Chapter 107: Systemic Lupus Erythematosus

Beth H. Resman-Targoff

KEY CONCEPTS

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1. Systemic lupus erythematosus (SLE) is considered a disease primarily of young women, but it can occur in anyone. The prevalence and severity vary with sex, race, ethnicity, and socioeconomic factors.

2. Understanding the etiology of SLE and environmental factors that can initiate or exacerbate the disease may make it possible to avoid those triggers.

3. SLE is an autoimmune disease characterized by the presence of autoantibodies, some of which may play a role in the pathogenesis of the disease. An understanding of disease mechanisms can lead to targeted drug therapy.

4. SLE is a multisystem disease that can involve almost any organ and may present in many different ways. Therapy is determined by the manifestations in each patient, which may change and fluctuate in severity over time.

5. Lifestyle changes can modify risk factors for SLE flares and complications.

6. The overall goals of therapy are to prevent disease flares and involvement of other organs, decrease disease activity and prevent damage, achieve and maintain remission, reduce use of corticosteroids, and improve quality of life, while minimizing adverse drug reactions and costs. Most patients with SLE should receive hydroxychloroquine alone or in combination with other therapy appropriate for the disease manifestations.

7. Pregnancy planning is essential for good outcomes. Pregnancy outcomes are best when the disease is controlled before conception. Drugs used to treat SLE may adversely affect fertility and the fetus.

8. Antiphospholipid antibodies are associated with arterial and venous thrombosis and obstetric complications.

9. Many drugs can induce a lupus-like syndrome. The manifestations and laboratory findings may be different between the traditional drug-induced lupus and that seen with tumor necrosis factor-alpha inhibitors.

10. Since SLE can present in many different ways, it is difficult to design standard response criteria. The development of appropriate criteria is essential for the approval of new drugs.

BEYOND THE BOOK

BEYOND THE BOOK

Lupus Canada: review the Living with Lupus Section (https://lupuscanada.org/living-with-lupus/)

Summarize what you learned about SLE from the Personal Stories section (https://lupuscanada.org/living-with-lupus/personal-stories/).

What questions would you have if you developed lupus?

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease associated with autoantibody production. The term "lupus" (Latin for wolf) was first used in medieval Europe to describe erosive lesions that looked like skin that had been bitten by a wolf. In the 1800s, it was recognized that other organs may be affected and we now know that SLE is a multisystem disease. The common finding in SLE is the production of autoantibodies.[1] This is an exciting time in the management of SLE because a better understanding of disease mechanisms has led to the development of new drugs. In addition, new response criteria are evolving to show efficacy of drugs, even with the background of standard therapy. This led to the first approval of a drug for the treatment of SLE in over 50 years with a new indication 9 years later. Two more drugs were approved for SLE management. Despite these advances, control of this disease remains a challenge. It has a myriad of manifestations and many of the drugs used to treat it are not approved for this indication. As a result, the dosing of many of the drugs considered to be standard-of-care therapy must be personalized.

EPIDEMIOLOGY

1 Systemic lupus erythematosus occurs most frequently in women of reproductive age (15-45 years).[2] This is especially characteristic of the disease in non-White women. The epidemiology of SLE depends on the population studied, method used to define cases, and definition of SLE.[3] These can have profound effects on estimates of incidence and prevalence, disease activity and severity, and mortality. In the US Medicare population, the incidence ranges from 3.7 to 49 per 100,000 person-years and the prevalence is 48 to 366.6 per 100,000 persons. The global incidence ranges from 1.5 to 11 per 100,000 person-years with a prevalence of 13 to 7,713.5 per 100,000 individuals, but there are little data from some parts of the world.[3] Rates are nine times higher in women than in men so the overall population statistics can be misleading.[2] It is affected by ethnicity, which includes genetic, geographic, cultural, social, and other aspects within a group. Rates are higher in non-White than in the White population.[4] It is most common in those of African origin, but is also more common in people of Asian, Arab, and Hispanic background, and Native American people (called First Nations in Canada) than in White people.[4,5] Most people are of mixed race, so race by itself can be difficult to analyze. Non-White patients tend to have an earlier onset, more severe disease, and a higher mortality rate, but it can be difficult to separate out the influence of socioeconomic factors, comorbidities, and access to medical care.[3] The disease tends to be more severe in men and children, and those with onset at a later age (over 50 years) have poor outcomes.[4]

Survival rates have improved with better therapy and earlier diagnosis and initiation of treatment. The standardized mortality ratio for SLE is two to three times higher than in the general population, most related to more cardiovascular and renal disease and infections.[3] Overall SLE survival is 95% at 5 years and 92% at 10 years after diagnosis. This is reduced to about 88% at 10 years with lupus nephritis and even less than that in African American patients with lupus nephritis.[6] The survival rate may be lower in men, but the small number of males in most studies makes this difficult to determine.[4]

ETIOLOGY

2 The exact etiology of SLE is unknown but many factors play a role in the disease. Some are predisposing factors and others are involved in the disease mechanisms. Categories of these elements include genetic influences, epigenetic regulation of gene expression, environmental factors, hormones, and abnormalities in immune cells and cytokines.[7]

The incidence of SLE is increased in affected families. First-degree relatives of patients with SLE are 20 times more likely to develop the disease than those in a general population.[8] Ten percent of patients with SLE have relatives with the disease. The concordance rate is 24% to 69% for identical twins

and 2% to 5% for fraternal twins and other full siblings.[9] The genetic predisposition to SLE results from the interplay between several genes. In rare cases, it results primarily from a single abnormal gene.[7] The major histocompatibility complex (MHC) class II alleles HLA-DR2 and HLA-DR3 are known to be linked to SLE. An increasing number of other gene loci have been associated with the disease.[10] Gene expression is regulated by deoxyribonucleic acid (DNA) methylation and histone modifications. These epigenetic changes can cause alterations that may influence SLE. Interestingly, hydralazine and procainamide, two drugs that may induce lupus, inhibit DNA methylation.[11]

In a genetically susceptible individual, environmental triggers can initiate or exacerbate the disease. The type of trigger may influence specific organ involvement. Cigarette smoke has many toxic combustion byproducts that can react with DNA molecules and increase cell apoptosis, NETosis, or necrosis. Chronic smokers with greater than 10 pack-year smoking history are more likely to have elevated titers of anti-double-stranded DNA (anti-dsDNA) and antiphospholipid antibodies.[12,13] Cigarette smoking damages the skin and worsens disease and quality of life.[14] Ultraviolet light can cause DNA damage and keratinocyte apoptosis with the release of cytokines and stimulation of the immune system causing skin injury and possible systemic flares.[14] Viruses may trigger SLE and the Epstein–Barr virus has been implicated.[10] Other implicated triggers include other infections; air pollution; medications; silica and asbestos; heavy metals such as uranium, cadmium, and lead; and polycyclic aromatic hydrocarbons used to make dyes, plastics, and pesticides.[14-16]

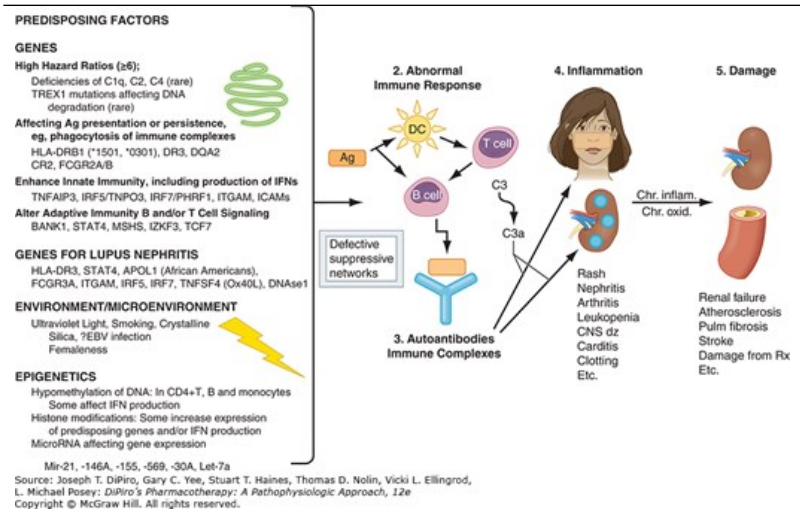
The higher prevalence in women suggests that hormones such as estrogens and progesterones play a role in SLE, but the presence of the X chromosome may also contribute. The TLR7 gene on the X chromosome increases susceptibility to autoimmune disease. The incidence of SLE is increased 14-fold in men with Klinefelter (XXY) syndrome and 2.5-fold in women with XXX syndrome, and decreased in women with Turner (XO) syndrome as compared to normal subjects.[17]

PATHOPHYSIOLOGY

3 Systemic lupus erythematosus is a multisystem disease characterized by disorders of the innate and adaptive immune systems (Fig. 107-1). T- and B-lymphocyte activation and signaling are altered in SLE and there is abnormal clearance of apoptotic debris containing nuclear material which can stimulate immune responses.[10] The number of plasma cells is increased in active SLE and these cells produce autoantibodies, which can cause tissue damage. Neutrophil dysfunction can increase the risk of infection.[18] Antibodies directed at dsDNA are seen in about 60% to 70% of patients with SLE and less than 0.5% of patients without the disease.[10] The titers of anti-dsDNA may fluctuate with disease activity and may predict disease flare. Some autoantibodies may play a role in the pathogenesis of clinical features of SLE; these autoantibodies may target Ro/SSA (antigen Ro/Sjögren syndrome A, ribonucleoprotein complex), La/SSB (antigen La/Sjögren syndrome antigen B, RNA-binding protein), C1q (subunit of the C1 complement component), Sm (nuclear particles), *N*-methyl-D-aspartate (NMDA) receptor (amino acid released by neurons), phospholipids, nucleosomes (from apoptotic cellular debris), and histones (protein core of nucleosomes). The autoantibodies can be present for many years before SLE is clinically apparent and they may be associated with specific organ involvement, such as anti-dsDNA, anti-Ro, anti-La, anti-C1q, and anti-Sm with lupus nephritis, and anti-NMDA associated with central nervous system (CNS) lupus.[10]

FIGURE 107-1

Pathogenesis of systemic lupus erythematosus (SLE). Pathogenesis is related in large part to the production of increased quantities and immunogenic forms of nucleic acids and other self-antigens, which drive autoimmune-inducing activation of innate immunity, autoantibodies, and T-cells. Interactions between genes, environment, and epigenetic changes drive increased autophagy, Ag presentation, neutrophil NETosis, autoantibody formation with increased plasma cells, and production of pathogenic effector T-cells in Th1, Th17, and Tfh subsets, with ineffective regulatory networks. (Ag, antigen; C1q, complement system; C2, C3, C4, complement components; CNS, central nervous system; DC, dendritic cell; EBV, Epstein–Barr virus; HLA, human leukocyte antigen; IFN, interferon UV, ultraviolet.) *(Reproduced, with permission, from Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson J. Harrison's Principles of Internal Medicine 21e; 2022. New York, NY: McGraw Hill; 2019.)*



