper back, and neck. The lesions begin as small, erythematous, scaly papules or plaques that can evolve into papulosquamous (psoriasiform) or annular polycyclic forms. The latter often coalesce to produce large confluent areas with central hypopigmentation. Generally, both forms are nonscarring. Antibodies to SSA/Ro ribonucleoproteins are commonly found in patients with SCLE.

Perhaps the most classic of all the rashes in SLE is the malar or butterfly rash, which is categorized among the acute rashes [Figure 15A-2(D)]. It occurs in 30% to 60% of all patients. This erythematous and edematous eruption simulates the shape of a butterfly with its body bridging over the base of the nose and wings spreading out over the malar eminences. At times the same rash can be seen on the forehead and chin but classically spares the nasolabial folds. The absence of discrete papules and pustules distinguishes it from acne rosacea. The rash is abrupt in onset and can last for days. Postinflammatory changes are common, particularly in patients

with pigmented skin. The butterfly rash is often initiated and/or exacerbated by exposure to sunlight. However, patients can have a photosensitive erythematous rash elsewhere on the body in the absence of a butterfly rash. The criteria for photosensitivity and butterfly rash are thus independent of each other albeit coexistent in the majority of patients. The Systemic Lupus Erythematosus International Cooperating Clinics (SLICC), a group of internationally recognized experts in SLE, are working on a revision of the ACR classification criteria, and the assignment of photosensitivity based on history alone may likely prove to be an insensitive parameter. A more widespread, morbilliform or exanthemous eruption is another acute cutaneous manifestation of SLE.

Alopecia associated with SLE may be diffuse or patchy, reversible or permanently scarring as a result of discoid lesions in the scalp. The breakage of hairs at the temples—so-called lupus frizz—can be observed.

Mucosal lesions are also part of the clinical spectrum of SLE and can affect the mouth (most commonly), nose, and anogenital area. While oral lesions can be seen on the buccal mucosa and tongue, sores on the upper palate are particularly characteristic [Figure 15A-2(E)]. They are typically described as painless but need not be. Central depression often occurs and painful ulcerations develop.

Vasculitis is another component of skin disease in SLE. It may be manifest as urticaria, palpable purpura, nailfold or digital ulcerations, erythematous papules of the pulps of the fingers and palms, or splinter hemorrhages [Figure 15A-2(F)].

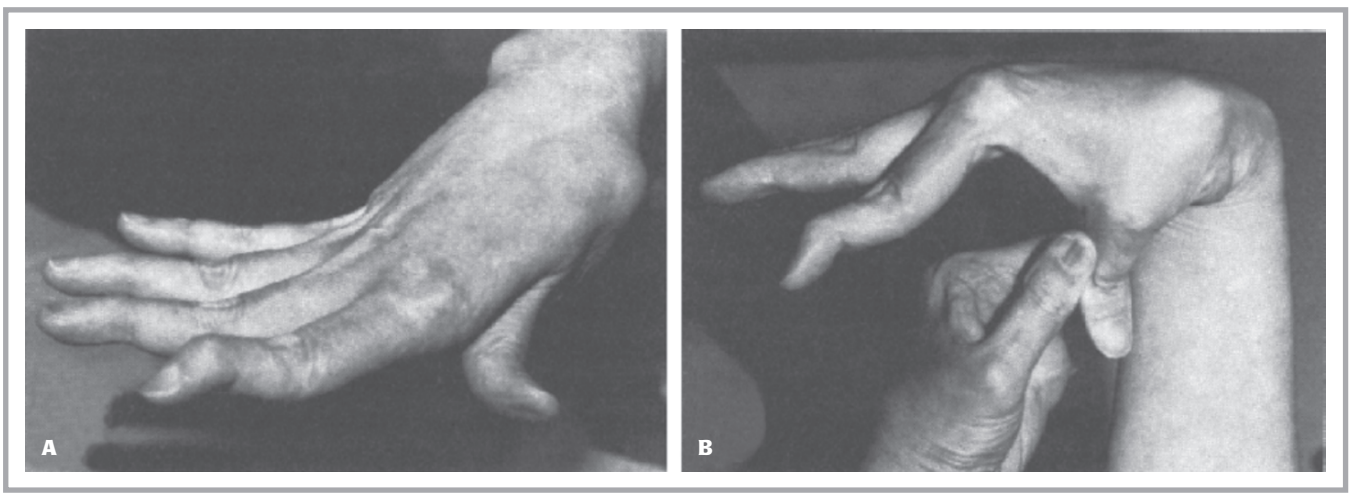
Because the skin can be an important marker of disease activity in SLE, the physical examination should always include inspection of often overlooked areas, the scalp, pinnae, behind the ears, palate, fingertips, and palms.

MUSCULOSKELETAL SYSTEM

Painful joints are the most common presenting symptom of SLE, with frequencies reported between 76% to 100%. In some cases the pain is more characteristic of arthralgia because it is unaccompanied by the traditional signs of inflammation. In others the classical signs of a true arthritis, such as swelling, erythema, heat, and decreased range of motion, are present. Notably, the patient's complaint of pain may be out of proportion to the degree of synovitis present on physical examination. Although arthritis can affect any joint, it is most often symmetrical with involvement of the small joints of the hands (proximal interphalangeal and metacarpal phalangeal), wrists and knees, but sparing the spine. The arthritis can be evanescent, resolving within 24 hours, or more persistent. Many of these features account for the initial diagnostic consideration of early rheumatoid arthritis (RA) in some patients. In contrast to RA, the arthritis in SLE is nonerosive and generally nondeforming. In those patients that do appear to have deforming features, such as ulnar deviation, hyperflexion, and hyperextension, the deformities are generally reducible (Figure 15A-3). These hypermobile digits with reducible deformities are secondary to involvement of paraarticular tissues, such as the joint capsule, ligaments, and tendons, and are referred to as Jaccoud-like arthropathy. Exceptions are certainly possible and, when present, erosions may be clinically difficult to distinguish from RA; however, they are usually nonprogressive and

FIGURE 15A-3

(A) Swan neck deformity of the second and third digits. (B) Hyperextension of the first interphalangeal joint. (Courtesy of Dr. Harry Fischer, Beth Israel Medical Center, New York, NY.)



likely result from capsular pressure and an altered mechanical situation caused by subluxation.

Effusions tend to be modest. The synovial fluid is clear to slightly cloudy with good viscosity and mucin clot, reflecting the absence of major inflammation. Antinuclear antibodies can be present. White blood cell counts are usually <2000/mm^3 with a predominance of mononuclear cells. The fluid can be transudative or exudative. The serum/synovial fluid ratios of complement, total protein, and IgG can all be 1, indicating a proportional escape of proteins into the joint space, or >1 for complement levels only, indicating local consumption, not simply a reflection of decreased serum complement. Larger effusions with warmth should prompt the consideration of septic arthritis. Rheumatoid nodules can occur in SLE accompanied by the presence of rheumatoid factor, but this is not common.

Rheumatic complaints localized to the hips should raise serious consideration of osteonecrosis, the frequency of which has been reported to be 5% to 10%. Although the femoral head is the most common site of involvement, other sites include the femoral condyles, talus, humeral head, and, occasionally, the metatarsal heads, radial head, carpal bones, and metacarpal bones. Bilaterality is frequent but not necessarily simultaneous. Most cases are associated with the use of corticosteroids, but causality has also been attributed to Raynaud's, small vessel vasculitis, fat emboli, or the presence of antiphospholipid antibodies. Typically, patients with osteonecrosis complain of persistent painful motion localized to a single joint, and symptoms are relieved by rest.

Generalized myalgia and muscle weakness, frequently involving the deltoids and quadriceps, can be accompanying features of disease flares. Overt myositis with elevations of CPK occurs in <15% of patients. Electromyogram (EMG) and muscle biopsy findings range from normal to those seen in dermato/polymyositis. Exceptionally high levels of creatine kinase (CPK) are rare. Patients with SLE can develop myopathy as a consequence of glucocorticoids or antimalarials.

Renal

The kidney is considered by many to be the signature organ affected by SLE. Essentially all studies of prognosis have identified lupus nephritis as an important predictor of poor outcome. Renal disease is present in one half to two thirds of patients and, with rare exception, is diagnosed based on the presence of proteinuria (dipstick 2+, >500 mg/24 hour). There is a spectrum of renal injury that can be assessed, in part on clinical grounds, and more definitively by biopsy (9). Initial categories of lupus nephritis were based on classification by the World Health Organization as assessed by histology and location of immune complexes (Table 15A-2) (10). Recently, this classification has been revised by the International Society of Nephrology and Renal Pathology Society (ISN/RPS; Table 15A-3) (11). The important difference is that this new classification is an attempt to stratify proliferative lesions—focal and diffuse (class III and IV, respectively)—as active versus chronic scarring, with the concept that the former is treatable. Furthermore, diffuse proliferative nephritis

TABLE 15A-2. WORLD HEALTH ORGANIZATION CLASSIFICATION OF LUPUS NEPHRITIS

			CLINICAL CLUES[a]					
CLASS	PATTERN	SITE OF IMMUNE COMPLEX DEPOSITION	Sediment	Proteinuria (24 h)	Serum creatinine	Blood pressure	Anti-dsdna	C3/C4
I	Normal	None	Bland	<200 mg	Normal	Normal	Absent	Normal
II	Mesangial	Mesangial only	RBC or bland	200–500 mg	Normal	Normal	Absent	Normal
III	Focal and segmental proliferative	Mesangial, subendothelial, ± subepithelial	RBC, WBC	500–3500 mg	Normal to mild elevation	Normal to elevated	Positive	Decreased
IV	Diffuse proliferative	Mesangial, subendothelial, ± subepithelial	RBC, WBC, RBC casts	1000–>3500 mg	Normal to dialysis-dependent	High	Positive to high titer	Decreased
V	Membranous	Mesangial, subepithelial	Bland	>3000 mg	Normal to mild elevation	Normal	Absent to modest titer	Normal

SOURCE: From Appel GB, Silva FG, Pirani CL (10), by permission of *Medicine*.
ABBREVIATIONS: RBC, red blood cells; WBC, white blood cells.
[a]These are only guidelines, and parameters may vary, substantiating the need for biopsy when precise diagnosis is required.

TABLE 15A-3. INTERNATIONAL SOCIETY OF NEPHROLOGY/RENAL PATHOLOGY SOCIETY (ISN/RPS) CLASSIFICATION OF LUPUS NEPHRITIS.

Class I	Minimal mesangial lupus nephritis	
Class II	Mesangial proliferative lupus nephritis	
Class III	Focal lupus nephritis	
	III (A):	Active lesions: focal proliferative lupus nephritis
	III (A/C):	Active and chronic lesions
	III (C):	Chronic inactive lesions with scars
Class IV	Diffuse lupus nephritis	
	IV-S (A):	Active lesions: diffuse segmental proliferative lupus nephritis
	IV-G (A):	Active lesions: diffuse global proliferative lupus nephritis
	IV-S (A/C):	Active and chronic lesions
	IV-G (A/C):	Active and chronic lesions
	IV-S (C):	Chronic inactive lesions with scars
	IV-G (C):	Chronic inactive lesions with scars
Class V	Membranous lupus nephritis[a]	
Class VI	Advanced sclerotic lupus nephritis	

SOURCE: Adapted from Weening JJ, D'Agati VD, Schwartz MM, et al. (11), by permission of *J Am Soc Nephrol*.
[a]Class V may occur in combination with class II or IV, in which case both will be diagnosed.

was divided into those cases with predominantly segmental lesions and those with predominantly global lesions. To date it is not clear whether this histologic division will have clinical and prognostic impact. Class V/membranous is now purely membranous, and if there is evidence of a proliferative lesion, both classes are specified, for example, V + III or V + IV.

Renal biopsy is abnormal in most patients, especially when tissue is evaluated by electron microscopy and immunofluorescence. Diffuse proliferative nephritis and progressive forms of focal proliferative nephritis are associated with a poorer prognosis than membranous or mesangial disease.

Clinical evaluation initially includes urine dipstick and microscopic analysis. A baseline 24-hour urine for measurement of protein and creatinine, even in the presence of 1+ dipstick, is common practice, especially in a patient with antibodies to double-stranded DNA (dsDNA) and low complement levels. Given the inconvenience of obtaining a 24-hour urine collection, many physicians utilize the spot protein/creatinine ratio to gauge the extent of proteinuria. The sediment can be bland (consistent with mesangial or membranous) or active containing red blood cell casts (consistent with proliferative lesions). Persistent hematuria with >5 red blood cells per high power field (in the absence of other causes such as menstruation) and/or pyuria with >5 white blood cells per high power field (excluding infection) would each be an unusual reflection of lupus nephritis in the absence of proteinuria (unless pathology is limited to the mesangium in the case of red blood cells and interstitium in case of white blood cells). An elevated creatinine without concomitant proteinuria is unexpected unless advanced renal insufficiency is present. While renal disease is frequently insidious, symptoms which occur with progressive activity include swollen ankles, puffy eyes upon waking in the morning, and frequent urination. A low serum albumin is an indicator of persistent proteinuria. Isolated hypertension outside of the norms for age, race, and gender should raise suspicion of underlying renal disease.

Biopsies are not required to diagnose lupus nephritis but are extremely helpful in certain settings because clinical parameters are not absolute. Given the importance of identifying pathologic features suggestive of more aggressive disease, such as crescents, some clinicians believe kidney biopsy to be the fulcrum for therapeutic decisions. Thus, treatment with alkylating agents, such as cyclophosphamide, which can result in premature ovarian failure, becomes readily justified in circumstances where the clinical picture may have suggested a more favorable histology. For example, there are patients who have rapidly rising titers of anti-dsDNA and falling complements but only modest proteinuria (400 mg–1 g), bland sediment, normal creatinine, and no other systemic manifestations to warrant intense immunosuppression. Other patients may have nephrotic-range proteinuria and an active sediment yet serologic parameters are normal. Renal biopsies in these somewhat ambiguous situations can be quite informative. In contrast, the decision to withhold aggressive therapy is also important and may be appropriate for irreversible late-stage sclerotic disease. Renal biopsies should be performed when the result will make a clear difference in the approach and/or is required as part of a research study. Renal ultrasound is another helpful guide to therapy because the chances of successful treatment become smaller with decreased size and increased echogenicity of the kidneys.

Urine protein is a critical measurement of ongoing renal lupus activity. While new proteinuria of 500 mg is significant, patients with membranous nephropathy, in particular, can have continued proteinuria between 500 mg and 2 g and still be considered stable. In such cases, an exacerbation is best defined as at least a doubling of baseline proteinuria. It is essential to monitor blood pressure because hypertension can be a reflection of renal disease activity and, as such, accelerates functional impairment.

Renal transplantation in lupus has been successful. However, lupus nephritis can recur (~10%), even in the absence of clinical or serologic evidence of active SLE (12) but is not always associated with allograft loss. Clinical and serological activity in SLE may improve in

patients who have end-stage renal disease (13), although this paradigm has recently been challenged (14).

Nervous System

Approximately two thirds of patients with SLE have neuropsychiatric manifestations. The pathophysiology of this broad clinical category is not well understood, which probably reflects the inaccessibility of the tissue involved. Proposed mechanisms include vascular occlusion due to vasculopathy, leukoaggregation or thrombosis, and antibody-mediated neuronal cell injury or dysfunction (15). Neuropsychiatric systemic lupus includes neurologic syndromes of the central, peripheral, and autonomic nervous systems, and psychiatric disorders in which other causes have been excluded. These manifestations may occur as single or multiple events in the same person. Symptoms can be present concomitantly with activity in other systems, or exist in isolation. While the formal ACR criteria for neuropsychiatric lupus include only seizures and psychosis, it has become increasingly clear that further descriptors might be important in diagnosis. In an effort to expand the criteria, an ACR Ad Hoc Committee has developed reporting standards, recommendations for laboratory and imaging evaluation, and case definitions for 19 neuropsychiatric syndromes observed in SLE (16).

A variety of psychiatric disorders are reported and include mood disorders, anxiety, and psychosis. Unequivocal attribution to lupus is difficult because such disorders may be related to the stress of having a major chronic illness, or be due to drugs, infections, or metabolic disorders. Patients can demonstrate significant cognitive defects, such as attention deficit, poor concentration, impaired memory, and difficulty in word finding. These abnormalities are best documented by neuropsychological testing and a decline from a higher former level of functioning. Another syndrome of diffuse neurologic dysfunction is termed *acute confusional state* and defined as disturbance of consciousness or level of arousal with reduced ability to focus, maintain, or shift attention, accompanied by cognitive disturbance and/or changes in mood, behavior, or affect. The syndrome often develops over a brief time frame, fluctuates over the day, and covers a wide spectrum ranging from mild alterations of consciousness to coma.

Inclusive in the neurologic manifestations of the central nervous system are seizures, which may be focal or generalized. Headache is a common complaint in patients but there is still debate as to whether this is a unique feature attributable to SLE. The lupus headache has been operationally defined as severe, disabling, persistent, and not responsive to narcotic analgesics. However, severe migraine in the absence of lupus may have these same characteristics. Benign intracranial hypertension is also included in the case definition of headache. The term *lupoid sclerosis* has been used to describe a rare condition in which patients exhibit complex neurologic deficits similar to those observed in multiple sclerosis. Myelopathy and aseptic meningitis are rare. Chorea, albeit infrequent, is the most common movement disorder observed in SLE. This and cerebrovascular accidents have been related to the presence of antiphospholipid antibodies.

Disturbances of the cranial nerves can result in visual defects, blindness, papilledema, nystagmus or ptosis, tinnitus and vertigo, and facial palsy. Peripheral neuropathy may be motor, sensory, mixed motor–sensory, or mononeuritis multiplex. Transverse myelitis presenting with lower extremity paralysis, sensory deficits, and loss of sphincter control has been observed in a limited number of patients. An acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barre syndrome) has been described.

Examination of the cerebrospinal fluid is useful to rule out infection. However, with regard to neuropsychiatric lupus, often the findings are nonspecific with elevated cell counts, protein levels, or both, found in only about one third of patients. The fluid may be completely normal in the face of acute disease. Computerized tomography is sufficient for the initial diagnosis of most mass lesions and intracranial hemorrhages. The findings of magnetic resonance imaging (MRI) reflect the histopathologic findings of vascular injury and may involve the white or gray matter (17). Abnormalities on MRI are more likely with focal findings. Unfortunately, the correlation between MRI findings and clinical presentation is low.

Cardiovascular System

A variety of cardiac complications are seen in SLE but certainly the most common is pericarditis, occurring in 6% to 45%. The clinical picture is usually typical with the patient complaining of substernal or pericardial pain, aggravated by motion such as inspiration, coughing, swallowing, twisting, and bending forward. Symptoms may either be severe and last for weeks, or mild and last for hours. A pericardial rub may or may not be present and can be heard in an asymptomatic patient. Although the electrocardiogram may show the typical T-wave abnormalities, echocardiography is the best diagnostic test. Most effusions are small to moderate. The pericardial fluid is straw-colored to serosanguinous, exudative, and can have a high white blood cell count with a predominance of neutrophils. LE cells can be seen in the centrifuged cell sediment. Cardiac tamponade is rare as is constrictive pericarditis. Importantly, when a young woman presents with shortness of breath and pleuritic chest pain, the differential diagnosis must include SLE, and the patient should be tested for ANA.

Primary myocardial involvement in SLE is uncommon, <10%. The patient may have fever, dyspnea, palpitations, heart murmurs, sinus tachycardia, ventricular arrhythmias, conduction abnormalities, or congestive heart failure. Percutaneous endomyocardial biopsy may be helpful. It is now well recognized that hemodynamically and clinically significant valvular disease occurs and may require prosthetic valve replacement. Aortic insufficiency represents the most commonly reported lesion and may be the result of multiple factors, including fibrinoid degeneration, distortion of the valve by fibrosis, valvulitis, bacterial endocarditis, aortitis, and Libman–Sacks endocarditis. Libman–Sacks atypical verrucous endocarditis, the classic cardiac lesion of SLE, is comprised of verrucous vegetations ranging from 1 to 4 mm in diameter, initially reported to be present on the tricuspid and mitral valves. Interestingly, it has been noted that neither the usual clinical and immunologic markers of lupus activity, nor its treatment, are temporally related to the presence of or changes in valvular disease (18). Prophylactic antibiotics for surgical and dental procedures have been recommended for all SLE patients.

Accelerated atherosclerosis has received considerable attention and is an important cause of morbidity and mortality in SLE. It has been established that the proportionate mortality from myocardial infarction is approximately 10 times greater in patients with SLE than in the general age- and sex-matched population (6,7,19). Autopsy studies support the clinical data, as severe coronary artery atherosclerosis is present in up to 40% of patients with SLE, compared with 2% of control subjects, matched for age at the time of death (20). Studies have identified hypercholesterolemia, hypertension, and lupus itself as risk factors in these patients (21). Glucocorticoid therapy contributes to the elevation of plasma lipids, while antimalarials may result in a reduction of plasma cholesterol, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). Coronary arteritis is rare and may coexist with atherosclerotic heart disease. Studies of clinical outcomes for atherosclerotic disease, including angina and myocardial infarction, have shown a prevalence of 6% to 12% in a number of SLE cohorts (6,7,21). More sensitive investigations, including carotid plaque and intima-media thickness (IMT) measured by B-mode ultrasound, revealed that 40% of 175 women with SLE had focal plaque (22).

Two recent articles further link SLE and premature atherosclerosis. Roman and colleagues (23) performed carotid ultrasonography, echocardiography, and assessment for risk factors for coronary artery disease (CAD) in a cross-sectional study of 197 patients with SLE and 197 controls. Atherosclerosis occurred prematurely in patients with SLE and was independent of traditional risk factors for cardiovascular disease. Among patients with SLE, plaque was independently associated with age, longer disease duration, higher damage index, and less frequent use of cyclophosphamide and antimalarial drugs, as well as a lower prevalence of anti-Sm antibody. Asanuma and colleagues (24) used electron beam computer tomography (EBCT) to evaluate 65 patients with SLE and 69 controls. Patients with SLE had higher coronary calcium scores, independent of other atherosclerotic risk factors. Furthermore, on analysis within age strata, patients with SLE were found to have coronary artery calcification at younger ages than controls.

Pleura and Lungs

The lungs and contiguous structures involved in normal respiration are commonly affected in SLE, but are generally not as life threatening as the renal and central nervous system complications. Over 30% of patients have some form of pleural disease in their lifetime, either as pleuritis with chest pain or frank effusion. Pleurisy is a more common feature of serositis than pericarditis. The pain of pleuritis can be quite severe and must be distinguished from pulmonary embolus or infection. Pleural rubs are less common than either clinical pleurisy or radiographic abnormalities. Pleural effusions are most often small and bilateral. The fluid is usually clear, exudative with increased protein, normal glucose, white blood cell count <10,000, a predominance of neutrophils or lymphocytes, and decreased levels of complement.

Pulmonary involvement includes pneumonitis, pulmonary hemorrhage, pulmonary embolism, pulmonary hypertension, and shrinking lung syndrome. The term *acute lupus pneumonitis* has been applied to individuals with an abrupt febrile pneumonitic process in whom infection has been ruled out. Prominent features are pleuritic chest pain, cough with hemoptysis, and dyspnea. Diffuse alveolar hemorrhage is considered a manifestation of acute lupus pneumonitis and associated with a 50% mortality rate. It can occur in the absence of hemoptysis and is suggested by a falling hematocrit and pulmonary infiltrates. Rare patients (<10%) develop a more chronic syndrome characterized by progressive dyspnea, nonproductive cough, basilar rales, and diffuse interstitial lung infiltrates.

Pulmonary hypertension should be suspected in patients complaining of progressive shortness of breath and in whom the chest radiograph is negative and profound hypoxemia is absent. Pulmonary function studies show a restrictive pattern with a reduction in the diffusing capacity for carbon monoxide. Doppler ultrasound studies and cardiac catheterization confirm the diagnosis. Frequently, these patients also have Raynaud's phenomenon. Intrapulmonary clotting and/or multiple pulmonary emboli must be addressed, especially in the setting of antiphospholipid antibodies. Recent studies

suggest that pulmonary hypertension is gradually progressive over time and related to an increase in pulmonary resistance (25).

LESS COMMONLY INVOLVED ORGAN SYSTEMS

Gastrointestinal Tract and Liver

Involvement of the gastrointestinal tract can, as in other organ systems, be quite varied, but for most patients is not the source of any diagnostic criteria. The peritoneum is the least likely of the serosal linings to be affected in SLE. Symptoms include rebound tenderness, fever, nausea, vomiting, and diarrhea. Unfortunately, confusion with serious abdominal pathology or infection can prompt surgical intervention. Abdominal pain in SLE can also be caused by pancreatitis and bowel vasculitis. Rectal bleeding can be present in mesenteric vasculitis. Protein-losing enteropathy is quite uncommon but should be considered in the face of low serum albumin, pedal edema, and the absence of proteinuria.

Parenchymal liver disease as a result of SLE is rare. However, elevated transaminases can be encountered during periods of active disease and/or following the use of many medications prescribed to treat lupus, such as nonsteriodal anit-inflammatory drugs (NSAIDs), azathioprine, and methotrexate. In the absence of known offending drugs, persistent signs of hepatitis may require a liver biopsy. The term *lupoid hepatitis* was coined by Bearn in 1956 and initially believed to be a manifestation of SLE. However, an individual need not have lupus; it is defined serologically and histologically and is a subset of chronic, active hepatitis. It is seen in less than 10% of patients who fulfill the ACR criteria for SLE.

Ocular System

With regard to the eye itself, "cotton wool spots" in the retina are generally cited as being the most common lesion, followed in frequency by corneal and conjunctival involvement, with only rare patients exhibiting uveitis or scleritis. Although also quite uncommon, retinal damage from antimalarials used in treating SLE is probably a greater cause of visual loss than is retinal involvement occurring in the natural course of the disease. Cotton wool spots (an ophthalmologic term) are not pathognomonic for lupus and result from focal ischemia. They occur preferentially in the posterior part of the retina and often involve the optic nerve head. Each spot appears as a grayish-white soft, fluffy exudate, averaging about one third of a disc diameter in width. Cytoid bodies refer to the histologic features of the cotton wool spot.

LABORATORY FEATURES

Hematologic Abnormalities

Each of the cellular elements of the blood can be affected in SLE. Accordingly, the complete blood count is a critical part of the initial and continued evaluation of all lupus patients. In the absence of offending medications, the "penias" are generally secondary to peripheral destruction, and not marrow suppression.

Autoimmune hemolytic anemia is present in <10% of patients. A Coombs test can be positive (both direct and indirect) without active hemolysis. A nonspecific anemia reflecting chronic disease is present in up to 80% of patients. Leukopenia is seen in over 50% of patients. Absolute lymphopenia is more common than neutropenia. Unfortunately, the criterion for lymphopenia (<1500/mm^3) is not very stringent and in most laboratories is not highlighted as abnormal. While leukopenia does represent some degree of disease activity and has been described as a signal of more systemic activity, there are clearly patients whose low white blood cell counts do not associate with disease flares in other organs and do not predispose them to infection. Thrombocytopenia can be modest (platelet counts of 50,000–100,000/mm^3), chronic and totally asymptomatic, or profound (<20,000/mm^3) and acute, with gum bleeding and petechiae. In some cases, thrombocytopenia is the sole manifestation of disease activity at a given point in time. Moreover thrombocytopenia can be the initial presentation of SLE, antedating the development of other symptoms or signs by years. Any young woman presenting with "idiopathic" thrombocytopenia should be evaluated for SLE. Fortunately, there are rarely qualitative defects in the platelets and therefore life-threatening bleeding is unusual. Analogous to the other cell lines, antiplatelet antibodies may be present without thrombocytopenia.

The erythrocyte sedimentation rate is frequently elevated in SLE and is generally not considered a reliable marker of clinical activity. A rise in the C-reactive protein may be an indicator of infection, but this has not proven to be absolute.

Hallmark Autoantibodies and Complement

Measurement of the so-called *serologic parameters* is an integral part of the baseline evaluation and follow-up of patients with SLE. The term simply refers to those tests performed using the serum component of whole blood, although testing for antibodies, but not functional assays

of complement, can be obtained using plasma. For example, testing the ability of serum complement to lyse sheep red blood cells in the CH50 test (see below) cannot be done using plasma, because it is generally accepted that complement activation does not proceed in EDTA- and citrate-plasma because of calcium chelation by EDTA and citrate.