The exact mechanism of autoantibody tissue destruction is unclear. Immune complexes form when autoantibodies bind to nuclear material and deposit in tissues.[10] They activate the complement cascade, leading to an influx of inflammatory cells and tissue injury.[18] Autoantibodies might also directly react with proteins in tissues. Antibodies to blood cells can cause cytopenias.[10] Antibodies against phospholipids can lead to thrombosis and fetal loss.[19]

T-cell abnormalities contribute to the immune disorders observed in SLE. There are increased T helper cells type 2 and 17 and diminished number and function of T regulatory (Treg) cells. Cytokines, such as tumor necrosis factor-alpha (TNF-α), interferon-gamma, and interleukin-10, produced by activated T-cells can stimulate B-cells.[10]

Cytokines play multiple roles in SLE and contribute to inflammation and tissue damage. Interleukin-10 stimulates B-cell proliferation and autoantibody production in renal cells and may affect skin and joint symptoms.[10] Increased T-cell production of interleukin-17 correlates with disease activity and may contribute to kidney and other tissue damage.[10,18] Interleukin-2 is decreased, which is important for Treg function and restriction of interleukin-17.[18] Plasmacytoid dendritic cells secrete type I interferon, which has a role in the pathogenesis of SLE and may correlate with disease severity. High concentrations of type I interferon are associated with mucocutaneous inflammation and high interferon-γ with nephritis and arthritis.[20] B-lymphocyte stimulator (BLyS), also known as B-cell activating factor of the TNF family (BAFF), increases survival and promotes differentiation of B-cells.[21] Interleukin-6 promotes production of antibodies and may play a role in lupus nephritis.[10] The role of TNF-α in SLE is unclear. It is harmful in some patients and protective in others.[10]

CLINICAL PRESENTATION

Systemic lupus erythematosus is an autoimmune disease that can involve almost any organ and may present in different ways. This can make it difficult to establish a diagnosis and an extensive workup may be needed to determine the full extent of involvement and to exclude other possible etiologies for the manifestations. Fatigue is common, but does not help distinguish SLE from other diseases.[22] SLE should be considered for patients with arthritis, mucocutaneous features, noninfectious fever, leukopenia, hemolytic anemia, serositis, and unexplained proteinuria.[22] Arthritis is experienced by 85% of patients with SLE.[13] SLE may present differently in men and women. In a Swedish study, men were found to have more severe disease with increased propensity for renal disorders and serositis. Skin manifestations were more common in women.[23] Race and ethnicity may also affect the specific manifestations and severity.[13]

Disease manifestations fluctuate with 70% of patients experiencing a relapsing-remitting course.[13] The presence of ANA may be used as a screening test for SLE. Most patients with SLE have these antibodies, but they are not specific for the disease.[24]

An international group of SLE researchers developed and validated criteria for classification of SLE in 2012. These are called the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria and were developed to identify patients with the disease for clinical studies. *They are*

not intended to establish a diagnosis in an individual patient but may help assess the likelihood that a patient has SLE. The widely used American College of Rheumatology (ACR) criteria were developed in 1982 and revised in 1997. The 1997 version was not validated. The SLICC criteria are more clinically relevant and sensitive than the 1997 ACR criteria. When validated, the SLICC criteria had a sensitivity of 97% and specificity of 84% compared to 83% and 93% for the 1997 ACR criteria.[24,25] The number of criteria was expanded from 11 to 17 and, unlike the 1997 ACR criteria, they are divided into clinical and immunologic parameters. The 1997 ACR criteria required 4 of the 11 elements to be present, serially or simultaneously. To satisfy the SLICC criteria, a patient must still meet at least four of the elements, but now these must include at least one clinical and one immunologic criterion or the patient must have biopsy-proven lupus nephritis with positive ANA or anti-dsDNA antibodies.[25] It may be possible to classify patients earlier in their disease course as having SLE with the SLICC criteria. An updated version of the SLICC criteria added weights to the variables.[26] These have both a sensitivity and specificity of 89%, but were not considered superior to the original SLICC criteria.[26] New classification criteria that focus on early diagnosis were developed through a collaboration of the ACR and the European Alliance of Associations for Rheumatology (formerly European League Against Rheumatism) (EULAR).[24] An abbreviated version of the SLICC criteria, with comparison to the 1997 ACR and the EULAR/ACR criteria, is shown in Table 107-1. The EULAR/ACR criteria require an entry criterion of an ANA positive at a titer of at least 1:80. They include seven clinical and three immunology domains with points assigned only for the most heavily weighted element in each domain. The elements could be present on at least one occasion and must not have an alternative explanation. There must be at least one clinical criterion. A score of at least 10 is required for the classification of SLE. These have a sensitivity of 96% and a specificity of 93%. The criteria worked well in all genders, ethnicities, ages, and disease duration.[22] Some may feel that calculation of weights is more cumbersome. Ultimately, the choice of criteria depends on the study investigators and the population studied.[26]

TABLE 107-1

2012 Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus (SLICC) Versus 2019 EULAR/ACR Criteria for SLE

Clinical Criteria-SLICC	Clinical Domains-EULAR/ACR	Weight
1. Nonscarring alopecia 2. Oral OR nasal ulcers 3. Chronic cutaneous lupus/discoid rash 4. Acute/subacute cutaneous lupus/malar rash[a]/photosensitive rash[a] 5. Arthritis/synovitis or tenderness 6. Serositis (pleuritis, pericarditis) 7. Renal (urine protein-to-creatinine ratio [or 24-hour urine protein] representing 500-mg protein/24 hr OR red blood cell casts) 8. Neurologic (seizure, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state) 9. Leukopenia OR lymphopenia[b,c] 10. Thrombocytopenia[b,d] 11. Hemolytic anemia[b]	*Mucocutaneous* Non-scarring alopecia Oral ulcers Subacute cutaneous OR discoid lupus Acute cutaneous lupus *Musculoskeletal* Joint involvement *Serosal* Pleural or pericardial effusion Acute pericarditis *Renal* Proteinuria >0.5 g/24 h Renal biopsy Class II or V nephritis Renal biopsy Class III or IV nephritis *Neuropsychiatric* Delirium Psychosis Seizure *Hematologic* Leukopenia[c] Thrombocytopenia[d] Autoimmune hemolysis *Constitutional* Fever (temperature >101°F [38.3°C])	 2 2 4 6 6 5 6 4 8 10 2 3 5 3 4 4 2
Immunologic Criteria	**Immunology Domains**	**Weight**
1. Antinuclear antibody (ANA) 2. Anti-double-stranded DNA (dsDNA)[e] 3. Anti-Sm[e] 4. Antiphospholipid antibody (lupus anticoagulant, anticardiolipin, anti-β_2-glycoprotein I, false-positive rapid plasma reagin test for syphilis)[e] 5. Low complement (C3, C4, CH50) 6. Direct Coombs test (without hemolytic anemia)	*ANA at titer ≥1:80 required* *SLE-specific antibodies* Anti-dsDNA antibody OR Anti-Smith antibody *Antiphospholipid antibodies* Anticardiolipin antibodies OR Anti-β2GP1 antibodies OR Lupus anticoagulant *Complement proteins* Low C3 OR low C4 Low C3 AND low C4	 6 2 3 4

[a] In the ACR Criteria, malar rash and photosensitivity are two separate criteria.

[b] In the ACR Criteria, hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia count as one criterion.

[c] Leukopenia is defined as <4,000 cells/mm^3 [4×10^9/L]; lymphopenia is <1,000 cells/mm^3 [1×10^9/L].

[d] Thrombocytopenia is defined as <100,000/mm^3 [100×10^9/L].

[e] In the ACR Criteria, anti-dsDNA, anti-Sm, and antiphospholipid antibody count as one criterion.

Data from References 24-26.

The SELENA-SLEDAI Flare Index defines an SLE flare as "changes in the SLEDAI score and/or individual manifestations and/or changes in treatment and/or need for hospitalization and/or changes in PGA."[13] The assessor must consider the increase in disease activity to be clinically significant, sufficient to consider a change or an increase in treatment. A need to increase a prednisone dose or hospitalization for SLE is especially pertinent.[13]

Some skin involvement is seen in up to 93% of patients with SLE and is the first sign of systemic disease in up to 25% of patients.[14] Cutaneous lupus is two to three times more common than SLE.[27] This can be disfiguring and affect a patient's health-related quality of life.[28] Four main types of cutaneous lupus erythematosus have been observed. They may occur with or without SLE and one-third of patients have two or more forms of cutaneous lupus.[29] *Acute cutaneous* lupus erythematosus is typically seen in patients with SLE and is characterized by a photosensitive malar rash over the cheeks and nose with sparing of the nasolabial folds. This is commonly called a "butterfly" rash. The malar rash is present in up to 52% of patients with SLE at the time of diagnosis. There can also be a generalized form with erythematous macules and papules in a photodistributed pattern.[27] *Subacute cutaneous* lupus erythematosus is highly photosensitive and is manifested by annular or papulosquamous lesions that usually heal without scarring.[27] It can be accompanied by musculoskeletal complaints such as arthralgias and arthritis, and proteinuria.[30] About 60% to 80% of these patients are ANA positive and 70% have anti-Ro/SSA autoantibodies. It is often seen in young to middle-aged Caucasian women and is more common than other types of cutaneous lupus erythematosus in patients with drug-induced lupus. About half of patients with subacute cutaneous lupus erythematosus meet the criteria for SLE.[27] Many subtypes of *chronic* cutaneous lupus erythematosus have been identified. The most common is discoid lupus, which is confined to the head and neck in most patients, but can also affect mucosal surfaces. It carries a high risk for scarring alopecia.[27] Discoid lupus progresses to SLE in less than 5% of patients.[30] Discoid lupus is more common in African American patients with a 5.4-fold higher risk than in Caucasian patients.[14,31] Some consider *intermittent* cutaneous lupus erythematosus to be a fourth form of cutaneous lupus.[31]

CLINICAL PRESENTATION: Systemic Lupus Erythematosus

Symptoms

- Fatigue, depression, anxiety, photosensitivity, joint pain, headache, weight loss, nausea/abdominal pain

Signs

- Rash, alopecia, fever, oral and nasal ulcers, arthritis, renal dysfunction, seizure, psychosis, pleuritis, pleural effusion, cardiovascular disease, pericarditis/myocarditis, heart murmur, hypertension, anemia, leukopenia, thrombocytopenia, lymphadenopathy, Raynaud's phenomenon, vasculitis

Diagnostic Tests

- Serology: autoantibodies, antiphospholipid antibodies, complement; inflammatory markers: C-reactive protein, erythrocyte sedimentation rate; blood chemistries; complete blood count; urinalysis; lumbar puncture; renal biopsy

Lupus nephritis is present at the time of SLE diagnosis in about 25% to 50% of adult patients and 60% of patients develop it during the disease course.