The presence of a positive ANA is clearly one of the most important abnormalities to identify at presentation because it establishes that the differential diagnosis includes autoimmunity. However, a positive ANA, particularly in young women, can be detected in about 2% of normals. This test should be considered a valuable guide but by no means diagnostic. Once documented, the continued measurement of the ANA is not useful as a gauge of disease activity. In contrast, the presence of antibodies to dsDNA [not single-stranded DNA (ssDNA)] is not only of major diagnostic significance but in select patients, particularly those with renal involvement (see below), a valuable means of predicting and assessing disease activity. Anti-Sm antibodies, which recognize determinants on proteins associated with small ribonucleoproteins involved in processing of messenger RNA, are of diagnostic importance but do not track disease. Antibodies reactive with SSA/Ro and SSB/La ribonucleoproteins, the latter involved in transcription termination, also do not correlate with activity, but are often seen in patients who may have one or more of the following: photosensitivity, dry eyes and dry mouth (secondary Sjögren's syndrome), subacute cutaneous lesions, risk of a child with neonatal lupus. Anti-SSA/Ro antibodies, depending on the methodology used for screening, can stain the cytoplasmic component of the cell and therefore account for some ANA-negative lupus. While ANA-negative lupus is considered, it is difficult to conceptualize a situation whereby an individual is said to have SLE, a prototypic autoimmune disease, yet has no detectable autoantibodies. The frequency of various autoantibodies and their clinical relevance are summarized in Table 15A-4. A very recently described autoantibody in the sera of about 30% of lupus patients is directed against an epitope of the glutamate/N-methyl-D-aspartic acid (NMDA) receptor subunits NR2a and NR2b (highly expressed in human brain) (26). Albeit not unambiguously proven, access of this antibody across the blood–brain barrier may result in neuropsychiatric abnormalities.

Complement proteins, the bullets of the antibodies and intrinsic components of immune complexes, can be measured both functionally (CH50) and antigenically (C3, C4). Most laboratories measure the C3 and C4 because they are stable and do not require special handling as does the CH50. The CH50 reflects the function of serum complement to lyse sheep red blood cells (RBCs); its value is the reciprocal of the dilution of serum that lyses 50% of antibody-coated sheep RBCs. A reduction of the CH50 occurs when individual complement component(s) are deficient or consumed. In fact, none of these traditional measures of the complement system discriminate between accelerated consumption of complement or decreased synthesis. Such distinction requires measurement of the complement split products (e.g., C3a), which is still considered a research tool and is not readily available in most commercial laboratories.

A challenge in the management of patients with SLE is to identify parameters that will stratify those at risk for disease flares, particularly flares which might lead to permanent damage in major organs. The presumption is that earlier treatment in the high-risk patient might have an impact on subsequent morbidity and mortality. Interest in measurements of the complement system and anti-DNA antibodies to evaluate lupus patients originates from the longstanding observation that decreased complement levels and rising titers of anti-DNA are often associated with severe disease (27).

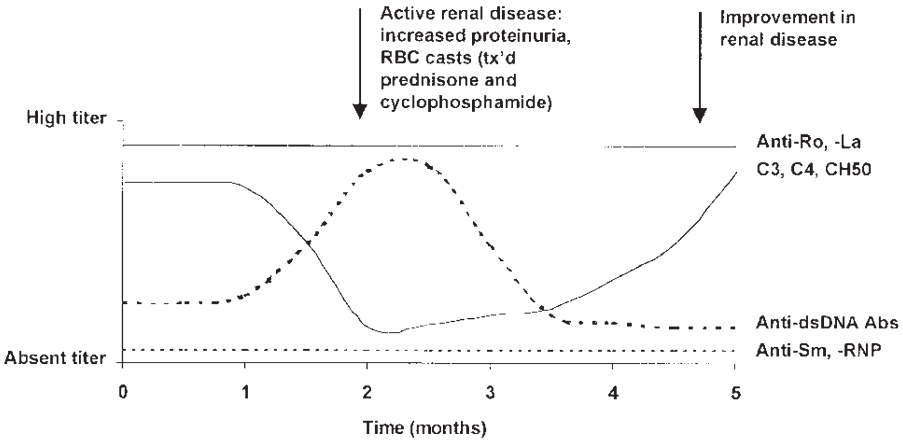
TABLE 15A-4. AUTOANTIBODIES AND CLINICAL FEATURES

ANTIBODIES	FREQUENCY	CLINICAL ASSOCIATIONS	RELATIONSHIP TO DISEASE ACTIVITY
ANA	> 90%	Nonspecific	For diagnostic purposes only
Anti-dsDNA	40%–60%	Nephritis	May predict disease flare and associates with flare
Anti-RNP	30%–40%	Raynaud's, musculoskeletal	Does not track disease
Antiribosomal P	10%–20%	Diffuse CNS, psychosis, major depression	Does not track disease
Anti-SSA/Ro	30%–45%	Dry eyes and mouth, SCLE, neonatal lupus, photosensitivity	Does not track disease
Anti-SSB/La	10%–15%	Dry eyes and mouth, SCLE, neonatal lupus, photosensitivity	Does not track disease
Antiphospholipid	30%	Clotting diathesis	Varied

ABBREVIATIONS: CNS, central nervous system. SCLE, subacute cutaneous lupus erythematosus.

FIGURE 15A-4

Longitudinal clinical and autoantibody profile in a patient with a lupus flare. This patient demonstrates concordance of clinical and serologic activity with regard to anti-dsDNA and complements. Note that despite changes in disease activity, titers of anti-Ro/La (elevated throughout) and anti-Sm/RNP (absent throughout) remain stable.



These findings are linked to the notion that immune complexes result in complement activation products that are present locally or in the circulation, and are capable of stimulating inflammatory cells with resultant vascular injury.

Measurements of anti-DNA antibodies and complement are an essential part of baseline evaluation, but treatment is dictated by the clinical picture, not necessarily the serologic one. Over time it should become obvious in an individual patient whether these parameters do predict and accompany disease flares. It is well appreciated that in certain patients low complements and elevated anti-DNA antibodies persist despite relative clinical quiescence. In contrast, there are patients who repeatedly demonstrate concordance of clinical and serologic activity (an illustrative case is provided in Figure 15A-4). In these individuals treatment may be considered solely on the basis of change in serologic parameters in advance of overt clinical disease, thus preventing relapse (28). These issues have been recently addressed in a prospective clinical trial to evaluate serologically active, clinically stable patients and determine whether anti-DNA, C3, C4, or the complement split product C3a are predictive of flare, and whether a short trial of glucocorticoids can avert major disease (29). Albeit a relatively small study, it appeared that preemptive therapy with glucorticoids did prevent flares. At the very least it is probably prudent to increase the frequency of simple dipstick analysis of the urine in a patient with rising titers of anti-DNA and falling complement levels. It has been suggested that antinucleosome antibodies constitute a selective biologic marker of active SLE, specifically for lupus nephritis (30).

Current studies are aimed at evaluating specific biomarkers in the urine that might predict onset and type of glomerulonephritis. Recently published candidates include adiponectin, an adipocyte-derived cytokine that has anti-inflammatory properties (31); monocyte chemoattractant protein (MCP-1), a key chemokine involved in monocyte chemotaxis (32); and soluble endothelial protein C receptor (sEPCR), a protein that promotes both procoagulant and proinflammatory responses (33,34).

SPECIAL CONSIDERATIONS

Systemic Lupus Erythematosus and Pregnancy

Sterility and fertility fates for women with SLE are comparable to control groups without disease. However, increased disease activity can be associated with secondary amenorrhea. Moreover, menstrual irregularities have been noted in patients taking high doses of glucocorticoids, and age-dependent premature ovarian failure occurs in those receiving cyclophosphamide. Women with SLE have a higher rate of spontaneous abortion, intrauterine fetal death, and premature birth compared to otherwise healthy women.

In contrast to the rule of remission during pregnancies in women with RA, the influence of pregnancy on SLE disease activity is variable. There are two principal areas of concern. The first is that the clinical and serologic expression of SLE may be adversely altered by pregnancy. The second is that the placenta and fetus may become targets of specific attack by maternal autoantibodies, resulting in a generalized failure of the pregnancy or specific syndromes of passively acquired autoimmunity, such as neonatal lupus (see below).

Pregnancy outcome is optimal when disease is in complete clinical remission for 6 to 12 months (35,36). Not unexpectedly, the most recent study to address the effect of SLE clinical status on pregnancy outcome identified that high lupus activity in the first and second trimesters led to a threefold increase in pregnancy loss (miscarriages and perinatal mortality) (37). Whether flare rates increase during or after pregnancy is still unsettled, because individual patient series vary in the characteristics of patients accepted for study and in the

definitions of flare. Current definitions of flare are imprecise, and accepted instruments used to measure disease activity—such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), British Isles Lupus Activity Group (BILAG), and Systemic Lupus Activity Measurement (SLAM)—do not account for the physiologic adaptations of pregnancy and have not been validated for pregnant lupus patients (38). Suggestions for valid criteria attributable to a flare are characteristic dermatologic involvement, arthritis, fever not secondary to infection, lymphadenopathy, leukopenia, alternative-pathway hypocomplementemia, and rising titers of antibodies to DNA. In contrast, invalid markers of disease activity include alopecia, facial or palmar blush, arthralgia, musculoskeletal aching, mild anemia, and fatigue, each of which may be present as part of the normal physiologic changes of pregnancy. Additionally, thrombocytopenia and proteinuria emerge in the setting of preeclampsia and cannot be attributed unambiguously to active lupus. In one major study comparing pregnant and nonpregnant women with SLE, the flare rates for both groups were similar (39). Despite a high overall flare rate in one series approaching 60% (35), recorded flares were usually not severe. In general, if all possible abnormalities are presumed due to SLE, disease exacerbation occurs in approximately 25%, and if only SLE-specific abnormalities are considered, disease exacerbation occurs in <13% (40).

In counseling a patient about the maternal risks of a prospective pregnancy, major issues include the presence of active nephritis and/or deterioration of renal function, neither likely in the absence of prior involvement. However, newly diagnosed lupus nephritis in the first trimester is associated with a poor fetal outcome. In a patient with established membranous nephritis, the normal increase in glomerular filtrate rate may result in protein excretion greater than 300 mg/24 hours, the upper limit accepted for an otherwise normal pregnancy. In some cases there will be coexistent hypertension which then must be differentiated (if possible) from preeclampsia, especially if it first becomes evident in the third trimester. In other patients, proteinuria will more clearly represent an exacerbation of lupus nephritis as suggested by cellular casts in the urinary sediment. Activation of the alternative complement pathway with a concomitant decrease in CH50 accompanies disease flares in SLE, a laboratory finding that may be useful in distinguishing active lupus nephritis from preeclampsia or pregnancy-induced hypertension (41). The presence of active lupus nephritis and/or preeclampsia increases the risk for pre-term delivery and fetal death. Encouragingly, women in whom renal disease is stable (serum creatinine <1.5 and 24-hour protein <2 g) prior to pregnancy can experience an uncomplicated course during pregnancy, despite a history of severe histopathologic changes and heavier proteinuria in the past. Additionally reassuring are the results of a recent Canadian study comparing 53 pregnant and 78 nonpregnant patients with lupus nephritis, which found that changes in renal disease activity and progression were similar in the two groups (42).

Neonatal Lupus

This illness of the fetus and neonate is considered a model of passively acquired autoimmunity, in which immune abnormalities in the mother lead to the production of anti-SSA/Ro-SSB/La antibodies that cross the placenta and presumably injure fetal tissue (43). The most serious manifestation is damage to the cardiac conducting system resulting in congenital heart block (CHB), which is most often third degree although less advanced blocks have been observed. CHB is generally identified between 16 and 24 weeks of gestation. The mortality rate is ~20% and the majority of children require pacing. Cutaneous involvement (erythematous and often annular lesions with a predilection for the eyes, face and scalp, frequently photosensitive) and, to a lesser extent, hepatic and hematologic involvement are also associated with maternal anti-SSA/Ro-SSB/La antibodies and are grouped under the heading of Neonatal Lupus Syndromes. Neonatal lupus—so termed because the dermatologic lesions of the neonate resembled those seen in SLE—is a misnomer in that less than a third of mothers of affected children actually have SLE (many are asymptomatic) and the neonatal disease is frequently only manifest as heart block, a problem rarely reported in adults with lupus. To date, complete block is irreversible. In contrast, the noncardiac manifestations are transient, resolving at about 6 months of life coincident with the disappearance of maternal autoantibodies from the neonatal circulation.

The incidence of neonatal lupus in an offspring of a mother with anti-SSA/Ro antibodies is estimated at 1% to 2%. No serologic profile is unique to mothers of affected children, but compared with mothers of healthy children, anti-SSA/Ro antibodies are usually of high titer (frequently anti-52kD SSA/Ro positive by immunoblot) and associated with anti-SSB/La antibodies (44). Reports of discordant dizygotic and monozygotic twins, and relatively low recurrence rates of CHB [in our series, 18 of 101 (18%) next pregnancies following the birth of a child with CHB] indicate that factors (likely fetal) in addition to anti-SSA/Ro and SSB/La antibodies contribute to the development of neonatal lupus (45). A Research Registry for Neonatal Lupus was established in 1994; with its current enrollment of 361 mothers and their 423 affected children, this database (along with available serum and DNA) provides a valuable resource for basic researchers and clinicians (43,45).

Antiphospholipid Antibody Syndrome

Antiphospholipid antibodies, ascertained by a variety of different assays, are associated with the risk of clotting. The clinical consequences include venous and arterial thromboses and placental insufficiency resulting in recurrent fetal loss. Except for manifestations of active SLE, lupus patients with antiphospholipid antibodies do not appear to have different pregnancy courses than patients with the primary antiphospholipid syndrome. Paradoxically, thrombocytopenia can also be part of the clinical spectrum because the surfaces of activated platelets display the anionic phospholipid target antigens. Patients who have antiphospholipid antibodies and one of the above clinical features in the absence of any other manifestations of SLE are classified as having primary antiphospholipid syndrome (APS), as outlined in Table 15A-5; 46,47). Alternatively a patient can have these antibodies in the context of SLE (secondary APS).

Currently, assessment of antiphospholipid antibodies is done by enzyme-linked immunosorbent assay (ELISA) to measure reactivity with cardiolipin, or by prolonged clotting in an in vitro system which is not corrected by mixing studies. The latter test is paradoxical because the readout is the inability to form a clot due to interference with proper assembly of the clotting factors, yet in vivo these antibodies are thrombogenic. Experimental data suggest that "antiphospholipid" antibodies are not directed against anionic phospholipids, as initially hypothesized, but are part of a larger group of autoantibodies that recognize phospholipid-binding proteins. At present, the best-characterized antigenic target is beta2-glycoprotein I (beta 2GPI) (48), which has been shown to possess multiple inhibitory functions in coagulation pathways. Although the measurement of antiphospholipid antibodies by ELISA is now well standardized, these new observations on beta 2GPI will require large-scale testing, the outcome of which may substantially alter current recommendations.

TABLE 15A-5. PRELIMINARY CLASSIFICATION CRITERIA FOR ANTIPHOSPHOLIPID SYNDROME (APS)*

CLINICAL CRITERIA

Vascular thrombosis
- ≥ 1 arterial, venous, or small-vessel thrombosis in any tissue or organ,

AND
- Confirmation by imaging or Doppler studies or histopathology (not SVT)

Pregnancy morbidity:
- ≥ 1 unexplained death(s) of normal fetus at ≥ 10 weeks gestation,

OR
- ≥ 1 premature birth(s) of normal neonate at ≤ 34 weeks gestation due to severe preeclampsia or placental insufficiency,

OR
- ≥ 3 unexplained consecutive spontaneous abortions < 10 weeks gestation (exclude anatomic, hormonal, or chromosomal abnormality)

LABORATORY CRITERIA

- Anticardiolipin antibody of IgG and/or IgM isotype
  - medium or high titer (15–80 GPL, 6–50 MPL)
  - on ≥ 2 occasions at least 6 weeks apart
  - measured by standard ELISA for beta2-glycoprotein I-dependent anticardiolipin antibodies

OR
- Lupus anticoagulant (LAC)
  - on ≥ 2 occasions at least 6 weeks apart

SOURCE: Adapted from Derksen RH, Khamashta MA, Branch DW (46), by permission of *Arthritis Rheum*.
ABBREVIATION: APS, antiphospholipid syndrome.
*APS considered definite if at least one clinical and one laboratory criteria are met.

Drug-Related Lupus

The term *drug-related lupus* (DRL) refers to the development of a lupuslike syndrome which follows exposure to chlorpromazine, hydralazine, isoniazid, methyldopa, minocycline, procainamide, or quinidine. In addition to these definitively associated drugs, there is a long list of other potential offending agents, such as diphenylhydantoin, penicillamine, and gold salts (49). There are no specified ACR criteria for DRL, but in general these patients present with fewer than four SLE criteria. A temporal association (generally a matter of weeks or months) between ingestion of an agent and development of symptoms is required. Following removal of the offending agent, there should be rapid resolution of the clinical features although autoantibodies may persist for 6 months to a year. Drugs capable of causing DRL do not seem to aggravate idiopathic SLE. The demographic features of DRL tend to reflect those of the diseases for which the offending drug has been prescribed. Accordingly, DRL occurs more frequently in the elderly, occurs only slightly more frequently in females than males, and is more common in Caucasians than African Americans.

Drug-related lupus patients frequently present with constitutional symptoms such as malaise, low grade fever, and myalgia, which may occur acutely or insidiously. Articular complaints are present in over 80%, with arthralgia being more common than arthritis. Pleuropulmonary disease and pericarditis are present most often in procainamide-related lupus. Other clinical manifestations of idiopathic SLE, such as dermatologic, renal, and neurologic, are rare in DRL. ANAs should be present in order to diagnose DRL. However, the development of an ANA without accompanying clinical features is insufficient for the diagnosis and not reason by itself to discontinue medication. Typically the ANA is a diffuse-homogenous pattern, which represents binding of autoantibodies to chromatin that consists of

DNA and histones. Anti-dsDNA and anti-Sm are not characteristic of DRL.

CONCLUSIONS

Systemic lupus erythematosus is a composite of clinically unrelated manifestations often accumulated over time which are unified, with rare exception, by the presence of antibodies directed against one or more self components of the nucleus, cytoplasm, and/or cell membrane. Greater awareness of the clinical features and advances in the laboratory evaluation of autoantibodies have facilitated diagnosis and eliminated much of the frustration previously experienced both by the patient and physician. In many patients flares are mimetic, but new manifestations can always be a threat. Physicians caring for patients with lupus should maintain high vigilance for the unexpected. The accurate prediction of flares and preemptive treatment in clinically quiescent patients is likely to result in longer periods of remission. Accordingly, the search for biomarkers to predict future morbidity and mortality offers unparalleled promise.

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CHAPTER 15

Systemic Lupus Erythematosus
B. Epidemiology, Pathology, and Pathogenesis

DAVID S. PISETSKY, MD, PHD

- Systemic lupus erythematosus (SLE) is primarily a disease of young women, though it can be seen in both pediatric and older patients where the sex ratio is more balanced.
- The pathologic findings of SLE occur throughout the body and are manifested by inflammation, blood vessel abnormalities that encompass bland vasculopathy and vasculitis, and immune-complex deposition.
- Autoantibodies can occur in the absence of clinical lupus, but pathogenic autoantibodies are important contributors to tissue damage in the kidney as well as in other involved organs.
- Autoantibodies in lupus may be driven by self-antigens implicating a more generalized immune cell dysfunction. which promotes B-cell hyperactivity.
- Genetic susceptibility to lupus is likely polygenic, as exemplified by multiple types of genes associated with lupuslike diseases in mice.
- Triggering events for disease initiation and flares may include may environmental exposures, such as hormones, infectious agents, diet, sunlight, toxins (including drugs), and others.

EPIDEMIOLOGY

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with diverse clinical manifestations in association with autoantibodies to components of the cell nucleus. SLE primarily is a disease of young women, with a peak incidence between the ages of 15 and 40 and a female:male ratio of 6 to 10:1. The age at onset, however, can range from infancy to advanced age; in both pediatric- and older-onset patients, the female:male ratio is approximately 2:1. In a general outpatient population, SLE affects approximately one in 2000 individuals, although the prevalence varies with race, ethnicity, and socioeconomic status (1).

Like other autoimmune diseases, SLE can display familial aggregation, with a higher frequency among first-degree relatives of patients. The disease occurs concordantly in approximately 25% to 50% of monozygotic twins and 5% of dizygotic twins. Moreover, in extended families, SLE may occur with other autoimmune conditions, such as hemolytic anemia, thyroiditis, and idiopathic thrombocytopenia purpura. Despite the influence of heredity, most cases of SLE appear sporadic.

IMMUNOPATHOLOGY

The pathologic findings of SLE occur throughout the body and are manifested by inflammation, blood vessel abnormalities that encompass bland vasculopathy and vasculitis, and immune-complex deposition. The best-characterized pathology involves the kidney, which displays increases in mesangial cells and mesangial matrix, inflammation, cellular proliferation, basement membrane abnormalities, and immune-complex deposition. These deposits are comprised of IgM, IgG, and IgA, as well as complement components. On electron microscopy, the deposits can be seen in the mesangium and the subendothelial and subepithelial sides of the glomerular basement membrane (Figure 15B-l). Renal pathology is classified according to two systems to provide information for clinical staging (see Chapter 15A) (2,3). With either system, lupus nephritis exhibits marked variability, differing in severity and pattern among patients, as illustrated in Figure 15B-2.

Skin lesions in SLE demonstrate inflammation and degeneration at the dermal–epidermal junction, and the basal or germinal layer is the primary site of injury. In these lesions, granular deposits of IgG and complement

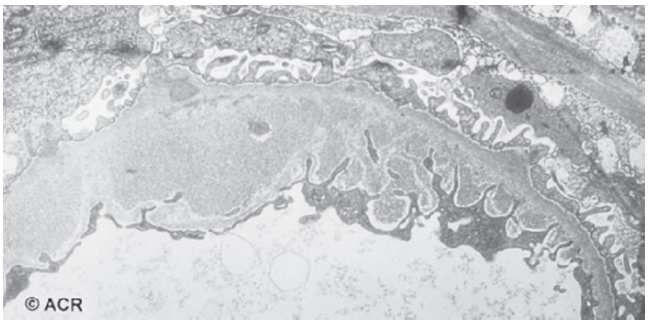


FIGURE 15B-1

Immune deposits in lupus nephritis. This electron micrograph illustrates large granular subendothelial immune deposits, as well as smaller subepithelial and intramembranous deposits. Broadening and fusion of the foot processes also are present. (Reprinted from the Revised Clinical Slide Collection on the Rheumatic Diseases, with permission of American College of Rheumatology.)

components occur in a bandlike pattern as observed by immunofluorescence microscopy. Necrotizing vasculitis also may cause skin lesions. Other organ systems affected by SLE usually display nonspecific inflammation or vessel abnormalities, although pathologic findings sometimes are minimal. For example, despite the severity of central nervous system (CNS) involvement, the typical findings are cortical microinfarcts and a bland vasculopathy with degenerative or proliferative changes; inflammation and necrosis indicative of vasculitis are found only rarely.

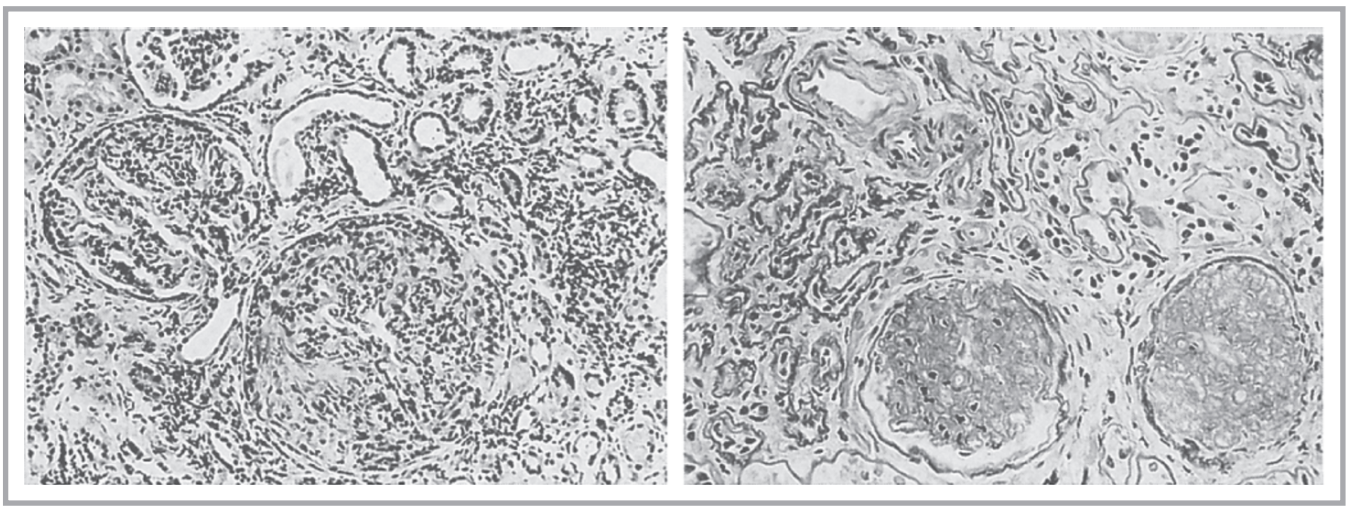
The heart may show nonspecific foci of inflammation in the pericardium, myocardium, and endocardium, even in the absence of clinically significant manifestations. Verrucous endocarditis, known as Libman–Sacks endocarditis, is a classic pathologic finding of SLE and is manifested by vegetations, most frequently at the mitral valve. These vegetations consist of accumulations of immune complexes, inflammatory cells, fibrin, and necrotic debris.

Occlusive vasculopathy with venous and arterial thrombosis is a common pathologic finding in SLE. Although coagulation can result from inflammation, autoantibodies also may trigger thrombotic events. These autoantibodies represent a spectrum of specificities designated as antiphospholipid antibodies, anticardiolipin antibodies, or lupus anticoagulants (4). Although some of these antibodies bind lipid antigens, others are directed to the serum protein beta$_2$-glycoprotein 1, a protein that can form complexes with lipids. Vessel abnormalities in SLE may also result from increases in endothelial cell adhesiveness by a mechanism analogous to the Schwartzman reaction triggered by Gram-negative bacteria.

Other pathologic findings prominent in SLE have an uncertain relationship to inflammation. Patients, including women without the usual risk factors for cardiovascular disease, frequently develop accelerated atherosclerosis and have an increased risk of stroke and myocardial infarction. It is unclear whether these lesions result from corticosteroid-induced metabolic abnormalities, hypertension, or vascular changes caused by a chronic burden of inflammation. Similarly, osteonecrosis, as well as neurodegeneration in people with chronic severe disease, may arise from vasculopathy, drug side effects, or persistent immunologic insults.

FIGURE 15B-2

(Left) Signs of "active" lupus nephritis showing glomerular proliferation, crescents, abundant inflammatory cell infiltration, and interstitial cell infiltrates (hematoxylin–eosin stain). (Right) Signs of "chronic" lupus nephritis showing glomerular cirrhosis, vascular thickening, tubular atrophy, and interstitial fibrosis (periodic acid, Schiff stain).



IMMUNOPATHOGENESIS OF ANTINUCLEAR ANTIBODIES

The central immunologic disturbance in SLE is autoantibody production. These antibodies are directed to a host of self-molecules found in the nucleus, cytoplasm, or surface of cells. In addition, SLE sera contain antibodies to such soluble molecules as IgG and coagulation factors. Because of the wide range of its antigenic targets, SLE is classified as a disease of generalized autoimmunity.

Among autoantibodies found in patient sera, those directed against components of the cell nucleus (antinuclear antibodies, or ANA) are the most characteristic of SLE and are found in more than 95% of patients (5). These antibodies bind DNA, RNA, nuclear proteins, and protein/nucleic acid complexes (Table 15B-1). As a group, the molecules targeted by ANA are highly conserved among species, serve important cellular functions, and exist inside cells as part of complexes (e.g., nucleosomes). Furthermore, these molecules, depending upon context (e.g., presence in immune complexes), display intrinsic immunological activity. This activity results from stimulation of the innate immune system via receptors known as the Toll-like receptors (TLR). The TLRs can recognize a diverse array of foreign and self-molecules, with DNA, single-stranded RNA and double-stranded RNA all TLR ligands (6).

Antibodies to certain nuclear antigens (e.g., DNA and histones) frequently occur together, a phenomenon known as linkage. Linkage suggests that a complex, rather than the individual components, serves as the target of autoreactivity, as well as its driving antigen. Among ANA specificities in SLE, two appear unique to this disease. Antibodies to double-stranded (ds) DNA and a nuclear antigen called Sm are essentially found only in people with SLE, and are included as serologic criteria in the classification of SLE (see Appendix I). Although both anti-DNA and anti-Sm are serologic markers, they differ in their pattern of expression and clinical associations. Whereas anti-DNA levels can fluctuate markedly over time, anti-Sm levels remain more constant. The anti-Sm and anti-DNA responses also differ in the nature of their target antigens. The Sm antigen is designated an snRNP (small nuclear ribonucleoprotein) and consists of uridine-rich RNA molecules complexed with proteins. In contrast to anti-DNA antibodies, which react to a nucleic acid determinant, anti-Sm antibodies target snRNP proteins and not RNA.

Perhaps the most remarkable feature of the anti-DNA response is its association with immunopathologic events in SLE, especially glomerulonephritis. This role has been established by correlating anti-DNA serum levels with disease activity, isolating anti-DNA in enriched form from glomerular eluates of patients with active nephritis, and inducing nephritis by administering anti-DNA antibodies to normal animals. The relationship between levels of anti-DNA and active renal disease is not invariable; some patients with active nephritis may lack serum anti-DNA, and others with high levels of anti-DNA are clinically discordant and escape nephritis (7).

The occurrence of nephritis without anti-DNA may be explained by the pathogenicity of other autoantibody specificities (e.g., anti-Ro or anti-Sm). The converse situation of clinical quiescence despite serologic

TABLE 15B-1. PRINCIPLE ANTINUCLEAR ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS.