It is more common in African American, Hispanic, and Asian patients than in White patients and more prevalent in men than in women. It is also more common in those with juvenile-onset SLE than those with adult-onset lupus.[32] The International Society of Nephrology/Renal Pathology Society devised a classification system for lupus nephritis based on histologic findings: Class I: minimal mesangial; Class II: mesangial proliferative; Class III: focal (less than 50% of glomeruli involved); Class IV: diffuse (50% or more of glomeruli involved); Class V: membranous; and Class VI: advanced sclerosing (at least 90% globally sclerosed glomeruli without residual activity). Patients with nephritis may also have hypertension and accelerated atherosclerosis.[32]

The central, peripheral, and autonomic nervous systems can be involved in SLE. The prevalence of this involvement is around 56.3% with 93.1% CNS and 6.9% peripheral, but depends on the population studied and methods for detecting the involvement.[33] About 50% of neuropsychiatric events appear within the first 3 to 5 years after the onset of SLE. Events can be categorized as ischemic, involving antiphospholipid antibodies, thrombosis, and immune complexes. These are often focal. Others result from an autoimmune-mediated neuroinflammatory pathway and are more likely diffuse in their manifestations. Only about one-third of neuropsychiatric events can be attributed to SLE.[33] Mild nonspecific neuropsychiatric findings such as headache, mood disorders, anxiety, and mild cognitive dysfunction are very common in SLE and are sometimes excluded in estimating prevalence. Findings more indicative of neuropsychiatric lupus include cerebrovascular disease (ischemic stroke and/or transient ischemic attack) and seizures; severe cognitive dysfunction, acute confusional state, peripheral neuropathy, and psychosis; and less commonly chorea, movement disorders, cranial nerve neuropathies, and aseptic meningitis.[33,34] Risk factors include general SLE disease activity, prior neuropsychiatric events, and presence of antiphospholipid antibodies. It is important to assess contributing factors and to rule out other possible etiologies of these manifestations such as medication use, infection, and metabolic abnormalities. The diagnostic approach will vary depending on the clinical presentation and preliminary findings, but can include a thorough history and physical, lumbar puncture with cerebrospinal fluid analysis (mostly to exclude infection), electroencephalogram, serology, complete blood count, blood chemistries, neuropsychological assessment of cognitive function, nerve conduction studies, and magnetic resonance imaging. An attribution algorithm to determine the likelihood of neuropsychiatric SLE was developed by a study group of the Italian Society of Rheumatology. It scores on timing with respect to SLE onset, nonspecific events, confounding factors, and favoring factors.[34]

Cardiovascular disease is a leading cause of death in patients with SLE.[3] Patients with SLE can not only present with pericarditis, myocarditis, and pulmonary arterial hypertension, but they are also at increased risk for accelerated atherosclerosis.[13,32] This is probably related to the chronic inflammation associated with the disease and adverse drug reactions to the drugs (eg, high-dose corticosteroids) used to treat it. Antiphospholipid antibodies and type I interferons may play a role in the pathogenesis.

Hematologic manifestations are often associated with SLE. Autoimmune cytopenias such as thrombocytopenia, leukopenia, and hemolytic anemia may be observed.[13]

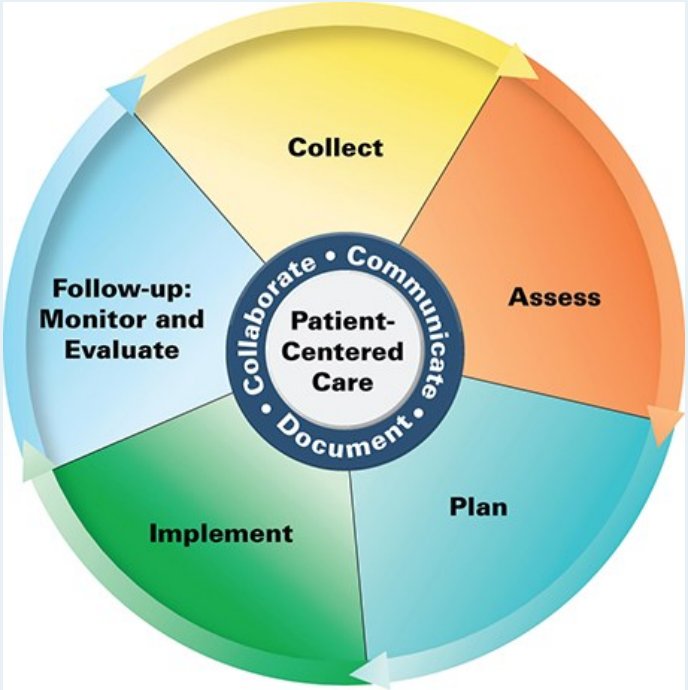
TREATMENT

Desired Outcomes

The goal of therapy should be identified. Ideally, the goal should be remission, but complete remission with the absence of clinical activity and no use of glucocorticoids or immunosuppressive therapy is rare. Achieving low disease activity based on assessment scores with use of antimalarials, prednisone doses no more than 7.5 mg, and well-tolerated immunosuppressive drugs can halt damage and prevent flares.[35] Patients should be involved in treatment decisions, taking into account their preferences, priorities, and pregnancy plans. Therapy should be designed to prevent disease flares and involvement of other organs, decrease disease activity and prevent damage, achieve and maintain remission, reduce use of corticosteroids, and improve quality of life, while minimizing adverse drug reactions and costs. Success in achieving these outcomes depends on disease severity and the type and extent of organ impairment. In general, the prognosis is better if lupus is limited to skin and musculoskeletal findings. The worst prognosis is seen with renal or CNS involvement.[32,33] Hydroxychloroquine is recommended for all patients with SLE and is the cornerstone of therapy.[35] Survival and quality of life have improved with a better understanding of disease mechanisms and new therapeutic options. Mortality is affected by SLE disease activity, cardiovascular risks, and infections.

PATIENT CARE PROCESS

Patient Care Process for Systemic Lupus Erythematosus



Collect

- Patient characteristics (eg, age, race, sex, pregnancy status)
- Patient history (past medical, pregnancies and outcomes, symptoms, family, social—dietary habits, alcohol, and tobacco use)
- Current medications and prior lupus medication use
- Immunization history
- Objective data (see Clinical Presentation box and Table 107-1)
  - BP, heart rate, height, weight, and BMI; other physical examination findings
  - Labs (metabolic panel, Scr, BUN, urinalysis, CBC, ANA, antiphospholipid antibodies, direct Coombs test, other lupus-associated antibodies, complement, inflammatory markers [ESR, CRP])
  - Other diagnostic tests when indicated (eg, ECG, CXR, skin, or kidney biopsy)

Assess

- Presence of cutaneous, renal, neurologic, hematologic, cardiac, or pleural manifestations of lupus
- Evidence of antiphospholipid syndrome (thromboembolic events, miscarriages)
- Current medications that could be associated with drug-induced lupus
- Appropriateness and effectiveness of current lupus regimen (see Figs. 107-2 and 107-3)
- Psychological effects of lupus

Plan*

- Tailored lifestyle modifications (eg, diet, exercise, weight management, protection from sun, smoking cessation, keeping warm if Raynaud's phenomenon occurs)
- Drug therapy regimen including specific medications based on disease manifestations, dose, route, frequency, and duration; specify the continuation and discontinuation of existing therapies (see Figs. 107-2 and 107-3 and Tables 107-2 and 107-3)
- Monitoring parameters including efficacy (eg, skin manifestations, cardiovascular events, thromboembolic events, miscarriages, kidney health, neurologic events), safety (medication-specific adverse drug reactions), and time frame
- Patient education (eg, purpose of treatment, dietary and lifestyle modifications, drug therapy, pregnancy considerations, osteoporosis prevention if taking corticosteroids)
- Self-monitoring of skin and BP—where and how to record results
- Immunizations as needed; consider timing of live vaccines with respect to immunosuppressive drug use and pregnancy
- Referrals to other providers when appropriate (eg, physician, dietician, counselor)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Determine goal attainment based on disease manifestations
- Presence of adverse drug reactions
- Occurrence of cardiovascular events, infections, and development/progression of kidney or other organ impairment
- Patient adherence to treatment plan using multiple sources of information

* ***Collaborate with patient, caregivers, and other healthcare professionals.***

General Approach

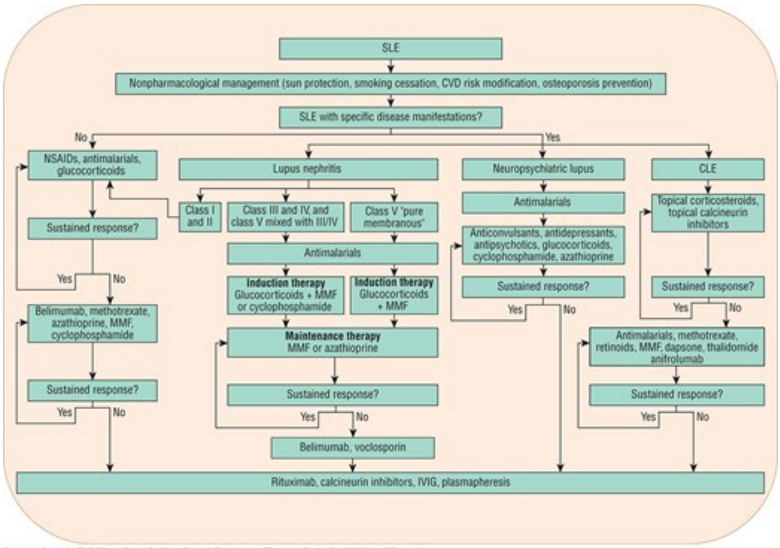
Patients with SLE should be counseled about the importance of lifestyle modifications such as protection from the sun, smoking cessation, exercise, and weight control. The need for immunizations should be assessed with consideration of appropriate timing with respect to immunosuppressive drug use. The effects of disease activity and treatment on pregnancy outcomes should be discussed. Patients should be evaluated and treated for comorbidities such as hypertension, hyperlipidemia, and depression.

Treatment of SLE depends on the patient's symptoms, organ involvement, comorbidities, and other patient-specific factors. Mild symptoms can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) with or without other analgesics.[36] Antimalarial drugs have numerous beneficial effects in SLE and many experts feel that most patients with the disease should always receive one of these drugs.[35] Corticosteroids are used to treat most forms of SLE and up to 57% to 86% of patients receive continuous/chronic therapy.[37] The need for osteoporosis prevention should be assessed.[38] If the above therapy is ineffective or major organs are involved, immunosuppressive or immunomodulatory drugs are added.[36] The specific treatment is determined by the organs involved and severity of the disease (Fig. 107-2).[39] Belimumab for lupus nephritis, anifrolumab, and voclosporin are approved drugs that have not been incorporated into guidelines other than by class. Patients must be educated about the importance of adherence to

treatment. Only 25% to 57% of patients with SLE are adherent to their medications and up to 33% discontinue therapy after 5 years.[40] The expected time for response to lupus medications also needs to be discussed because patients may interpret delayed onset as ineffectiveness.