SPECIFICITY	TARGET ANTIGEN	FUNCTION
Native DNA	dsDNA	Genetic information
Denatured DNA	ssDNA	Genetic information
Histones	H1, H2A, H2B, H3, H4	Nucleosome structure
Sm	snRNP proteins B, B′, D, E	Splicesome component, RNA processing
U1RNP	snRNP proteins, A, C, 70K	Splicesome component, RNA processing
SSA/Ro	60- and 52-KDa proteins, complexed with Y1-Y5 RNAs	Unknown
SSB/La	48-kDa protein complexed with various small RNAs	Regulation of RNA polymerase-3 transcription
Ku	86- and 66-kDa proteins	DNA binding
PCNA/cyclin	36-kDa protein	Auxillary protein of DNA polymerase alpha
Ribosomal RNP	38-, 16-, 15-kDa phosphoproteins, associated with ribosomes	Protein synthesis

SOURCE: Modified from Tan EM, Adv Immunol 1989;44:93–151, with permission of *Advances in Immunology*.
ABBREVIATIONS: ss, double-stranded; ss, single-stranded; snRNP, small nuclear ribonucleoprotein.

activity suggests that only some anti-DNA provoke glomerulonephritis. Antibodies with this property are denoted as pathogenic or nephritogenic. Features promoting pathogenicity may include isotype, charge, ability to fix complement, and capacity to bind glomerular preparations (7). In this regard, anti-DNA antibodies appear to be a subset of pathogenic antibodies that bind to nucleosomes, the likely form of DNA in the circulation as well as in immune deposits. Unless the full range of antinucleosomal antibodies is assessed, the presence of nephritogenic antibodies may be missed.

In addition to their direct role in nephritis, antibodies to DNA may promote immune system disturbances that potentiate inflammation systemically as well in the kidney. Thus, immune complexes containing DNA can promote the expression of interferon alpha (IFN-alpha) by a specialized population of dendritic cells known as plasmacytoid dendritic cells. This response requires the presence of both antibody and DNA in an immune complex and depends upon Fc receptors. While the basis of this response is not well understood, stimulation may involve the TLRs as well as other non-TLR signaling systems that respond to internalized nucleic acids. Antibodies to other nuclear antigens, including RNP complexes, can also stimulate this response, raising the possibility that immune complexes, in addition promoting organ damage, can contribute to the overall disturbance in the immune system in patients (8).

In addition to anti-DNA, other autoantibodies may have a clinical impact because of effects on organ-specific manifestations. Associations of other autoantibodies with disease events include antibodies to ribosomal P proteins (anti-P) with neuropsychiatric disease and hepatitis; antibodies to Ro with neonatal lupus and subacute cutaneous lupus; antibodies to phospholipids with vascular thrombosis, thrombocytopenia, and recurrent abortion; and antibodies to blood cells with cytopenias.

The contribution of ANAs to clinical events in SLE has been difficult to understand because the intracellular location of the target antigens should protect them from antibody interactions. The location of these antigens may not be fixed, however, and some antigens may translocate to the membrane and become accessible to antibody attack either during development or during apoptosis. Thus, during cardiac development, a molecule bound by anti-Ro appears on the surface of myocytes and, in the presence of complement, lead to local inflammation and damage to the conducting system (9).

Because of the impact of kidney disease on morbidity and mortality, nephritis has been the clinical event in SLE most intensively studied mechanistically. Clinical observations strongly suggest that SLE renal disease results from the deposition of immune complexes containing anti-DNA, because active nephritis is marked by elevated anti-DNA levels with a depression of total hemolytic complement. Because anti-DNA shows preferential renal deposition, these findings suggest that DNA/anti-DNA immune complexes are a major pathogenic species. DNA in these complexes likely is in the form of nucleosomes, suggesting that antibodies to other components of this structure may participate in immune-complex formation.

Although immune complexes may provoke renal injury in SLE, the amounts of such complexes in the serum appear limited. This finding has suggested that complexes may form in situ, rather than within the circulation. According to this mechanism, immune complexes assemble in the kidney on DNA or other nucleosomal components adherent to the glomerular basement membrane. Another mechanism for nephritis in SLE is the direct interaction of autoantibodies with glomerular antigens. Many anti-DNA antibodies are polyspecific and interact with molecules other than DNA. The binding of anti-DNA to these molecules could activate complement and inciting inflammation.

The pathogenesis of other SLE manifestations is less well understood, although immune-complex deposition at relevant tissue sites generally has been considered a likely mechanism. Indeed, the frequent association of depressed complement levels and signs of vasculitis with active SLE suggests that immune complexes are important agents for initiating or exacerbating organ damage. These considerations do not exclude the possibility that tissue injury results from either cell-mediated cytotoxicity or direct antibody attack on target tissues. Consistent with the operation of such a mechanism, a cross-reactive population of antibodies to the NMDA receptor may CNS disturbances by inducing excitotoxic damage (10).

DETERMINANTS OF DISEASE SUSCEPTIBILITY

Studies of patients suggest that SLE is caused by genetically determined immune abnormalities that can be triggered by exogenous or endogenous factors. Although the predisposition to disease is hereditary, it is likely multigenic and involves different sets of genes in different individuals (see Chapter 5). Analysis of genetic susceptibility has been based primarily on the search for gene polymorphisms occurring with greater frequency in people with SLE than in control populations. The study of genetic factors predisposing to SLE also has involved genomewide scans of siblings with SLE or multiplex families. Although this approach has led to the identification of chromosomal regions that contain genes potentially relevant to pathogenesis, the identities of these genes are not yet known definitively. Fur-

thermore, the regions associated with disease may differ depending upon racial and ethnic group (11).

Of genetic systems that could predispose to autoimmunity, the major histocompatibility complex (MHC) has been most intensively scrutinized for its contribution to human SLE. Using a variety of MHC gene markers, population-based studies indicate that the susceptibility to SLE, like many other autoimmune diseases in humans, involves class II gene polymorphisms. An association of human leukocyte antigen (HLA)-DR2 and HLA-DR3 (and various subspecificities) with SLE has been commonly observed, with these alleles producing a relative risk of disease that ranges approximately from 2 to 5. This analysis of MHC gene associations is complicated by the existence of extended HLA haplotypes in which class II genes are in linkage disequilibrium with other potential susceptibility genes. Because the MHC is rich in genes for immune-system elements, the association of disease with a class II marker does not denote a specific functional abnormality promoting pathogenesis.

Among other MHC gene systems, inherited complement deficiencies can influence disease susceptibility. Like class I and II molecules, complement components, in particular C4a and C4b, show striking genetic polymorphism, with a deficiency of C4a molecules (null alleles) a common occurrence in the population. As many as 80% of people with SLE have null alleles irrespective of ethnic background, with homozygous C4a deficiency conferring a high risk for SLE. Because C4a null alleles are part of an extended HLA haplotype with the markers HLA-B8 and HLA-DR3, the influence of these class I and class II alleles of disease susceptibility may reflect linkage disequilibrium with complement deficiency. SLE also is associated with inherited deficiency of Clq, Clr/s, and C2 (12).

An association of SLE with inherited complement deficiency may seem surprising because of the prominence of immune-complex deposition and complement consumption during disease. However, a decrease in complement activity could promote disease susceptibility by impairing the clearance of foreign antigen or apoptotic cells. Apoptosis, or programmed cell death, is associated with the breakdown of DNA, the rearrangement of intracellular constituents, and the release DNA and RNA into external milieu where these molecules, alone or in the context of immune complexes, could stimulate the immune system by the TLRs.

As shown in in vitro and in vivo systems, the clearance of apoptotic cells, a process called *efferocytosis*, involves diverse cellular and humoral pathways, including the complement system. Clq, for example, binds to apoptotic cells, initiating complement's role in clearance. In the absence of complement, apoptotic cells may persist and stimulate immune responses. The importance of complement deficiency to autoimmunity is illustrated by the features of mice in which C1q has been eliminated by genetic knockout techniques. C1q-deficient mice have elevated anti-DNA levels, glomerulonephritis, and increased apoptotic cells in the tissue (13). Impairment of other aspects of the clearance system (e.g., IgM and DNase) can also provoke immune system abnormalities, including the stimulation of interferon by dead and dying cells and their constituents.

GENETICS OF MURINE SYSTEMIC LUPUS ERYTHEMATOSUS

Several strains of inbred mice with inherited lupuslike disease have been studied as models to elucidate the human disease. These mice mimic human SLE in ANA production, immune complex glomerulonephritis, lymphadenopathy, and abnormal B-cell and T-cell function. These strains differ in the expression of certain serologic and clinical findings (e.g., anti-Sm, hemolytic anemia, and arthritis), as well as in the occurrence of disease among males and females. Among various lupus strains described (NZB, NZB/NZW, MRL-lpr/lpr, BXSB, and C3H-gl/lgld), the development of a full-blown lupus syndrome requires multiple unlinked genes (11).

In mice, single mutant genes (lpr, gld, and Yaa) can promote anti-DNA production and abnormalities in the number and function of B and T cells. In lpr and gld mice, these abnormalities result from mutations in proteins involved in apoptosis. Apoptosis plays a critical role in the development of the immune system, as well as in the establishment and maintenance of tolerance. The lpr mutation leads to the absence of Fas, a cell-surface molecule that triggers apoptosis in lymphocytes, and gld affects a molecule that interacts with Fas, the Fas ligand. These gene defects appear to operate in peripheral, in contrast to central, tolerance and allow the persistence of autoreactive cells. Among humans, while mutations of Fas can lead to lymphoproliferation and autoantibody production, clinical and serologic findings of SLE are uncommon, suggesting that in humans, as in the mouse, SLE requires more than one gene.

The interaction of genes in SLE also occurs in New Zealand mice. NZB/NZW F1 mice develop an SLE-like illness that results from genes contributed by both NZB and NZW parents. Among these genes, an interferon inducible gene called Ifi202 contributes powerfully to the development of autoimmunity, providing additional evidence between the link between the interferon system and SLE (8). In the NZM2410 model, extensive genetic studies have shown that genes that can promote as well as suppress autoimmunity. Individually, genes

that promote autoimmunity (denoted sle1, sle2, sle3) lead to distinct immune disturbances, including expression of ANA. When these genes are co-expressed because of genetic crosses, the clinical and serologic features of SLE occur. Importantly, other genes can suppress the development of SLE in mice, indicating complexity in the genetic predisposition for disease (11).

Among lupus mice, New Zealand strains have an MHC-linked deficiency in the expression of the proinflammatory cytokine tumor necrosis factor alpha (TNF-alpha). This deficiency may be pathogenic because administration of TNF-alpha to mice with low endogenous production ameliorates disease. In humans, TNF blockers have not been extensively used to treat patients because of concerns that it can potentiate autoreactivity; in small clinical trials, however, such therapy did not exacerbate disease (14). A role of TNF-alpha in the pathogenesis of autoimmunity is also suggested by the development of anti-DNA antibodies in patients with rheumatoid arthritis treated with TNF blockers, although the full development of SLE is very uncommon in this setting.

A variety of new SLE models have been created using molecular genetic techniques. These models reflect aberrant patterns of gene expression that occur in mice in which specific genes are eliminated by knockout techniques or enhanced by transgene expression. Studies of these mice suggest that a variety of genetic abnormalities may predispose to autoimmunity and genes regulating immune cell life span or signaling threshold may lead to autoantibody production. These genetic defects may affect the establishment of tolerance or the persistence of autoreactive cells.

IMMUNE CELL DISTURBANCES

Autoantibody production in SLE occurs in the setting of generalized immune cell abnormalities that involve the B cell, T cell, and monocyte lineages. These immune cell disturbances appear to promote B-cell hyperactivity, leading to hyperglobulinemia, increased numbers of antibody-producing cells, and heightened responses to many antigens, both self and foreign. Another consequence of B-cell and T-cell disturbance in SLE may be abnormal tolerance. In healthy individuals, anti-DNA precursors are tolerated by anergy or deletion; however, people with SLE or animals with SLE models may retain such precursors, which can be stimulated to generate high affinity autoantibody responses (15).

While these immune cell disturbances can affect multiple cell types and lineages, the appearance of an interferon signature is a prominent feature in peripheral blood cells of patients. As shown using microarray and related molecular techniques, peripheral blood cells of SLE patients demonstrate patterns of gene expression consistent with stimulation by IFN-alpha. Furthermore, this signature appears to be associated with antibodies to DNA or RNP antigens, consistent with stimulation of this cytokine by the nucleic acid components of immune complexes impacting on Toll-like receptors (TLR) or other receptors (see Chapter 4) (16,17). In view of the broad effects of the type I interferons on the immune system, a host of nonspecific functional abnormalities could result from the presence of high levels of this cytokine.

Although nonspecific immune activation can provoke certain ANA responses, it does not appear to be the major mechanism for inducing pathogenic autoantibodies, especially anti-DNA. Levels of these antibodies far exceed the extent of hyperglobulinemia. In addition, anti-DNA antibodies have features indicative of in vivo antigen selection by a receptor-driven mechanism. These features include variable-region somatic mutations that increase DNA binding activity and specificity for dsDNA. The generation of such responses also may be affected by the composition of the pre-immune repertoire and the content of precursors that can be mutated under influence of self-antigen drive.

The ability of DNA to drive autoantibody production in SLE contrasts with the poor immunogenicity of mammalian DNA when administered to normal animals. This discrepancy suggests that SLE patients either have a unique capacity to respond to DNA or are exposed to DNA in a form with enhanced immunogenicity (e.g., surface blebs on apoptotic cells or nucleosomes). Although serologic profiles of people with SLE and mice with murine models of SLE point to nucleosomes as the driving antigen, bacterial or viral DNA may stimulate this response. Bacterial DNA, because of characteristic sequence motifs, can stimulate a TLR directly and has potent adjuvant properties. As a result, bacterial DNA is immunogenic and may be able to elicit anti-DNA autoantibodies in a genetically susceptible host (18).

The specificity of ANA directed to nuclear proteins supports the hypothesis that these responses are antigen driven, because these antibodies bind multiple independent determinants found in different regions of these proteins. The pattern of ANA binding minimizes the possibility that molecular mimicry is the exclusive etiology for autoimmunity in SLE. This type of cross-reactivity has been hypothesized for many different autoimmune diseases, and it has been suggested for SLE because of the sequence similarity between certain nuclear antigens and viral and bacterial proteins. However, if SLE autoantibodies resulted from molecular mimicry, they would be expected to bind self-antigen only at sites of homology with foreign antigen, rather than throughout the entire molecule. While self-antigen

can sustain ANA production, a cross-reactive response to a foreign antigen can initiate it. A role of infection in SLE is suggested by the finding that people with SLE are infected more commonly with Epstein–Barr virus than are control populations (19).