FIGURE 107-2

Algorithm for the treatment of SLE. (CLE, cutaneous lupus erythematosus; CVD, cardiovascular disease; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus.) *(Reprinted, with permission, from Xiong W, Lahita RG. Pragmatic approaches to therapy for systemic lupus erythematosus. Review. Nat Rev Rheumatol. 2014;10(2):97–107.)*



Nonpharmacologic Therapy

5 Patient perceptions of well-being and quality of life are affected not only by disease activity, but also by social support, coping mechanisms, feelings of helplessness, and abnormal illness-related behaviors.[36] Good social support can improve outcomes, in part by making it easier for patients and their families to navigate the healthcare system and utilize resources.[41] Counseling and support groups may help patients' mental well-being and coping mechanisms, but do not affect SLE disease activity. Aerobic exercise may help decrease patients' risk for cardiovascular events and osteoporosis and may also improve fatigue, depression, anxiety, and sleep disturbances, which are frequently experienced in SLE.[42] Exercise can also help with weight loss. Obesity is associated with worse patient-reported outcomes including quality of life and disease activity.[43]

Since photosensitivity is common in SLE, patients should wear protective clothing and broad-brim hats and use sunscreens with UV-A and UV-B filters to protect themselves from the sun.[30] Since there is systemic absorption of sunscreen ingredients, the FDA recommends use of barrier sunscreens that contain zinc oxide or titanium dioxide as being safer.[44] Sunscreens should be applied in sufficient quantity (about 2 mg/cm^3) 20 to 30 minutes before sun exposure. People with SLE should avoid tanning salons.[30]

Patients should be counseled to stop smoking. Smoking cessation is important, not only because it decreases cardiovascular risk, but because smoking can exacerbate SLE and diminish the effectiveness of antimalarials and belimumab.[12] Smoking damages the skin, resulting in increased cutaneous lupus disease activity and worse quality of life.[14]

Pharmacologic Therapy

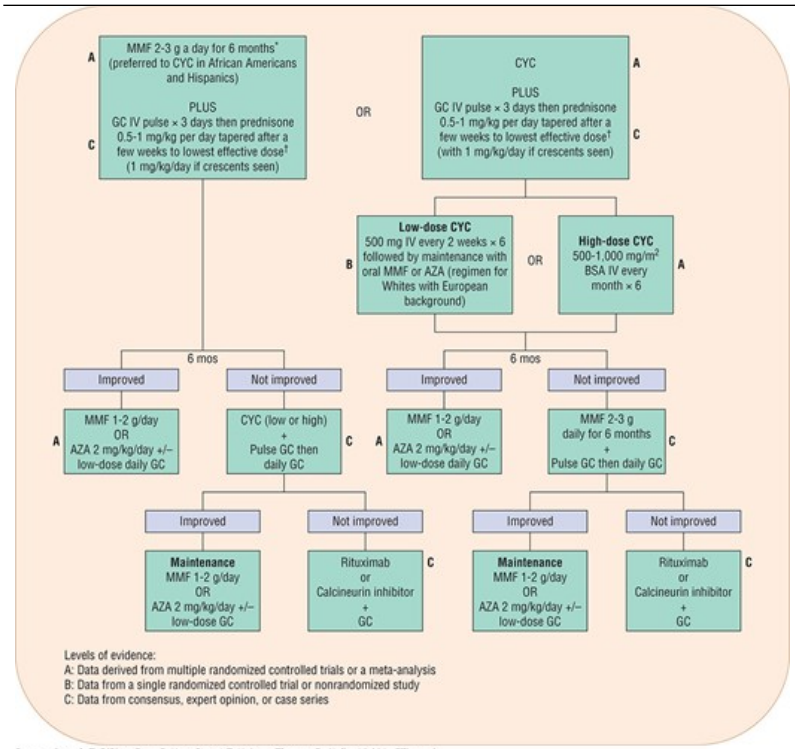
6 Treatment is personalized based on the manifestations of SLE in the patient. It consists of a combination of immunosuppression and symptomatic and supportive therapies. The only drugs approved by the FDA for treatment of SLE are aspirin, prednisone, hydroxychloroquine, belimumab, anifrolumab, and voclosporin. The use of other drugs for SLE, even those considered "standard of care," is considered "off-label" use. For many of

these drugs, the optimal doses and duration of therapy for induction and maintenance of response in SLE have not been determined. Ideally, drugs should be safe, effective, and affordable.[45]

Organization or expert task force treatment recommendations have been published for lupus nephritis, neuropsychiatric lupus, and antiphospholipid antibody carriers.[6,19,46,47] An ACR committee developed guidelines for screening, treatment, and management of lupus nephritis.[6] All patients with nephritis should receive hydroxychloroquine to reduce damage and flares. An angiotensin-converting enzyme inhibitor or angiotensin receptor blocker can reduce proteinuria by about 30% in those with proteinuria of 0.5 g/day or more and delay progression of renal disease. Blood pressure should be maintained at no more than 130/80 mm Hg. Patients with low-density lipoprotein cholesterol greater than 100 mg/dL (2.59 mmol/L) should receive a statin to prevent accelerated atherosclerosis. More specific treatment is based on the type of nephritis. The first two classes, minimal mesangial and mesangial proliferative lupus nephritis, do not usually need immunosuppressive therapy. Focal and diffuse lupus nephritis (Classes III and IV) are treated similarly with aggressive use of glucocorticoids and immunosuppressive therapy. Figure 107-3 shows the induction regimens for these patients and the levels of evidence to support the recommendations. White patients with Western or Southern European backgrounds respond as well to low-dose IV cyclophosphamide ("Euro-Lupus" regimen of 500 mg every 2 weeks for six doses) as to high-dose regimens (500-1,000 mg/m^2 body surface area once a month for six doses) (Level B evidence). African American and Hispanic patients respond less well to IV cyclophosphamide than do White or Asian patients. Those of African or Hispanic origin may respond better to mycophenolate mofetil than to cyclophosphamide.[32] Asian patients require lower doses of mycophenolate mofetil (Level C evidence).[6] Patients with a combination of Class V with III or IV would be treated similar to those with only III or IV. The initial cyclophosphamide or mycophenolate mofetil therapy should be continued for 6 months unless proteinuria or serum creatinine worsens by 50% or more at 3 months (Level A evidence). After 6 months of induction therapy, patients who have improved can be maintained on mycophenolate mofetil or azathioprine, with low doses of corticosteroids if needed. Patients with pure Class V, membranous lupus nephritis, and nephrotic range proteinuria of more than 3 g/day should receive induction therapy with mycophenolate mofetil 2 to 3 g/day with prednisone 0.5 mg/kg/day for 6 months (Level A evidence). Those who improve can be maintained on mycophenolate mofetil 1 to 2 g/day or azathioprine 2 mg/kg/day. Patients who do not respond should be treated with cyclophosphamide 500 to 1,000 mg/m^2/month for 6 months with IV pulse glucocorticoids, followed by prednisone 0.5 to 1 mg/kg/day.[6] Maintenance therapy should be continued for at least 3 to 5 years in complete renal remission and some experts recommend not less than 6 years since the risk of flares decreases after that. Tapering of therapy should start with glucocorticoids, followed by immunosuppressives.[47] Patients with advanced sclerosing lupus nephritis (Class VI) should be considered for renal replacement therapy.[6] EULAR/European Renal Association-European Dialysis and Transplant Association updated their guidelines for management of lupus nephritis in 2019.[47] They recommend a renal biopsy for any patient with SLE and evidence of kidney involvement such as persistent proteinuria of 0.5 g/24 hr or more or a urine protein to creatinine ratio of at least 500 mg/g in morning first void urine (Level 2b, Grade B). The overall recommendations are similar to those of the ACR with some key differences. They recommend the higher initial dose of cyclophosphamide only for patients at high risk for kidney failure. They suggest the addition of a calcineurin inhibitor (especially tacrolimus) to mycophenolate mofetil as alternative initial therapy, especially for patients with nephrotic range proteinuria or the calcineurin inhibitor as monotherapy for pure Class V nephritis. Another difference is after intravenous pulse doses of methylprednisolone (total dose 500-2,500 mg), oral prednisone should be started at a dose of 0.3 to 0.5 mg/kg/day for up to 4 weeks, then tapered to a dose of 7.5 mg/day or less by 3 to 6 months (Level 2b/C). For pure Class V, the prednisone should be started at 20 mg/day and tapered to 5 mg/day or less by 3 months (Level 2b/C).[47] Since proteinuria at 12 months is a good predictor of risk for end-stage renal disease, a goal of therapy is at least a 50% decrease in proteinuria at 6 months with less than 0.5 to 0.7 g/24 hr by 12 months. It may take longer to reach this goal if the patient initially has nephrotic-range proteinuria.[47] They noted the promising results of trials adding belimumab, voclosporin, rituximab, or obinutuzumab to standard-of-care therapy for lupus nephritis.

FIGURE 107-3

American College of Rheumatology guidelines for therapy for Class III/IV lupus nephritis. (AZA, azathioprine; BSA, body surface area; GC, glucocorticoids; MMF, mycophenolate mofetil.) *Preference of MMF over cyclophosphamide (CYC) in patients who desire to preserve fertility. †Recommended background therapies discussed in text. *(Reprinted, with permission, from Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64(6):797–808.)*



A task force of the European League Against Rheumatism (EULAR) developed recommendations for the management of neuropsychiatric lupus. Treatment depends on the manifestations. Symptomatic therapy (eg, anticonvulsants and antidepressants) should be given as needed. More specific treatment depends on whether the problem is determined to be inflammatory or thrombotic or both. If there is inflammation or neurotoxic damage in the presence of generalized SLE activity, glucocorticoids alone or in conjunction with immunosuppressive drugs such as azathioprine or cyclophosphamide should be given (Strong evidence). If the condition does not respond, other treatments such as plasma exchange, IV immunoglobulin, or rituximab can be tried. If the problem is related to moderate-to-high titers of antiphospholipid antibodies and/or thrombosis, anticoagulants and/or inhibitors of platelet aggregation should be used (Sufficient evidence).[46] Recommendations have not significantly changed over the years. Antimalarials may decrease the risk for seizures and brain atrophy through their anti-inflammatory and antithrombotic effects. Results of clinical trials of rituximab, belimumab, anifrolumab, and mycophenolate mofetil have been promising.[33]

Arthralgias and arthritis are common in SLE.[48] Patients often have prolonged morning stiffness and mild-to-moderate joint swelling. Treatment can include low-dose glucocorticoids and antimalarials. If these are inadequate, methotrexate can be added.[48] NSAIDs should be avoided or used with great caution because of their adverse renal effects.[47] For refractory cases, other disease-modifying antirheumatic drugs such as leflunomide, azathioprine, mycophenolate mofetil, or tacrolimus may be tried.[49] Although there is concern about drug-induced lupus with TNF-α inhibitors, successful use of etanercept for resistant lupus arthritis has been reported.[49]