Studies analyzing the genetics of SLE and the pattern of ANA production both strongly suggest that T cells are critical to disease pathogenesis. In murine models of lupus, the depletion of helper T cells by monoclonal antibody treatment abrogates autoantibody production and clinical disease manifestations. The basis of T-cell help in autoantibody responses may differ, however, from conventional responses because of the nature of the antigens. Most SLE antigens exist as complexes, such as nucleosomes, containing multiple protein and nucleic acid species. Because these antigens may trigger B-cell activation by multivalent binding, T-cell help for autoimmune responses could be delivered by nonspecifically activated T cells. Alternatively, T-cell reactivity to these antigens could be elicited to only one protein on a complex, allowing a single helper T cell to collaborate with B cells for determinants.

TRIGGERING EVENTS

Although inheritance and the hormonal milieu may create a predisposition toward SLE, the initiation of disease and its temporal variation in intensity likely result from environmental and other exogenous factors. Among these potential influences are infectious agents, which could induce specific responses by molecular mimicry and perturb overall immunoregulation; stress, which can provoke neuroendocrine changes affecting immune cell function; diet, which can affect production of inflammatory mediators; toxins, including drugs, which could modify cellular responsiveness and the immunogenicity of self-antigens; and physical agents, such as sunlight, which can cause inflammation and tissue damage. The impingement of these factors on the predisposed individual is likely to be highly variable, providing a further explanation for the disease's heterogeneity and its alternating periods of flare and remission.

Because many patients with SLE can show serological abnormalities years in advance of clinical disease manifestations (20), mechanistically, disease may develop sequentially, with one step leading to autoantibody expression, and another step leading to clinical manifestation. The second triggering event could lead, for example, to the release of self-antigen and allow the formation of immune complexes to drive cytokine production. The separation of these events could also explain the phenomenon of serologically active, clinical quiescent lupus and the occurrence of remission in some patients following a flare.

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CHAPTER 15

Systemic Lupus Erythematosus
C. Treatment and Assessment

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- Global management of systemic lupus erythematosus (SLE) importantly includes education, photoprotection, maintaining good physical conditioning, appropriate immunization, and identifying and treating risk factors for cardiovascular disease.
- Many traditional treatments are available for the nonorgan manifestations of SLE, including nonsteriodal anti-inflammatory drugs (NSAIDs), corticosteroids, and antimalarials.
- Treatment of severe organ involvement typically requires immunosuppressive agents.
- Targeted biologic therapies are under development that may change treatment algorithms in the future.

The significant improvement in survival and quality of life in patients with systemic lupus erythematosus (SLE) is the result of major advances over the past half century in the management of SLE. Milestones in the treatment of lupus include the discovery and use of corticosteroids in the 1950s, renal dialysis in the 1960s, and cyclophosphamide in the 1970s. However, there has been a drought of almost 40 years when it comes to new therapeutic agents for lupus. Corticosteroids, hydroxychloroquine, and aspirin are the only three drugs currently approved by the US Food and Drug Administration (FDA) for treatment of SLE. Novel therapeutics with more specific targets directed toward the autoimmune aspects of SLE are on the horizon. The goals of therapy are the reduction of both autoimmunity and target organ damage from inflammation and injury. In addition, side effects of therapy must be addressed as part of the management of SLE. It is crucial to recognize the wide spectrum of clinical manifestations in SLE. The treatment should be tailored based on the clinical manifestations in an individual patient because SLE manifests a unique disease profile in everyone afflicted.

GENERAL MANAGEMENT

Patient education directed toward understanding of the disease and therapy is fundamental in management of any chronic illness. Many patients may already have begun their own investigation through the information highway, primarily the Internet. It is the duty of the physicians and health care providers to clarify the confusion and alleviate the fear caused by learning about the worst-case scenarios of SLE through the means of Internet, friends, and family members.

Fatigue is very common in patients with SLE. The cause may be multifactorial, and include other comorbid conditions, such as hypothyroidism, depression, fibromyalgia, and deconditioning from chronic illness. Thus, therapy relies on identifying the underlying etiologies. Patients with photosensitivity can also develop fatigue and disease flare following exposure to ultraviolet light. Photoprotection includes avoidance of excess sunlight during mid-day, routine sunscreen/sunblock, and photoprotective clothing. Window films and fluorescent light shields reduce ultraviolet light exposure and can minimize the risk of lupus flare due to photosensitivity. Patients also need to be cautioned regarding drug-induced photosensitivity, commonly seen with antibiotics. Sedentary lifestyle resulting from chronic illness, depression, or fibromyalgia is another prominent feature in patients with SLE. This problem can lead to obesity and poor physical and cardiac health. SLE patients have been found to have diminished aerobic capacity (1). Low impact aerobic exercise, such as aquatic therapy, and walking exercise should be considered part of the nonpharmacologic regimen in patients with SLE.

Infections are common in SLE due to the intrinsic immune dysregulation and chronic immunosuppressive

use. Patients should be advised to seek medical attention for unexplained fevers and not immediately attribute these fevers to lupus flares. Judicious use of corticosteroids and immunosuppressive agents and appropriate immunization with influenza and pneumococcal vaccines can minimize the risk of infection.

Patients with SLE are at increased risk of premature cardiovascular disease (CVD). It is important to reduce modifiable risk factors including tobacco use, obesity, sedentary lifestyle, dyslipidemia, and hypertension. The disease and its treatment can exacerbate these known CVD risk factors. Smoking cessation, weight reduction by dietary and exercise modalities, good blood pressure control, and annual monitoring of fasting lipid profiles are ways that may reduce the CVD risk in SLE patients. Similarly, osteoporosis is quite common, especially in patients that require prolonged corticosteroid therapy. Several studies have demonstrated that the heightened risk of bone loss in lupus is seen in all ethnicities, including African American women, who are normally less susceptible. Calcium plus vitamin D supplementation and antiresorptive agents (bisphosphonate) should be instituted appropriately. The safety of bisphosphonates in young individuals and those in childbearing age remains unclear. Because of recent evidence to support a high prevalence of vitamin D deficiency in SLE, it is advisable to check levels of 25-hydroxy vitamin D as a part of routine health maintenance.

Women with SLE may be at increased risk for cervical dysplasia and cervical cancer, in part due to the chronic infection from human papilloma virus. Similarly, a recent international collaborative study reported an increased risk of malignancy, particularly non-Hodgkin's lymphoma, in patients with lupus (2). Whether this increased risk is related to the underlying disease or the drugs used to treat lupus is unclear. Age-appropriate health maintenance, including gynecological and breast examination, and colonoscopy is recommended.

CURRENT THERAPY

The key to selecting appropriate therapies relies on the careful assessment of the organ involvement and the severity of lupus disease activity. Because most medications have potential adverse reactions, Table 15C-1 outlines the strategies for toxicity monitoring of medications commonly used in SLE.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in pain relief and are widely used in patients for diverse manifestations including arthritis, myalgia, serositis, and headaches. The choice of NSAID is determined by cost, effectiveness, and side effects. The effectiveness of these agents varies among individual patients and also can change in the same patient over time. In patients with renal impairment from lupus nephritis, both selective and nonselective NSAIDs should be avoided because the inhibition of cyclooxygenase (COX) by NSAIDs can further impair the renal blood flow and the maintenance of tubular transport through the reduction of both prostaglandins and prostacyclins. Side effect profiles for renal, hepatic, and central nervous system (CNS) toxicities are similar in nonselective COX inhibitors and selective COX-2 inhibitors. These side effects may be confused with SLE activity. Mild and reversible increases in hepatic enzymes are common side effect of NSAIDs. Similarly, aseptic meningitis, headache, confusion, cognitive dysfunction, and even psychosis may be seen in patients using NSAIDs. Selective COX-2 inhibitors reduce the gastrointestinal side effects, namely peptic ulcers and bleeding. However, due to the increased risk of cardiovascular events in selective COX-2 users, these agents should generally be avoided in patients with known coronary heart disease. Only one selective COX-2 inhibitor (celecoxib) remains in the current market. The antiplatelet effect of nonselective COX inhibitors can increase the risk of bleeding during surgical procedures and with concomitant use of anticoagulants; thus, nonselective COX inhibitors should be discontinued prior to surgery and should be used judiciously in the setting of anticoagulation. NSAIDs should be discontinued towards the third trimester in pregnant patients, due to the risk of premature closure of ductus arteriosus.

Corticosteroids

Corticosteroids are effective in the treatment of various inflammatory rheumatic diseases; they can also provide immediate relief of many manifestations of SLE. Topical corticosteroids are frequently used for local treatment of mucocutaneous disease. Systemic corticosteroids ranging from 5 mg to 30 mg equivalent dose of prednisone in single or divided doses given daily are effective in treatment of mild-to-moderate SLE disease, including cutaneous disease, arthritis, and serositis. More severe organ involvement, specifically nephritis, pneumonitis, hematologic abnormalities, CNS disease, and systemic vasculitis, require high dosages of corticosteroids in oral or parental preparations in equivalent dosages of prednisone of 1 to 2 mg/kg/day. Intravenous pulse methylprednisolone (1 g) can be given for three consecutive days when these severe manifestations of SLE are life threatening.

Systemic corticosteroids can act as bridging therapy for the slower-acting immunomodulatory agents (discussed later). Corticosteroids can then be tapered when

TABLE 15C-1. RECOMMENDED MONITORING FOR TOXICITIES OF DRUGS USED IN SYSTEMIC LUPUS ERYTHEMATOSUS.

			MONITORING		
DRUG	**ADVERSE REACTIONS**	**PREGNANCY**	**Baseline evaluation**	**Routine evaluation**	**Annual evaluation**
NSAIDs	GI bleeding, hepatotoxicity, nephrotoxicity, hypertension, headache, aseptic meningitis	Discontinue in third trimester	CBC, creatinine, urinalysis, AST, ALT	Creatinine, AST, ALT every 6 months	CBC
Corticosteroids	Cushingoid features (hypertension, dyslipidemia, hyperglycemia), cataracts, osteonecrosis, osteoporosis	Safe but keep to the lowest dose	Fasting lipid profile, DXA, glucose, blood pressure	Blood pressure, glucose	DXA and fasting lipid profile
Antimalarials	Retinopathy, GI complaints, rash, myalgia, headache; hemolytic anemia in patients with G6PD deficiency	Safe	Eye exam in patients over 40 years old or with previous eye diseases; G6PD level in high risk patients;	Fundoscopic and visual field exams every 6–12 months	
Dapsone	Hemolytic anemia in patients with G6PD deficiency; methemoglobinemia	Discontinue 4 weeks before delivery	CBC, platelets, creatinine, AST, ALT; G6PD level in high-risk patients	CBC and platelet every 1–2 weeks with changes in dose (every 1–3 months afterwards)	
Azathioprine	Myelosuppression, hepatatoxicity, lymphoproliferative disorders	Safe	CBC, platelets, creatinine, AST, ALT, hepatitis B and C serology	CBC and platelet every 1–2 weeks with changes in dose and then AST, ALT every 1–3 months afterwards	Pap test and age-appropriate routine health maintenance
Methotrexate	Mucositis, myelosuppression, hepatatoxicity, cirrhosis, pneumonitis, pulmonary fibrosis	Teratogenic	CBC, platelets, creatinine, AST, ALT, hepatitis B and C serology	CBC and platelet, AST, ALT, albumin, creatinine every 1–2 months	Pap test and age-appropriate routine health maintenance
Mycophenolate mofetil	Myelosuppression, GI complaints, myalgia	Limited data (avoid)	CBC, platelets, creatinine, AST, ALT, hepatitis B and C serology	CBC and platelet, AST, ALT, albumin, creatinine every 1–2 months	Pap test and age-appropriate routine health maintenance
Cyclosporine	Myelosuppression, gingival hypertrophy, hepatotoxicity, nephrotoxicity, dyslipidemia, hyperuricemia	Safe	CBC, platelets, creatinine, AST, ALT, hepatitis B and C serology, urinalysis	CBC and platelet, AST, ALT, albumin, creatinine, urinalysis every 1–2 months	Fasting lipid profile; Pap test and age-appropriate routine health maintenance
Cyclophosphamide	Myelosuppression, hemorrhagic cystitis, lymphoproliferative disorders, malignancy, infertility	Teratogenic	CBC, creatinine, AST, ALT, hepatitis B and C serology, urinalysis	CBC and platelet, AST, ALT, creatinine, urinalysis monthly	Urine cytology; Pap test and age-appropriate routine health maintenance

ABBREVIATIONS: ALT, alanine transaminases; AST, aspartate transaminases; CBC, complete blood cell count; DXA, bone densitometry; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; Pap, Papanicolaou.

the immunomodulator begins to take effect. Once the disease activity is under control, corticosteroids are tapered to none or minimal daily (prednisone ≤5 mg/day) or alternate-day dosing for maintenance therapy. The goal of successful tapering of the corticosteroids is to reduce the numerous potential but common side effects of prolonged corticosteroid therapy while avoiding disease relapse or exacerbation. Common side effects of systemic corticosteroids include emotional lability, glaucoma, cataracts, peptic ulcer disease, osteoporosis, osteonecrosis, increased infection risk, and Cushingoid features (central obesity, striae, hypertension, diabetes mellitus, and dyslipidemia).

Topical Agents

Similar to minimizing the use of systemic corticosteroids, topical corticosteroids can be tapered to discontinuation or on an as-needed basis once the slower-acting immunomodulators or immunosuppressive agents are instituted. Clobetasol (high potency) in the preparation of solution or foam can be used to treat alopecia caused by SLE-associated rashes. The use of high potency or fluorinated topical corticosteroids should be avoided on the face and intertriginous areas due to the increased risk of developing skin atrophy and telangiectasias. In addition, topical corticosteroids should not be used continuously due to the development of tachyphylaxis. Typically, patients can apply the topical corticosteroids on weekdays and none on weekends. Other steroid-sparing topical agents, such as tacrolimus or pimecrolimus, can be given during "steroid-drug" holidays. Intralesional triamcinolone may be administered in hypertrophic lupus lesions. Both topical tacrolimus and pimecrolimus ointments are FDA approved for atopic dermatitis. They inhibit T-cell proliferation and release of cytokines. Unlike corticosteroids, they do not affect keratinocytes, endothelial cells, and fibroblasts, and thus do not induce skin atrophy. Topical retinoids, including tretinoin and tazarotene, have both anti-inflammatory and immunosuppressive effects and have been used successfully for the treatment of chronic cutaneous lupus. Common side effects include local skin irritation.