The first step in the management of cutaneous lupus erythematosus is counseling patients to protect themselves from ultraviolet light and stop smoking as described above.[14] Drug treatment is personalized based on the extent and severity of involvement. Recent guidelines from EULAR, the European Dermatology Forum/European Academy of Dermatology and Venereology, and S2k recommend topical therapy as first-line treatment for cutaneous lupus.[35,50] Topical corticosteroids are commonly used, but may not provide adequate clearing of lesions when used alone.[44] The choice of corticosteroid depends on the location of application. Low-potency corticosteroids (eg, fluocinolone acetonide 0.01% and hydrocortisone acetate 1%) should be used on areas with thin skin such as the face and groin, mid-potency (eg, triamcinolone acetonide, and hydrocortisone valerate or butyrate) for trunk and extremities, and high potency (eg, clobetasol propionate and betamethasone dipropionate) for thick-skin areas such as scalp, soles, and palms. Creams or, for more severe disease, ointments, are used on the body, and foams or solutions on the scalp.[44] Intralesional triamcinolone acteonide may be considered, but should not be repeated more often than every 4 to 6 weeks.[50] To avoid the adverse drug reactions of topical corticosteroids, such as skin atrophy, telangiectasias, and steroid-induced dermatitis, the lowest effective potency and duration of therapy should be

used. A common recommendation is to use topical corticosteroids for 2 weeks (not more than a few), then only on weekends for maintenance.[44] Alternatively or in addition, topical calcineurin inhibitors such as pimecrolimus or tacrolimus may be used. Other topical products that have been tried are R-salbutamol, Janus kinase inhibitors, clindamycin, and retinoids.[44] Antimalarials have photoprotective effects and are commonly used as first-line systemic therapy in the management of severe or disseminated cutaneous lupus.[50] If hydroxychloroquine alone is ineffective, quinacrine (mepacrine), if available from compounding pharmacies, may be added.[44] For refractory disease, other systemic drugs such as corticosteroids, methotrexate, mycophenolate mofetil, azathioprine, dapsone, thalidomide, lenalidomide, baricitinib, oral retinoids, or biologics (eg, rituximab, belimumab, or anifrolumab) may be added.[44] Patients should be screened for glucose-6-phosphate dehydrogenase (G6PD) deficiency before getting dapsone.[50] Vitamin D should also be considered. It has some immunomodulating effects and patients with cutaneous lupus may be vitamin D deficient because of their sun avoidance.[50] More studies are needed to support the use of these drugs in patients with cutaneous lupus. The choice of agents may be guided by other organ involvement.

Dosing information for selected drugs is given in Table 107-2. Since most of the drugs used to treat SLE are not FDA-approved for that indication, the doses given are based on other uses for those drugs. Table 107-3 lists adverse drug reactions and drug monitoring parameters. Selected issues concerning the drugs are discussed below.

TABLE 107-2

Dosing of Drugs Used to Treat Systemic Lupus Erythematosus

Drug	Brand Name	Initial or Starting Dose	Usual Range or Maintenance Dose	Special Population Doses	Comments (adverse drug reactions, special populations)
NSAIDs/salicylates	Various drugs				Caution in patients with renal insufficiency, cardiovascular disease, gastrointestinal problems
Glucocorticoids	Deltasone (prednisone), Medrol (prednisolone)	0.3-1 mg/kg/day PO	Prefer ≤5-10 mg/day PO		Dose depends on organ involvement and severity; initial dose may be given for 4-6 weeks, then tapered for maintenance; no standard dose
	Solu-Medrol (methylprednisolone)	100-1,000 mg IV daily × 3			Severe disease; later, dose tapered and changed to PO
Hydroxychloroquine	Plaquenil	400 mg PO daily or 200 mg twice daily	200-400 mg PO daily	Dosing adjustment may be needed with renal or hepatic dysfunction	Dose should not exceed 5 mg/kg/day actual weight to minimize retinopathy risk
Belimumab	Benlysta	10 mg/kg IV every 2 weeks × 3 or	10 mg/kg IV every 4 weeks or	No adjustment for hepatic impairment; no adjustment for renal impairment if CrCl ≥15 mL/min (0.25 mL/s); no studies in pregnant or breastfeeding women	IV infusion over 1 hour; consider premedication to prevent infusion and hypersensitivity reactions; observe for infusion reaction after first two infusions; if switching from IV to SC for SLE, give first SC dose 1-4 weeks after last IV dose; if for nephritis, switch 1-2 weeks after last IV dose
		SLE: 200 mg SC weekly	200 mg SC weekly		

		Lupus nephritis: 400 mg SC weekly × 4			
Voclosporin	Lupkynis	23.7 mg PO every 12 hours	23.7 mg PO every 12 hours	Dose adjustment for renal or hepatic impairment	Do not use if baseline BP >165/105 mm Hg or baseline eGFR ≤45 mL/min/1.73 m^2
Anifrolumab-fnia	Saphnelo	300 mg IV every 4 weeks	300 mg IV every 4 weeks		IV infusion over 30 minutes; risk of hypersensitivity and infusion reactions
Cyclophosphamide	Cytoxan	500-1,000 mg/m^2 BSA IV every month × 6 or 500 mg IV every 2 weeks × 6		Dosing adjustment might be needed with renal dysfunction; low and high doses may have equivalent efficacy in White patients with European background	Infertility in women and men, teratogenicity of concern
Mycophenolate mofetil	Cellcept	2-3 g/day PO divided into 2-3 doses for 6 months	0.5-3 g/day PO	Lower doses may be needed in Asian patients (1.5-2 g/day) than non-Asian patients; may be more effective than cyclophosphamide in Black and Hispanic patients	Contraindicated in pregnancy
	Myfortic (enteric coated mycophenolate sodium)	720 mg PO twice daily	360 mg PO twice daily		
Azathioprine	Imuran	2 mg/kg/day PO	1.5-2 mg/kg/day PO	Pregnant patients ≤2 mg/kg/day	Lower dose if thiopurine methyltransferase (TPMT) deficient
Methotrexate	Trexall, Otrexup, Rasuvo, RediTrex, Xatmep	5-15 mg PO or SC weekly	15-25 mg PO or SC weekly		Decrease toxicity by giving with folic acid
					Avoid use in elderly or if GFR <30 mL/min (0.5 mL/s)
Rituximab	Rituxan	375 mg/m^2 BSA IV		Variable doses have been used	Alternative for patients refractory to other treatments; may be more effective in Black patients

		weekly × 4 or 500-1,000 mg IV on days 1 and 15			

BSA, body surface area; CrCl, creatinine clearance; IV, intravenously; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, orally.

TABLE 107-3

Monitoring of Drugs Used to Treat Systemic Lupus Erythematosus

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
NSAIDs/salicylates	Gastrointestinal bleeding, hepatic toxicity, renal toxicity, hypertension, cardiovascular events, aseptic meningitis	CBC[a], platelets[a], creatinine[a], urinalysis, AST/ALT[a], blood pressure[a]	Antihypertensive effects of calcium channel blockers affected less than other classes
Glucocorticoids, systemic	Osteoporosis, cataracts, glaucoma, hyperglycemia/diabetes, hypertension, dyslipidemia, thinning of the skin, weight gain, fat redistribution, sleep/mood disturbances	Blood pressure[a], serum glucose[a], lipid panel[a], bone densitometry, ophthalmic examinations	Patients should receive osteoporosis preventive therapy; high doses of systemic corticosteroids are associated with infections, myopathy, psychological disturbances, osteonecrosis, and stroke
Glucocorticoids, topical	Skin atrophy, telangiectasias, dermatitis	Skin appearance	Avoid prolonged use, especially of high-potency steroids
Hydroxychloroquine	Retinal toxicity, gastric intolerance, rash, skin hyperpigmentation	Funduscopic and automated visual field examinations, consider spectral domain optical coherence tomography, multifocal electroretinogram, or fundus autofluorescence (frequency depends on risk), CBC, AST/ALT, albumin, chemistry panel, creatinine	Risk for retinal toxicity increased with doses >5 mg/kg/day actual body weight, more than 5 years therapy, renal or macular disease, or concurrent tamoxifen use
Belimumab	Infusion reactions, hypersensitivity, nausea, diarrhea, fever, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine	Monitor for serious infections, hypersensitivity/infusion reactions, worsening depression, mood changes, or suicidal thoughts	No live vaccines 30 days before or during belimumab therapy; consider premedication with antipyretic and antihistamine
Voclosporin	Infections, lymphomas, other malignancies; QT interval increase, hyperkalemia, neurotoxicity	Monitor for infections, BP, eGFR, potassium, electrocardiogram	Limit sun exposure; reduce dose if given with CYP3A4 inhibitors
Anifrolumab-fnia	Upper respiratory tract infections, nasopharyngitis,	Monitor for infections	Insufficient data on use during pregnancy or lactation

	herpes zoster, anaphylaxis, angioedema		
Cyclophosphamide	Myelosuppression, opportunistic infections, hemorrhagic cystitis, bladder malignancy, infertility	CBC[b], platelets[b], creatinine, AST/ALT, urinalysis[b], urine cytology[a], PAP test[a]	Greater risk for cystitis with oral form than IV; decrease with hydration and mesna
Mycophenolate mofetil	Myelosuppression, nausea, vomiting, diarrhea	CBC[c], platelets[c], creatinine, chemistry panel, AST/ALT, chest x-ray	Gastrointestinal side effects may limit use and compliance; these symptoms may be less with an enteric-coated form
Azathioprine	Myelosuppression, hepatotoxicity	CBC[c,d], platelets[c,d], creatinine[e], AST/ALT[c,f], chemistry panel[e], albumin, TPMT assay, PAP test	Test thiopurine methyltransferase (TPMT) before starting; toxicity greatly increased if deficient
Methotrexate	Hepatic, hematologic, pulmonary toxicity, stomatitis	CBC[c,g], platelets[c,g], creatinine[c,g], AST/ALT[c,g], albumin[c,g], bilirubin, chemistry panel[h], alkaline phosphatase[c], chest x-ray	Check hepatitis B and C serologies before starting if at risk
Rituximab	Infusion reactions, infections, neutropenia, mucocutaneous reactions, fever, fatigue, progressive multifocal leukoencephalopathy	CBC[i], platelets[i], creatinine, vital signs, human antichimeric antibody (HACA) titers	Consider pretreatment with acetaminophen, diphenhydramine, corticosteroid to decrease infusion reactions

[a]52 weeks

[b]4 weeks

[c]12 weeks

[d]Every 1-2 weeks after dose change

Monitoring parameters should be checked at baseline and at interval noted:

[e]26 weeks

[f]Every 2 weeks after dose change

[g]2-4 weeks during 3 months after dose change

[h]8 weeks

[i]8-16 weeks

Data from References 51,52,68,98.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as first-line treatment for arthritis, musculoskeletal complaints, fever, and serositis.[39] They

are not disease-modifying, but are used to relieve symptoms.[51] Low-dose aspirin is used in patients with antiphospholipid antibodies.[19] One concern with NSAIDs is that they can decrease renal function which can complicate evaluation of lupus nephritis. They have the potential to increase cardiac events in patients who already are at elevated risk. Other adverse drug reactions include hepatotoxicity, gastrointestinal (GI) bleeding, and aseptic meningitis.[39]

Corticosteroids

Corticosteroids, as monotherapy or as adjuncts to other treatments, can control flares and maintain low disease activity in SLE. Their effects have a rapid onset, whereas other therapies may take months or over a year to achieve their maximum benefits. The corticosteroids can be used topically or systemically.