Antimalarials

Antimalarial agents are the most common background therapy for SLE. Hydroxychloroquine (HCQ) is the agent most frequently prescribed in the United States, followed by chloroquine and quinacrine. The antimalarials are commonly used as the first-line immunomodulatory agents in the treatment of mild SLE disease manifestations, including constitutional, cutaneous, and musculoskeletal. HCQ is usually initiated at 200 mg/day dosage and eventually increased to 200 mg twice daily or 400 mg/day (5–6.5 mg/kg/day). The response of HCQ is very slow and typically occurs after 6 weeks; its peak efficacy may not be reached for 4 months. Hydroxychloroquine demonstrated clinical efficacy in a randomized withdrawal trial when patients who discontinued HCQ were 2.5 times more likely to develop mild lupus flare than those who maintained the treatment (3). Long-term follow-up of this study suggested a trend towards reduction in flares in those who remained on HCQ, although this reduction was not statistically significant (4). In addition, HCQ use appeared to predict renal remission within 1 year in lupus patients treated with mycophenolate mofetil for membranous glomerulonephritis (5). Two studies have shown that cigarette smoking may interfere with the efficacy of antimalarials in treating patients with discoid lupus and subacute cutaneous lupus (6,7). Smokers were found to be less responsive to the antimalarial therapy than nonsmokers with a dose effect, meaning patients who smoked the most had the least response to antimalarials (7). In addition, improvement of skin lesions occurred once the patients stopped smoking while remaining on antimalarial therapy.

Chloroquine is used at 250 mg/day (3.5 mg/kg/day) with effects seen within 3 to 4 weeks, sooner than that of HCQ. Quinacrine, which has a rapid onset of action similar to chloroquine, is usually dosed at 100 to 200 mg/day (2.5 mg/kg/day). Combination therapy with HCQ (or chloroquine) and quinacrine is commonly used with success when one agent alone is not effective.

Gastrointestinal side effects are the most common. They are often transient and reduced by lowering the dose of the antimalarials or administering brand rather than generic. Most common complaints include crampy abdominal pain, nausea, vomiting, bloating, or diarrhea. Chloroquine less frequently causes gastrointestinal reactions followed by hydroxychloroquine and quinacrine. Chloroquine has a higher incidence of retinal toxicity causing visual field defects than HCQ. Therefore, HCQ and chloroquine should be used together with caution because the risk of retinopathy is high with this combination. Other visual symptoms include blurred distance vision, difficulty in reading, photophobia, and flashing lights. The risk of retinal toxicity can be minimized when the total daily recommended dose of HCQ is kept ≤6.5 mg/kg/day, chloroquine ≤3 to 4 mg/kg/day, and quinacrine ≤2.5 mg/kg/day. A long-term follow-up study demonstrated a very low incidence of HCQ-related retinopathy (0.5%) in 400 patients who were treated with the recommended dosages for >6 years (8). Despite the rarity of retinal toxicity, patients receiving antimalarials should have ophthalmologic evaluations at baseline and then at 6- to 12-month intervals. This evaluation should include a fundoscopic examination, visual field, and visual acuity testing. Antimalarials may cause hyperpigmentation on nails,

anterior legs, face, and, rarely mucous membranes, predominantly on sun-exposed areas. Bluish-gray to dark purple discoloration is associated with HCQ therapy, while yellow discoloration with quinacrine. Hypopigmented lesions that involve mainly the hair or lentigines may occur with chloroquine therapy. These cutaneous lesions can gradually resolve after discontinuation of the drug. Rare but serious cardiotoxicity from HCQ and chloroquine with the presentation of myocardial dysfunction has been reported, although less than half of the cases were biopsy proven (9–12). Histologic findings of the endomyocardial biopsy may reveal myeloid and curvilinear bodies (lipid-rich structures representing abnormal lysosomes) with variable myofiber atrophy and necrosis (13). Older women with long duration of antimalarial therapy appeared to be in greater risk for this cardiotoxicity. Drug-induced myopathy from HCQ has also been reported with the presence of curvilinear bodies in skeletal muscle biopsy.

Hydroxychloroquine has hypoglycemic properties that could improve glycemic control in patients with poorly controlled type 2 diabetes (14). In addition, HCQ may lower the insulin requirement in patients with type 2 diabetes on insulin therapy, thereby placing these patients at greater risk for hypoglycemic events. Thus, patients should be aware of the hypoglycemic effects of HCQ. Another precaution of antimalarials is the risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency is more common in the Mediterranean regions, Middle East, Africa, and the Indian subcontinent. Physicians need to be aware of this increased risk in patients of these descents. HCQ has been shown to be safe during pregnancy (15). No retinal toxicity or otoxicitiy in children born to women on HCQ has been reported. The safety of HCQ, chloroquine, and quinacrine in breastfeeding has not been established.

Dapsone

Dapsone is a sulfone antibiotic used in the treatment of leprosy and for the prophylaxis of *Pneumocystis jirovecii* pneumonia (previously known as *Pneumocystis carinii* pneumonia). Dapsone has additional immunomodulatory properties, particularly effective against neutrophil-mediated processes, and is used to treat various bullous disorders, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, cutaneous vasculitis, and cutaneous lupus. Dapsone (100 mg/day) alone or in combination with systemic corticosteroids/antimalarials, is the drug of choice for bullous SLE as well as for cutaneous lesions involving the small dermal vessels, such as leukocytoclastic vasculitis.

The most serious but rare side effect is the hypersensitivity syndrome, characterized by fever, rash, lymphadenopathy, hepatitis, and hepatosplenomegaly. Another serious adverse effect is bone marrow suppression, which appears to be an idiosyncratic reaction to dapsone that is exacerbated by the concomitant use of a folate antagonist. Similar to antimalarials, patients with G6PD deficiency are at increased risk of developing hemolytic anemia while taking dapsone. Although dapsone is not teratogenic, it can increase the risk of methemoglobinemia and cyanosis in neonates as observed in adults (16). Discontinuation of dapsone therapy 1 month before the expected date of delivery to minimize the theoretical risk of kernicterus is recommended (17). Breastfeeding by mothers taking dapsone should be cautioned because this drug is secreted in breast milk and can place the infants at risk of developing hemolytic anemia.

Azathioprine

Azathioprine (2–2.5 mg/kg/day) is frequently used as a steroid-sparing agent in patients with mild-to-moderate disease activity, and as an alternative maintenance therapy to cyclophosphamide in patients with lupus nephritis and other organ-threatening manifestations. This agent is a purine analog and a mercaptopurine immunosuppressant that inhibits nucleic acid synthesis and thus affects both cellular and humoral immune function. Azathioprine can be used during pregnancy in women who may require an immunomodulator stronger than the antimalarials can provide. Azathioprine passes into breast milk; thus mothers on azathioprine should not breastfeed their infants.

The main adverse reaction of azathioprine is acute myelotoxicity, manifesting as pancytopenia in patients who are deficient in the enzyme thiopurine methyltransferase (TPMT) that inactivates azathioprine. Drug interaction between azathioprine and allopurinol (used in the treatment of gout) can also cause acute pancytopenia. This combination should be avoided. The other common side effect is gastrointestinal toxicity similar to the antimalarials. Azathioprine requires regular monitoring of renal and liver functions because of the hepatic metabolism and renal excretion. Dosage should be adjusted in patients with renal or hepatic dysfunction.

Methotrexate

Methotrexate has been the standard therapy of rheumatoid arthritis, with extensive data demonstrating its efficacy and safety in this disease. However, there are only a few prospective randomized trials of methotrexate therapy for SLE, with conflicting results. Numerous case series and few retrospective studies have demonstrated success in the treatment of active cutaneous and/or articular involvements, allowing corticosteroid taper.

Methotrexate is an analog of dihydrofolic acid, which inhibits dehydrofolate reductase, and has

immunomodulatory effects at low doses without the cytotoxic or antiproliferative effects seen in the very high doses that are typically given in chemotherapy. Side effects are common and include gastrointestinal complaints, mucositis, alopecia, hepatic enzyme elevations, and infections, especially when the dosage is high. These side effects may be minimized if the methotrexate is given in the range of 7.5 to 15 mg/week. Addition of daily folate or weekly folinic acid supplementation may alleviate the common side effects of oral ulcers and alopecia. Injectable administration of methotrexate can improve the bioavailability of this medication and may also minimize the gastrointestinal complaints (nausea, vomiting, diarrhea, and abdominal cramps). Abnormal liver function tests are of concern if the elevations persist; however, they are often poor predictors of the severity of hepatotoxicity by histopathology. Patients taking methotrexate should be advised against regular alcohol consumption because the combination of methotrexate and alcohol can further increase the risk of hepatotoxicity. A rare but potentially life-threatening pulmonary complication is methotrexate-induced pneumonitis. This adverse reaction can develop early as well as late in the course of the treatment and needs to be distinguished from infectious pneumonia and lupus pneumonitis. Discontinuation of methotrexate is warranted when either pneumonia or methotrexate-induced pneumonitis is suspected. The teratogenicity of methotrexate is well established. Methotrexate should therefore be discontinued 6 months prior to pregnancy, regardless of the patient's gender.

Cyclosporine

Cyclosporine primarily inhibits the proliferation of T lymphocytes and selectively inhibits T-cell–mediated responses, such as interleukin 2 (IL-2), IL-3, and interferon gamma (IFN-gamma), and other cytokines at the transcriptional level from naive T cells. Although SLE has been thought to arise from B-cell–mediated autoimmunity with autoantibody production and immune-complex formation, there is evidence that indicates a primary role for T cells. In murine models of SLE, depletion of CD4+ T cells prevents disease onset (18) and athymic mice do not develop SLE (19). Dosages of cyclosporine ranging from 2.5 to 5 mg/kg/day are generally well tolerated, with reduction of corticosteroid dosage and improvement in disease activity, proteinuria, leukopenia, thrombocytopenia, and complement levels (20). Limited pregnancy data primarily from the transplant patients showed no increased in adverse outcomes in pregnancy. This medication is not teratogenic in animals. Cyclosporine can be continued in pregnant patients with SLE if the benefits outweigh the risks. Mothers taking cyclosporine are advised against breastfeeding because cyclosporine passes into breast milk.

Most side effects are dose dependent and reversible. They include hypertension, elevations in serum creatinine and hepatic enzymes, tremor, hypertrichosis, gingival hypertrophy, parathesis, gastrointestinal complaints, and infections. Cyclosporine can also cause hyperkalemia, dyslipidemia, and worsen hyperuricemia that can lead to a gouty flare. Although cyclosporine appears to be effective in treatment of refractory nephrotic syndrome or membranous glomerulonephritis (WHO class V), long-term therapy can result in structural changes in the kidneys, such as interstitial fibrosis and tubular atrophy. Therefore, regular monitoring of renal function and blood pressure are advised.

Cyclophosphamide

Cyclophosphamide is an alkylating and cytotoxic agent, which cross-links DNA and DNA-associated proteins. It is reserved for the treatment of severe SLE, including lupus nephritis, central nervous system disease, pulmonary hemorrhage, and systemic vasculitis. The results of the landmark randomized trial by the National Institutes of Health (NIH) in 1986 set the gold standard for treatment of patients with diffuse proliferative glomerulonephritis (21). In this study, patients treated with corticosteroids and intermittent cyclophosphamide (intravenous bolus regimens of 0.5–1 g/m^2 body surface area) had significantly better renal survival than those treated with corticosteroids alone. However, no significant difference in renal survival was found between this regimen and the one with azathioprine. The traditional cyclophosphamide regimen for diffuse proliferative glomerulonephritis is 6 to 7 monthly pulse of cyclophosphamide alone or with pulse methylprednisolone in the induction, and then quarterly pulse cyclophosphamide for 2 years. The intravenous administration of cyclophosphamide has the advantage over oral formulations in that the bladder can be protected by intravenous infusion of mesna (mercapto-ethanesulphonic acid) along with rigorous hydration to prevent hemorrhagic cystitis and bladder cancer from acrolein, a toxic metabolite of cyclophosphamide. Variations of shorter duration and/or lower dose of cyclophosphamide therapy have been studied with varying results; however, due to the toxicity of an extended cyclophosphamide regimen, attempts to reduce exposure by changing to alternate treatments are an active area of investigation.

Adverse effects of cyclophosphamide include nausea and vomiting, alopecia, bone marrow suppression, increased risk of infections, and bladder carcinoma. Cyclophosphamide has been associated with increased risk for cervical dysplasia and cervical intraepithelial neoplasia (22,23). Nausea and vomiting can be prevented with anti-emetic drugs such as ondansteron and dolasetron, given on a regular schedule during the first

24 hours and then as needed afterwards. A dose-dependent nadir leukocyte count should be checked 8 to 12 days after intravenous cyclophosphamide therapy. Infertility due to gonadal toxicity from cyclophosphamide is one of the most concerning side effects. The two key factors associated with the risk of ovarian failure in women are older age at the start of treatment and higher cumulative dose of cyclophosphamide. Use of cyclophosphamide during pregnancy and lactation is prohibited.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an inactive prodrug of mycophenolic acid (MPA), which inhibits inosine monophosphate dehydrogenase, lymphocyte proliferation, and both T- and B-cell function. MMF has been widely used to prevent renal allograft rejection. Many case series and small controlled trials have suggested the effectiveness of MMF in treatment of lupus nephritis. A recent randomized, open-label, noninferiority trial supports the notion that MMF appeared to be as effective as intravenous cyclophosphamide in inducing short-term remission of lupus nephritis with a better safety profile (24). The role of MMF in improving long-term outcomes of lupus nephritis remains unknown. An ongoing larger, multicenter, randomized, controlled trial will examine effectiveness of MMF compared to intravenous cyclophosphamide during induction, and MMF compared to azathioprine during the maintenance phase. MMF is a promising addition to the armamentarium of treatment of lupus nephritis, particularly in young women of childbearing potential when there are concerns of infertility. Pregnancy safety data of MMF is limited; thus, it should be avoided during pregnancy and lactation.

Mycophenolate mofetil is generally well tolerated at the dosing range from 500 mg to 1500 mg twice daily. Side effects include gastrointestinal complaints (nausea, bloating, and diarrhea), cytopenias, and increased risk of infections. The gastrointestinal reactions can be minimized with gently escalating dosing of MMF or the use of a preparation that comes in 250 mg capsules.

Leflunomide

Leflunomide is effective in the treatment of rheumatoid arthritis. It inhibits dihydro-orotate dehydrogenase, a key enzyme in de novo pyrimidine synthesis, and thus decreases T- and B-cell proliferation. A few small studies of short duration showed that leflunomide was well tolerated in patients with SLE (25,26). Due to the relative lack of renal toxicity, and mainly hepatic and gastrointestinal metabolism, leflunomide appears to be more favorable than cyclosporine or methotrexate in those with renal impairment. Larger and long-term prospective studies are needed to provide more information on the efficacy and safety of leflunomide in treatment of SLE.