Although corticosteroids have been used to manage SLE since the 1950s, optimal doses, duration of therapy, and tapering regimens have not been determined. High doses given in a pulse IV administration regimen are generally free of serious adverse drug reactions and rapidly produce strong immunomodulatory effects. They are used to treat flares and quickly reduce inflammation. Doses should slowly be tapered down to the lowest effective dose.[52] Corticosteroids are the foundation for treatment of most forms of SLE, but high-dose oral corticosteroid use is associated with increased lupus organ damage accrual, infection, and death. Oral maintenance doses should be kept as low as possible with pulse methylprednisolone doses used for disease flares and in combination with other drugs that are steroid-sparing.[52]

Common adverse drug reactions to low (prednisone less than 7.5 mg/day)-to-moderate (7.5-30 mg/day) doses are shown in Table 107-3. Although higher doses may be divided, single morning doses may be associated with fewer adverse drug reactions and less adrenal suppression. Chronic use of any dose is associated with cardiovascular complications, psychological disturbances, glaucoma, cataracts, hyperglycemia, weight gain, avascular necrosis of bone, and osteoporosis.[37] Corticosteroids decrease absorption of vitamin D and increase catabolism of 25(OH) vitamin D and $1,25(OH)_2$ vitamin D. According to the 2017 ACR guideline for the prevention and treatment of glucocorticoid-induced osteoporosis, all patients taking prednisone at a dose of 2.5 mg daily or more for at least 3 months should optimize calcium and vitamin D intake in addition to lifestyle changes such as balanced diet, maintenance of recommended weight, smoking cessation, and limiting alcohol intake. Additional treatment is based on Fracture Risk Assessment Tool (FRAX) score (Conditional recommendation-limited data).[38] To avoid adrenal insufficiency, patients on chronic corticosteroid therapy should not have treatment stopped abruptly. Some clinicians will increase doses during times of stress such as surgery because of concerns regarding adrenal insufficiency and hypotension, but this can increase the risk of hyperglycemia, postoperative infections, and impaired wound healing. These supraphysiologic doses may not be necessary for minor/intermediate intensity surgeries such as joint arthroplasty in adults taking less than 20 mg/day prednisone.[53] For major surgeries, patients may be given hydrocortisone 50 mg IV intraoperatively and every 8 hours after surgery until the patient's usual oral dose can be resumed.[54] Prolonged use of topical corticosteroids can lead to atrophy of the skin and telangiectasias (small dilated blood vessels).[44]

Antimalarials

The antimalarials, such as chloroquine and hydroxychloroquine, have long been used in rheumatology practice. Hydroxychloroquine has fewer adverse reactions and is the preferred drug. In the past, hydroxychloroquine was primarily used for skin and joint manifestations of SLE, but most experts believe that all patients, including pregnant and lactating women, with SLE should receive hydroxychloroquine. There is high-quality evidence that shows it prevents lupus flares and improves long-term survival; moderate-quality evidence that it protects against bone mass loss, and has protective effects against thrombosis and irreversible organ damage.[55] It has a beneficial effect on lipids and fasting blood glucose, decreases the risk of thrombosis in patients with antiphospholipid antibodies, and decreases infections. It can allow corticosteroid doses to be decreased.[52] When given to patients with some findings consistent with SLE, it can delay the time for them to fully meet criteria for the disease. Patients receiving hydroxychloroquine often have disease flares when the drug is discontinued.[56]

Hydroxychloroquine has anti-inflammatory, immunomodulatory, and antithrombotic effects. It reduces concentrations of inflammatory cytokines such as interleukins 1, 2, 6, 17, and 22, interferon alpha and gamma, and TNF-α. It alters antigen presentation and T-cell proliferative responses. Its key activity may be decreasing activation of toll-like receptors, which are important in innate immunity and autoimmune diseases. It reduces platelet aggregation and thrombosis.[56] Finally, it may reduce cardiovascular risk factors such as hyperlipidemia and diabetes mellitus and improve survival.[52] The LUMINA (LUpus in MInorities, NAture vs nurture) multiethnic study found that hydroxychloroquine has a protective effect on survival. It may delay

the development of renal damage and the occurrence of integument damage (severe skin damage including scarring, ulcers, and scarring alopecia).[55,56]

Although some studies showed reduced disease activity and flares with hydroxychloroquine whole blood concentrations over 1,000 ng/mL (µg/L; 2,980 nmol/L), other studies where doses were adjusted to achieve that concentration did not show better disease control. Studies of cutaneous lupus showed good improvement at 750 ng/mL (µg/L; 2230 nmol/L), while others considered 500 ng/mL (µg/L; 1490 nmol/L) to be the minimum therapeutic concentration. Hydroxychloroquine concentration monitoring may be used as a measure of adherence to therapy.[57] The drug is primarily eliminated by the kidneys and has a long tissue half-life of about 40 to 50 days. Low concentrations may therefore be an indicator of consistent nonadherence or abnormal metabolism.[57] It may take 2 to 8 weeks to see the therapeutic effects of hydroxychloroquine and up to 3 to 6 months for maximum clinical efficacy.[57]

Adverse drug reactions with hydroxychloroquine are usually mild. Most common are GI and skin reactions and they usually improve with dose reduction.[56] Prolongation of the QT interval on electrocardiograms is rare at the doses used for SLE.[52] The main concern is retinal toxicity, but the incidence is low and may be less than that seen with chloroquine. The cumulative risk depends on the duration of therapy and is less than 1% in patients receiving the drug at recommended doses for 5 years, less than 2% up to 10 years, and less than 5% after 20 years.[58] Major risk factors are the duration of use over 5 years, daily doses more than 5 mg/kg actual body weight, concurrent use of tamoxifen, or preexisting kidney dysfunction or macular disease. Advanced retinal damage has a characteristic bull's-eye appearance on funduscopic examination and is irreversible, but this should not be seen with appropriate monitoring. Patterns of damage are different in East Asian patients. Early recognition of damage may minimize vision loss. The current ACR/American Academy of Dermatology/American Academy of Ophthalmology 2020 monitoring recommendations are to have baseline screening tests within the first few months, including retinal examination with optical coherence tomography and automated visual fields. After 5 years, patients should begin annual examinations unless the patient is considered to be at high risk, in which case yearly testing would begin earlier. If there are suspicious findings, other tests such as multifocal electroretinogram and fundus autofluorescence should be performed. If toxicity is suspected, the drug should be discontinued or the patient counseled about risks of blindness versus disease flares.[58]

Biologic Agents

Since autoantibody formation is an important feature of SLE, B-cells are a logical target for SLE therapy. B-lymphocyte stimulator (BLyS) is a cytokine that is important for B-cell survival, maturation, and differentiation. Belimumab is a fully human IgG1-λ monoclonal antibody that binds to soluble BLyS, which prevents BLyS from binding to receptors on B-cells and promotes apoptosis of B-lymphocytes. Belimumab is FDA-approved for treatment of autoantibody-positive active SLE in addition to standard therapy. It was the first drug approved by the FDA in over 50 years for management of SLE.[21] Approval of intravenous belimumab was based on two international phase III trials: BLISS-76, conducted primarily in Europe and North America, and BLISS-52, which was carried out in Eastern Europe, South America, and the Asia-Pacific region. These trials had strict entry criteria and used the new SLE Responder Index (SRI) assessment criteria. For both studies, the primary efficacy endpoint was the SRI at 52 weeks. Entry requirements included positive ANA or anti-dsDNA, and active SLE (SELENA-SLEDAI [measure of disease activity] score of 6 or greater) while receiving standard treatment (prednisone, NSAIDs, antimalarials, and/or immunosuppressive drugs [but not IV cyclophosphamide or other biologics]). Patients had to be on stable therapy for at least 30 days. The most common organ systems involved were musculoskeletal and mucocutaneous. Patients with severe active lupus nephritis or CNS lupus were excluded. Patients received belimumab 1 mg/kg, 10 mg/kg, or placebo by IV infusion every 2 weeks for two doses, then every 4 weeks, in addition to their standard therapy. There were restrictions on concomitant medications, and those became stricter as the studies progressed. The response rate was significantly higher in the group receiving belimumab 10 mg/kg as compared to placebo in both studies. Patients receiving belimumab also had greater improvement in health-related quality of life and fatigue. Patients of African descent did not benefit from belimumab.[21] However, later studies such as the EMBRACE trial, reported favorable responses to belimumab in all racial and ethnic groups.[21,59] Open-label trials showed extended benefit to 10 years. The 52-week BLISS-SC trial showed the safety and efficacy of subcutaneously administered belimumab and patients preferred the convenience of self-administration.[21] Belimumab was approved by the FDA for treatment of lupus nephritis based on the 2-year BLISS-LN study. This international double-blind study compared belimumab to placebo added to standard therapy. Significantly more patients in the belimumab group achieved the primary efficacy renal response of urinary protein to creatinine ratio of 0.7 or less, an eGFR no worse than 20% below the pre-flare value or an eGFR of at least 60 mL/min/1.73 m^2, and no rescue therapy use.[60]

Rituximab is a chimeric monoclonal antibody directed at the CD20 antigen on B-cells.[61] Although many case reports and open-label trials have reported

beneficial effects of rituximab in SLE, randomized, placebo-controlled trials of rituximab have not demonstrated efficacy in SLE. The largest of these trials was the EXPLORER (Efficacy and Safety of Rituximab in Moderately-to-Severely Active Systemic Lupus Erythematosus) trial, which evaluated patients with extrarenal involvement treated with rituximab and immunosuppressive drugs and the LUNAR (LUpus Nephritis Assessment with Rituximab) trial that examined use of rituximab with mycophenolate mofetil and corticosteroids in patients with lupus nephritis.[61] The negative trial results could be related to the short duration of the trials, overuse of corticosteroids, high background immunosuppressive regimens, or the choice of endpoints.[45] Further improvement was observed in the second year of therapy. Exploratory analyses of specific patient subgroups or different response criteria suggested some benefit. In a small study of rituximab given shortly after diagnosis, followed by mycophenolate mofetil and hydroxychloroquine, about 90% of the patients with lupus nephritis achieved a complete or partial remission without oral corticosteroids.[45] It may serve as an alternative therapy in refractory lupus nephritis, severe hematological lupus, and some CNS manifestations of the disease and is included in some guidelines.[33,45] It may also prove useful for maintenance therapy, as a steroid-sparing agent, or when preservation of fertility is desired.[61]

Other drugs targeting B-cells are being investigated in SLE. Examples of these are other anti-CD20 monoclonal antibodies such as ofatumumab, ocrelizumab, and obinutuzumab.[45] Other biologic agents have been tried in SLE with varying degrees of success, often failing in large phase III clinical trials.[45] In general, biologic drugs should not be combined. However, depletion of B-cells is associated with an increase in BAFF/BLyS and some ongoing trials use rituximab in sequence or together with belimumab to treat SLE.[45]

Anifrolumab is a fully human IgG1κ monoclonal antibody that targets type I interferons through binding the type I interferon receptor subunit 1.[51] It was studied in the MUSE, TULIP-1, and TULIP-2 trials. Patients had moderate-to-severe SLE while taking one or more standard therapies including oral corticosteroids, antimalarials, and immunosuppressives. Those with severe lupus nephritis or neuropsychiatric lupus were excluded. Most of the subjects had active skin and joint disease. After the SRI endpoint was not reached in TULIP-1, the protocol for TULIP-2 was changed to use a new endpoint—BICLA, a composite of BILAG, SLEDAI-2K, and Physician Global Assessment. Anifrolumab decreased flares and disease activity by week 8 to 12 and was steroid-sparing. Severe skin disease improved by CLASI scores. Patients with overexpression of type I interferon-regulated genes (high interferon gene signature) may respond better to anifrolumab.[51]

As discussed later, TNF-α inhibitors may induce lupus. However, good results have been observed with etanercept as long-term treatment of refractory lupus arthritis.[49]

Immunosuppressive Drugs

Cyclophosphamide has long been used to treat severe or refractory organ involvement in SLE such as lupus nephritis, neuropsychiatric lupus, vasculitis, and hematologic disease.[52] Its role in therapy is being redefined because of the availability of newer drugs, as discussed elsewhere in this chapter. Response rate and dosing requirements may vary with patient race.[52]

Cyclophosphamide is an alkylating agent that causes cross-linkage of DNA and inhibits B- and T-cell proliferation and antibody production.[48] The drug can potentially cause hemorrhagic cystitis and bladder cancer due to acrolein, a metabolite of the drug that concentrates in the bladder.[62] The risk is greater with oral administration, higher cumulative doses, and in smokers. Intermittent pulse IV doses, hydration, and frequent voiding may decrease the risk of these adverse drug reactions. With oral administration, patients are advised to take the drug in the morning and to drink fluids for several hours. Adherence is not good with this regimen. With IV administration, IV fluids are begun before administration of the cyclophosphamide and continued for several hours after. Patients are encouraged to maintain oral hydration for 72 hours. Another method to decrease bladder toxicity is to give sodium-2-mercaptoethane sulfonate (mesna), which binds acrolein and prevents its harmful effects on the bladder. Although mesna is sometimes used with high-dose cyclophosphamide, it is only FDA-approved for use with ifosfamide. Mesna used with daily oral cyclophosphamide is expensive and inconvenient based on available dosage forms. The recommended mesna regimen with IV pulse doses of cyclophosphamide is to give IV doses, each equivalent to 20% of the cyclophosphamide dose, 15 to 30 minutes before the cyclophosphamide, then 4 and 8 hours after. Since oral mesna is about 50% bioavailable, the 4- and 8-hour mesna doses after cyclophosphamide may be given orally, each in doses equivalent to 40% of the administered dose of cyclophosphamide.[62] In practice, a variety of mesna regimens are used. The effectiveness of mesna for uroprotection in patients receiving cyclophosphamide for rheumatologic diseases has been questioned.

Mycophenolic acid (MPA) reversibly inhibits the enzyme inosine 5-monophosphate dehydrogenase (IMPDH), which is important for de novo synthesis of purine (guanosine) nucleotides. This inhibits lymphocyte proliferation, chemotaxis, and antibody production. Genetic polymorphisms of the IMPDH

proteins may influence the effects of MPA, but routine testing is not recommended at this time.[47] The drug also has other immunomodulating effects such as induction of activated T-cell apoptosis, inhibition of adhesion molecule expression, and fibroblast proliferation.[48]

Mycophenolate mofetil is about 94% absorbed and is hydrolyzed to MPA, its active form. MPA is bound to albumin, so unbound drug concentrations can be affected by changes in albumin. MPA is glucuronidated in the liver to an inactive metabolite, mycophenolic glucuronide. The metabolite is excreted in the urine but also undergoes enterohepatic recycling, with conversion back to the active form. Some studies have reported better lupus nephritis response with higher trough MPA concentrations or 12-hour MPA areas under the curve, but optimal values have not been determined and these did not correlate with toxicity, so measurement is not common practice.[57] Larger trials may support the benefits of individualized dosing based on therapeutic drug monitoring.[32]

Mycophenolate mofetil has been extensively studied in the treatment of lupus nephritis. It is at least as effective as cyclophosphamide for induction therapy and as effective as azathioprine for maintenance treatment.[32] The Aspreva Lupus Management Study (ALMS) was an international study of lupus nephritis. The 6-month induction phase showed mycophenolate mofetil to be equivalent in efficacy in White and Asian patients to monthly IV pulse doses of cyclophosphamide.[32] Black and Hispanic patients responded better to mycophenolate. The response to therapy at 6 months correlated with the baseline complement C4 concentration, time since diagnosis of lupus nephritis, and eGFR. Normalization of complement C3 and/or C4 and reduction in proteinuria of at least 25% at 8 weeks also predicted renal improvement at 6 months.[63] Responders at 6 months entered a 36-month maintenance phase in which mycophenolate mofetil was superior to azathioprine in maintaining renal response and preventing disease relapse. Although adverse drug reactions occurred in more than 97% of patients in both groups, more patients receiving azathioprine withdrew from the study due to adverse drug reactions than those receiving mycophenolate mofetil.[64] The MAINTAIN trial did not find a difference in the rate of renal flare with mycophenolate mofetil compared to azathioprine 5 and 10 years after induction with low-dose IV cyclophosphamide. The difference in these results compared to the ALMS trial may be related to the difference in induction therapy, selection of patients for the maintenance phase, and in populations studied. The MAINTAIN trial studied predominantly (83%) White European patients, whereas the larger ALMS trial included a more racially diverse population (56% non-Caucasian patients). The MAINTAIN trial did find a correlation between achieving a proteinuria value of less than 0.5 g/day at 12 months and good long-term renal outcome.[65] Mycophenolate mofetil is preferred for maintenance therapy if it is used for induction.[47]

Mycophenolate mofetil may also be useful for nonrenal manifestations of SLE such as cutaneous lupus, hemolytic anemia, thrombocytopenia, vasculitis, and musculoskeletal and neuropsychiatric diseases, and can be steroid-sparing.[52]

The most common adverse drug reactions with mycophenolate mofetil are gastrointestinal complaints and infections.[52] These may be severe enough to require discontinuation of therapy. The adverse drug reactions may be managed with a reduction in dose.[48] Use of an enteric-coated form of mycophenolate sodium may decrease gastrointestinal symptoms. Hematologic effects ranging from cytopenias to red cell aplasia may also be seen. Teratogenicity has been reported with mycophenolate mofetil and it is contraindicated in pregnancy.[66]

Azathioprine is a purine analog that is metabolized to mercaptopurine. It inhibits nucleic acid synthesis and affects cellular and humoral immune functions.[39,67] Mercaptopurine is inactivated by thiopurine methyltransferase (TPMT). Patients should have TPMT testing before receiving azathioprine.[65] If the activity of that enzyme is low, patients may experience more severe toxicity. Myelosuppression and gastrointestinal adverse effects correlate with TPMT polymorphism, but hepatotoxicity may not. Other metabolic pathways are also involved in the elimination of azathioprine.[67] The metabolism of azathioprine and mercaptopurine is inhibited by allopurinol and febuxostat. If the combination of these drugs is to be used, a reduction in azathioprine dose is required.[68] Azathioprine is less effective than cyclophosphamide for induction therapy in lupus nephritis, but it can be an alternative to mycophenolate mofetil for maintenance treatment.[32] Azathioprine may also be used for SLE-related arthritis, serositis, and mucocutaneous manifestations. It has steroid-sparing effects, allowing the use of lower doses of corticosteroids.[39]

Methotrexate is an inhibitor of dihydrofolate reductase, which is needed for DNA synthesis and cell proliferation.[36] Its toxicities are reduced by folic acid administration. It is dosed once weekly in the management of SLE. It is used for musculoskeletal, skin, and serosal disease and as a steroid-sparing drug.[52]

Calcineurin is a serine-threonine phosphatase that stimulates hyperactivation of T-cells, resulting in cytokine release and costimulation of B-cells with release of autoantibodies. Calcineurin also adversely affects podocytes which are important for maintaining the glomerular filtration barrier in the

kidneys. Calcineurin inhibitors decrease inflammation and proteinuria.[2] Voclosporin, a calcineurin inhibitor, was the first oral drug approved by the FDA for the treatment of active lupus nephritis. Voclosporin is an analog of cyclosporine with much higher immunosuppressive effect. Voclosporin is used in combination with mycophenolate mofetil and corticosteroids. Approval was based on the randomized double-blind AURORA 1 trial that compared voclosporin to placebo added to mycophenolate mofetil and rapidly tapered oral corticosteroids in patients with active class III to V lupus nephritis. The primary endpoint was complete renal response defined as urinary protein to creatinine ratio of 0.5 mg/mg or less, with an eGFR of at least 60 mL/min/1.73 m^2 (or no decrease from baseline of more than 20%), use of no more than 10 mg prednisone equivalent per day, and no rescue medication at 52 weeks. This response was achieved in 40.8% of those receiving voclosporin compared to 22.5% on placebo.[69] The interim analysis for Aurora 2, a 104-week extension study of AURORA 1, showed that patients receiving voclosporin maintained reductions in proteinuria with no change in mean eGFR at 30 months of treatment.[70]

Other calcineurin inhibitors have also been used to treat lupus nephritis and may be a treatment option for women who are pregnant or breastfeeding.[2] Tacrolimus has a different structure with higher immunosuppressive effects and less nephrotoxicity than cyclosporine. Most of the tacrolimus studies have been conducted in Asian populations. It has been used as monotherapy for induction and maintenance therapy. It has also been used in combination with mycophenolate mofetil for induction therapy for patients with nephrotic range proteinuria.[2] The most recent European recommendations for treatment of lupus nephritis include a calcineurin inhibitor (especially tacrolimus) as alternative monotherapy for class V nephritis (Level 2b/B) or in combination with mycophenolate for patients with nephrotic range proteinuria (Level 1b/B).[47]

Janus-kinase inhibitors such as tofacitinib and baricitinib are being studied for musculoskeletal and cutaneous lupus with some success.[45] Numerous other immunosuppressive drugs have been used in SLE, especially in patients who have contraindications to the agents already discussed or who cannot tolerate them, or those whose disease is refractory to conventional treatment.