The most common adverse reaction is diarrhea, which is usually transient or improves with dose reduction. Other common side effects include elevation in hepatic enzymes, hypertension, and transient leukopenia. Subacute cutaneous lupus precipitated by leflunomide has been reported (27). Leflunomide is teratogenic. Because the half-life of leflunomide is quite long (~15 days) due to enterohepatic circulation, its use is contraindicated in patients who are pregnant or who plan to have a child. Breastfeeding is not advised while taking leflunomide. Before pregnancy is considered, plasma concentration of its active metabolite (A77 1726) should be <0.2 mg/L on two occasions ≥2 weeks apart. In the event of pregnancy or toxicity, leflunomide can be eliminated by administering 8 g cholestyramine three times daily for 11 days. Therefore, use of leflunomide may not be recommended in young SLE patients of childbearing age.

Hormonal Therapy

Dehydroepiandrosterone (DHEA) is an adrenal steroid with mild androgenic activity that has shown some promise for the treatment of mild-to-moderate SLE disease activity in several clinical trials. Preliminary results from a recent randomized, controlled trial showed that prasterone (DHEA) preserved bone mineral density (BMD) and significantly improved the BMD in women with SLE receiving chronic corticosteroids (28). However, the findings were not considered robust enough for approval by the FDA. This drug is well tolerated, with acne being the most frequent adverse effect. Another hormonal therapy studied in SLE is bromocriptine, a dopamine analog and a selective inhibitor of anterior pituitary secretion of the immune-stimulatory hormone prolactin. Bromocriptine has shown benefit in improving disease activity in SLE patients with and without hyperprolactinemia (29). However, bromocripine therapy remains experimental. Danazol, a weak androgen, has been shown to be effective in the treatment of autoimmune cytopenias, particularly thrombocytopenia and hemolytic anemia (30).

Thalidomide

Much of the controversy associated with the use of thalidomide concerns its well-recognized teratogenicity. Thalidomide is an immunomodulator with anti-angiogenic effects. It is highly effective at dosage ranging from 50 to 400 mg/day for treatment of refractory chronic cutaneous lupus although the precise mechanism remains unclear. There is a high rate (~68%) of relapse off the drug (31). Another common adverse effect is peripheral neuropathy, reported in up to 50% of patients,

although there is a wide range of incidence rates (32). The neuropathy is not felt to be dose related and can be irreversible if the drug is not discontinued or the dose is not reduced promptly. An important complication of thalidomide is deep venous thrombosis, which occurs in up to 30% of patients with malignancy and has also been reported in patients with SLE (33,34).

Intravenous Immunoglobulin

High dose intravenous immunoglobulin (IVIG) has been used in the treatment of hypogammaglobulinemia, refractory thrombocytopenia, and Kawasaki's disease. The mechanisms of action are thought to include the blockade of Fc receptors, complement inhibition, and immunomodulation of T- and B-cell functions. Improvement in thrombocytopenia, arthritis, nephritis, and immunologic parameters have been reported after treatment with IVIG. Because IVIG provides protection against infections in immunodeficient patients, it is a favorable treatment alternative in acutely ill patients with SLE when there is a concern for a commitment infection. IVIG can be administered in the usual dose of 2 g/kg, divided into 2 to 5 daily doses. Common side effects of IVIG include fever, myalgia, arthralgia, and headache. Rarely, aseptic meningitis and thromboembolism can occur. Patients with IgA deficiency will develop serious anaphylactic reactions to IVIG infusion; thus, its use is contraindicated in these patients. Quantitative immunoglobulins should be checked for IgA deficiency prior to the IVIG therapy. Patients with a hypercoagulable state, such as antiphospholipid syndrome, should be cautioned against the use of IVIG therapy due to the increased risk of thromboembolism.

Plasmapheresis

Plasma exchange or plasmapheresis is an effective but costly therapy to rapidly remove circulating autoantibodies and immune complexes. It also comes with the price of heightened risk of infection and anaphylaxis. The most common indications for plasmapheresis in SLE include thrombotic thrombocyptopenic purpura (TTP), catastrophic antiphospholipid syndrome, pulmonary hemorrhage, cryoglobulinemia, and hyperviscosity syndrome. Other life-threatening complications of SLE may also be treated with plasmapheresis if conventional therapy has failed.

Immunoablation with Autologous Stem Cell Transplantation

In severe cases of SLE, cyclophosphamide is the mainstay of therapy with its dose limited by myelosuppression. The rationale behind immunoablation with cyclophasmide followed by stem cell transplantation is to rescue bone marrow of the patient with autologous stem cell transplantation after receiving a high myeloablative dose of cyclophosphamide. In addition, a high dose cyclophosphamide regimen is purported to reset the naive immune response in the bone marrow stem cells by destroying the autoreactive lymphocytes. In the retrospective analysis of 53 patients with refractory SLE who underwent immunoablation and autologous stem cell transplantation, a European group found a remission rate based on a reduction of SLE disease activity index (SLEDAI) to less than 3 in 66% of these patients (35). However, 1-year transplant related mortality was high at 12%. A recent open-label study demonstrated a reduction in disease activity by nonmyeloablative autologous hematopoietic stem cell transplantation in patients with refractory SLE (36). There is a heightened infection and mortality risk associated with immunoablation therapy.

Immunoablation Without Stem Cell Transplantation

High dose cyclophosphamide without stem cell transplantation is another approach that can lead to rapid hematopoietic reconstitution through granulocyte cell stimulating factor (G-CSF) therapy and clinical improvement in patients with refractory SLE. Durable complete remission of SLE has been reported in some patients with treatment-refractory moderate-to-severe disease (37). These studies are not randomized and thus are still preliminary. These approaches require further validation by controlled randomized studies.

Renal Dialysis and Transplantation

The availability of renal dialysis and transplantation has improved survival of patients with SLE. Aside from an increased risk of infection, SLE patients generally do well with dialysis. For those patients who undergo renal transplantation, long-term patient and renal graft survival are similar to those transplant patients without SLE (38). However, the risk for thrombotic complications, such as early graft thrombosis, may be greater in SLE patients, particularly those with positive antiphospholipid antibodies. The outcome of kidney transplantation largely depends on the clinical condition at the time of transplantation. The risk of recurrence of lupus nephritis in the transplanted kidneys ranges between 2% and 30% (39).

NOVEL THERAPIES

Moving away from global immunosuppression by traditional drug therapies for SLE, designed therapeutics of the future provide improved efficacy and lower toxicity

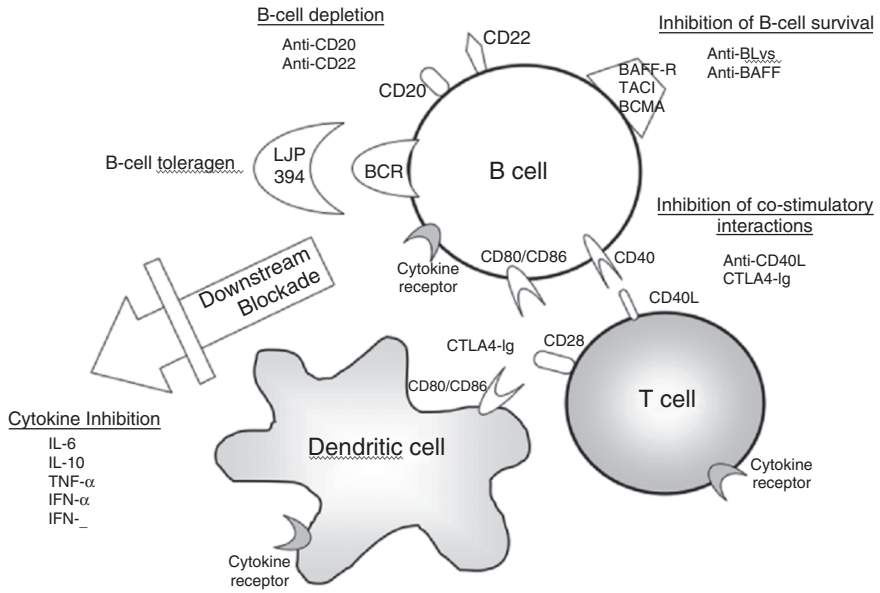

FIGURE 15C-1

Targets for novel therapies in systemic lupus erythematosus. Abbreviations: BCR, B-cell receptor; BAFF-R, B-cell activating factor receptor; TACI, transmembrane activator and cyclophilin ligand interactor; BCMA, B-cell maturation activator; IL, interleukin; TNF, tumor necrosis factor; CTLA4-Ig, cytotoxic T-lymphocyte antigen-4 Ig.

by targeting specific steps in the pathogenesis of SLE while preserving immunocompetence. Many of the novel therapeutics are being developed and studied currently in clinical trials. Some of the promising novel therapies are discussed in the following overview. Figure 15C-1 depicts the specific targets for the novel therapies.

B-Cell Depletion

Rituximab and epratuzumab are two antibody-based agents, which target a specific cell-surface antigen on B cells and result in B-cell depletion. Rituximab is a chimeric monoclonal antibody that binds CD20 on the surface of B cells. It is the first monoclonal antibody therapy approved by the FDA for the treatment of non-Hodgkin's lymphoma. Rituximab is currently approved for use in rheumatoid arthritis that is refractory to anti–tumor necrosis factor (TNF) alpha therapy. In small anecdotal and clinical studies, rituximab has been shown to be beneficial in the treatment of patients with SLE. Various dosing regimens have been used to achieve complete B-cell depletion. A multicenter, randomized, placebo-controlled (phase II/III) trial has begun to study the efficacy of rituximab in patients with moderate-to-severe lupus flares. Another similar phase III trial will study the efficacy of rituximab in the treatment of lupus nephritis in adult patients.

Epratuzumab is a human monoclonal antibody that targets CD22 on B cells. In an open-label phase II trial, epratuzumab showed efficacy in patients with SLE, despite causing only modest B-cell depletion. Two ongoing phase III clinical trials of epratuzumab will validate its safety and efficacy in patients with SLE.

B-Cell–Specific Toleragen

Abetimus sodium (LJP 394) is a tetramer of double-stranded oligonucleotides that can bind to DNA-reactive B cells and induce B-cell anergy or apoptosis, resulting in reduction of circulating double-stranded DNA antibodies. Results of a clinical trial in SLE patients with renal disease showed that abetimus was well tolerated and potentially effective in preventing renal flares in a subset of patients with sustained reductions in anti–double-stranded DNA (anti-dsDNA) antibodies.

Inhibition of B-Cell Survival

B-cell activating factor (BAFF)/B-cell stimulator (BlyS) modulates B-cell survival and maturation, and is a member of the TNF superfamily. Belimumab is a human BAFF monoclonal antibody that recognizes BlyS and reduces B-cell proliferation and differentiation in animal models. A phase II clinical trial failed to demonstrate efficacy. However, in a subset of SLE patients with elevated anti-dsDNA antibodies and low serum C3, there was a significant reduction in disease activity. Thus, a phase III trial may be needed for further validation.

Inhibition of Costimulatory Interactions

Dendritic or antigen presenting cells link innate to adaptive immunity and thus play an important role in

both initiating and maintaining inflammatory and immune responses. These cells also possess costimulatory potential, sufficient to activate naive T cells. Abatacept is a fusion protein of CTLA4-Ig that binds to B7 molecules (CD80/CD86) on dendritic cells and blocks the binding of costimulatory molecules CD80 and CD86 with CD28 on T cells, thereby interrupting signals required for the activation of naive T cells and their downstream effects on B-cell activation. This drug has been approved by the FDA for the treatment of rheumatoid arthritis. Multicenter clinical trials of two available compounds, abatacept and RG2077, are currently under way in SLE.

The interaction of CD40 on B cells and CD40 ligand (CD40L) on T cells is also essential for B-cell activation and antibody production. The therapeutic blockade of the CD40–CD40L interaction has been studied extensively in animal models. However, clinical trials of two such monoclonal antibodies (IDEC-131 and BG9588) against CD40L that interrupts the CD40–CD40L interaction revealed disappointing results. IDEC-131 was shown to be safe but ineffective, whereas BG9588 was associated with a high incidence of thromboembolic events unacceptable for clinical use, despite limited data demonstrating potential efficacy.

Cytokine Blockade

Tumor necrosis factor alpha inhibitors (etanercept, infliximab, and adalimumab) have been very successful in treatment of rheumatoid arthritis and psoriatic arthritis. A small open-label study of infliximab in SLE showed significant improvement in patients with refractory nephritis, despite a parallel increase in levels of anti-dsDNA antibodies (40). However, anti–TNF-alpha therapy has been associated with autoantibody production, specifically anti-dsDNA antibodies, in patients with various autoimmune conditions. Although this autoantibody production may be common in RA patients on this therapy, it is not frequently associated with a lupuslike syndrome. Anti–TNF-alpha therapy has also been associated with several cases of demyelinating disease. Controlled clinical trials are needed to determine the long-term safety and efficacy of this therapy in SLE. The potent anti-inflammatory effects of anti–TNF-alpha therapy may make it suitable for short-term induction therapy in lupus nephritis without the concern of long-term effects on autoantibody production.

Interleukin 10 (IL-10) is a cytokine that may participate in the pathogenesis of SLE. A small open-label study of six SLE patients using murine monoclonal antibody against IL-10 showed improvement of cutaneous and articular symptoms (41). However, all of the patients developed antibodies to the murine monoclonal antibodies.

Interleukin 6 (IL-6) is another proinflammatory cytokine secreted predominantly by macrophages and T cells and has a wide range of biologic activities that mediate immune regulation and inflammation in autoimmune diseases like SLE. It also induces terminal differentiation of B lymphocytes into antibody-forming plasma cells and the differentiation of T lymphocytes into effector cells. IL-6 is highly expressed in lupus nephritis (42). In murine models, IL-6 promotes disease activity whereas IL-6 blockade delays the development of lupus nephritis (43). Tocilizumab is a humanized monoclonal antibody against IL-6 receptor (IL-6R) that suppresses IL-6 signaling mediated by both membranous and soluble IL-6R. An open-label trial of IL-6 blockade is currently under way.

Elevated serum levels of IFN-alpha are found in patients with SLE. IFN-alpha has been associated with B-cell lymphopenia, germinal center differentiation, generation of antibody-forming plasma cells, and activation of dendritic cells, findings relevant to the immunologic characteristics of SLE. The concept of disease pathogenesis by IFN-alpha is supported by the finding of patients with lupuslike illness on IFN-alpha therapy. More recent studies showed a striking IFN-alpha signature on gene expression in peripheral blood mononuclear cells of patients with SLE compared with those of controls (44). IFN-alpha modulation may be another promising therapeutic target for use in the treatment of SLE.

This is an exciting time for drug development in SLE, and several of these novel biologic agents appear to be promising. The complexity of lupus and the wide range of severity in different organ systems will likely translate into the need for a variety of therapeutic options.

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