Alternative Treatments

Patients receiving conventional treatment for SLE frequently feel they have unmet needs. Often these are psychosocial and may include anxiety or depression. These needs can lead patients to try alternative therapies. Clinicians should have an open dialogue with patients about these therapies so that patients will report them. This allows practitioners to monitor for interactions with other treatments and to guide patients to therapies with greater potential for benefit and less for harm.[71]

Complementary and alternative medicine includes health systems, products, and practices that are outside the realm of conventional medicine. In general, these have not been evaluated in randomized controlled trials involving SLE patients.[71]

Concentrations of dehydroepiandrosterone (DHEA), a weak adrenal androgen, are typically decreased in SLE. DHEA supplementation may offer some limited benefit for patients' assessment of disease activity, steroid effects on bone mineral density, and time to flares in SLE.[71] Effects on oral ulcers and alopecia have also been studied.[72]

Vitamin D concentrations are decreased in SLE, especially in patients with high disease activity and those with darker skin pigmentation (eg, African American patients). A contributing factor to the deficiency is that patients are instructed to protect themselves from sunlight because of the photosensitivity that accompanies SLE.[73] Another factor may be polymorphisms in the gene involved in vitamin D degradation. Vitamin D deficiency is associated with high concentrations of inflammatory cytokines. Deficiencies not only affect bone health, but low vitamin D concentrations may also be associated with greater SLE disease activity, insulin resistance, and fatigue.[74] Low concentrations also correlate with increased cardiovascular risk factors such as hypertension and hyperlipidemia. B- and T-lymphocytes, dendritic cells, macrophages, and neutrophils have vitamin D receptors, which suggests a role for vitamin D in both innate and adaptive immune processes.[74] Baseline 25(OH) vitamin D concentrations should be checked with a current goal of at least 30 ng/mL (75 nmol/L).[50] Some suggest a daily intake of vitamin D3 of 30 to 50 µg (1,000-2,000 IU). This is especially important for patients taking corticosteroids.

Special Populations

Pregnancy and Contraception

7 Pregnancy planning with assessment of risk factors is key for achieving good outcomes for women with SLE and healthy babies. ACR issued recommendations for reproductive health in patients with rheumatic and musculoskeletal diseases.[75] The guideline summarizes information about pregnancy, contraception, assisted reproductive technologies, fertility preservation, hormone replacement therapy, breastfeeding, and use of medications. It distinguishes SLE with and without antiphospholipid antibodies in its recommendations. Timing of pregnancies with respect to disease activity and potential use of teratogenic medications makes contraception counseling very important. Women should be educated about fertility issues related to age and effects of medications. Cyclophosphamide therapy is associated with ovarian insufficiency, although the low-dose regimen may have minimal impact on ovarian reserve.[52] This is especially of concern in older women who wish to conceive. Estrogen-containing oral contraceptives or hormone replacement therapy are associated with SLE flares and with thrombosis, especially in women with antiphospholipid antibodies or other risk factors. The risk of flares is low in patients with stable disease.[76] Combined estrogen-progestin pill or vaginal ring or progestin-only oral contraceptives or intrauterine devices (IUDs) can be offered to women whose SLE is inactive or stable active and who do not have antiphospholipid antibodies (low-moderate strength of evidence).[75] Short-term use of hormone replacement therapy may be considered for women with severe menopausal symptoms who have stable/inactive disease and do not have antiphospholipid antibodies (moderate evidence). Copper or progestin IUDs and progestin implants are considered to be highly effective and may be better choices for contraception in patients with SLE. Since mycophenolate can reduce the effectiveness of oral contraceptives, IUDs or two other forms of contraception are recommended for patients taking that drug. The IUDs or progestin-only pills are recommended for those with antiphospholipid antibodies. Progestin-only pills are considered effective and are an alternative for those who do not want an IUD. The copper IUD may increase menstrual bleeding and cramping after insertion. However, these symptoms decrease with the progestin IUD, which may be a consideration for patients receiving anticoagulants.

Pregnancy during SLE is considered to be high risk. The risk of maternal mortality, cesarean delivery, preterm labor, lupus nephritis flares, gestational diabetes, preeclampsia, Hemolysis with Elevated Liver tests and Low Platelets (HELLP) and the risk of thrombotic, infectious, and hematologic complications are increased.[36,66,77] Fetal risks include fetal loss, preterm birth, preterm premature rupture of membranes, and intrauterine growth restriction.[66] Preeclampsia occurs in 13% to 35% of women with SLE[66] and is defined as hypertension and proteinuria (greater than 300 mg/24 hr) that develop for the first time after 20 weeks of gestation.[78] This can be difficult to distinguish from lupus nephritis. The risk for preterm preeclampsia is decreased with daily use of low-dose aspirin begun before 16 weeks gestation.[66] Hydroxychloroquine also protects against preeclampsia.[79] Flares during pregnancy may be difficult to identify because they share characteristics of a normal pregnancy.[77] The complications are more likely in patients with active disease, especially lupus nephritis. If the mother has anti-Ro/SSA or anti-La/SSB antibodies, the fetus is at risk for neonatal lupus with rash, hematologic, hepatic, and cardiac abnormalities including heart block. These risks decrease with continued use of hydroxychloroquine.[77] Treatment of pregnant women with antiphospholipid antibodies is discussed below. Pregnancy should be discouraged in patients with severe pulmonary hypertension, advanced renal insufficiency, severe restrictive lung disease, heart failure, or a history of severe preeclampsia. It is also not advised within 6 months of a severe SLE flare, active lupus nephritis, or a stroke. The best pregnancy outcomes are observed in patients who have had inactive disease for at least 6 months prior to the pregnancy. Drugs used to control the SLE should be those, such as hydroxychloroquine, that can be continued throughout the pregnancy and may decrease the risk of flares, disease activity, and heart block in at-risk pregnancies.[77] Any potentially teratogenic drugs (eg, methotrexate, mycophenolate, cyclophosphamide, and thalidomide) should be stopped before attempting pregnancy.[75] The time before conception is 1 to 3 months for methotrexate and thalidomide, more than 6 weeks for mycophenolate, and 3 months for cyclophosphamide. This also allows time to evaluate whether disease activity is still controlled. Leflunomide should be removed through the oral cholestyramine elimination procedure (8 g three times a day for 11 days with confirmation of undetectable serum concentrations) preferably before conception or at least when pregnancy is confirmed.[75,77] Close monitoring and disease management of the mothers and fetuses are essential during pregnancy. The risks of drug use and harmful effects of disease flare need to be considered.[80] If a flare occurs and an immunosuppressive drug is required during the pregnancy, azathioprine may be considered because limited placental transfer occurs and the fetal liver is unable to metabolize it to its active form.[81,82] The dose should not exceed 2 mg/kg/day. Calcineurin inhibitors (cyclosporine, tacrolimus) are alternative choices. Supplements with calcium, vitamin D, and folic acid should be offered.[80,81] If corticosteroids are needed, maintenance doses should be kept as low as possible (preferably 7.5 mg or less) to decrease the risk of gestational diabetes mellitus, hypertension, infections, pre-eclampsia, and premature rupture of membranes.[66,77] Patients on long-term steroid therapy may need stress doses at the time of delivery. Fluorinated corticosteroids (such as dexamethasone or betamethasone) cross the placenta and should be avoided unless they are being used to treat the fetus.[66] Cyclophosphamide should only be used during the second or third trimester of pregnancy if alternatives failed and the mother's life is in danger.[80,81] If treatment of hypertension is needed, methyldopa, beta-blockers (except atenolol), or calcium channel blockers are considered safe, although there are some

concerns about fetal bradycardia and intrauterine growth restriction with beta-blockers.[81] Labetalol is the preferred beta-blocker. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may cause fetal malformations, oligohydramnios, and fetal renal damage.[81] NSAIDs should be discouraged in the preconception period due to concerns of NSAID-induced unruptured follicle syndrome and in the first trimester due to increased risk of miscarriage.[81] They should not be used in the third trimester of gestation because they increase the risk of premature closure of the ductus arteriosus, oligohydramnios, neonatal renal failure, and pulmonary hypertension. The safety of selective COX-2 inhibitors during pregnancy is not known. The safety of biologics is also not known, but they can be used preconception. The 2020 ACR guideline strongly recommends continuing certolizumab (which lacks an Fc chain) during pregnancy since minimal placental transfer occurs.[75] The guideline conditionally recommends discontinuation of other TNF-α inhibitors (infliximab, etanercept, adalimumab, golimumab) in the third trimester when placental transfer increases. The guideline also conditionally recommends stopping anakinra, belimumab, abatacept, tocilizumab, secukinumab, and ustekinumab once pregnancy is confirmed. Rituximab given during the second half of pregnancy can cause neonatal B-cell depletion and should be avoided unless the woman has severe life- or organ-threatening disease.[75] There is insufficient data on the safety of tofacitinib, baricitinib, and apremilast for any recommendation, but they likely cross the placenta.[75] The ACR guideline also included recommendations regarding men planning to father a child. Since cyclophosphamide can damage sperm, it is strongly recommended that men stop cyclophosphamide 12 weeks prior to attempted conception and consider sperm cryopreservation before starting treatment. It conditionally recommends discontinuation of thalidomide 4 weeks before.

SLE–Antiphospholipid Syndrome Overlap

The antiphospholipid antibodies are a group of antibodies including anticardiolipin, anti-β-2-glycoprotein I, and lupus anticoagulant. They can promote clotting and pregnancy morbidity.[83] Complement also plays a key role in antiphospholipid syndrome (APS) pathogenesis.[84] The diagnosis of APS requires at least one clinical and one laboratory feature. The clinical aspects are vascular events such as venous or arterial thrombi and/or obstetric complications. The obstetric complications meeting the criteria are three or more unexplained consecutive miscarriages before the 10th week of gestation, one or more unexplained deaths of fetuses at or beyond the 10th week of gestation, and one or more births of infants before the 34th week of gestation associated with eclampsia or severe preeclampsia or features of placental insufficiency.[85] Adverse pregnancy outcomes are especially associated with the presence of lupus anticoagulant.[66] Laboratory criteria are the presence of antiphospholipid antibodies on two separate occasions, 12 weeks apart.[85] Antiphospholipid antibodies are found in about 40% of patients with SLE, but less than 40% of those experience thrombotic events.[84] Patients at high risk for thrombotic and obstetric events are those with lupus anticoagulant or a combination of two or three antiphospholipid antibodies or the presence of persistently high antiphospholipid antibody titers.[19] Patients with isolated positive anticardiolipin or anti-β_2-glycoprotein I at low-medium titers, especially if transiently positive, are considered to be at low risk. Patients with thrombosis often have other cardiovascular risk factors (such as hypertension, hyperlipidemia, smoking, or use of estrogen-containing medications) or an underlying autoimmune disease such as SLE.[84] It is recommended that any modifiable factors be controlled. In deciding choice, intensity, and duration of treatment, the clinician should balance benefits with the patient's risk of bleeding. Consideration should also be given to whether thrombotic events are associated with identified transient precipitating factors. A EULAR Task Force developed recommendations for the management of APS in adults that consider individual risk assessments (Table 107-4).[19]

TABLE 107-4

Recommendations for Thromboprophylaxis in Patients with Systemic Lupus Erythematosus and Antiphospholipid Antibodies

Recommendation	Level of Evidence/Grade of Recommendation
Asymptomatic aPl carriers with no history of thrombosis or pregnancy complications, low-dose aspirin is recommended	2a/B
Patients with no history of thrombosis or pregnancy complications with high-risk aPl profile, low-dose aspirin is recommended	2a/B
Patients with no history of thrombosis or pregnancy complications with low-risk aPl profile, low-dose aspirin can be considered	2b/C
Nonpregnant women with a history of obstetric complications, low-dose aspirin is recommended	2b/B
Patients with APS and first venous thrombosis, warfarin with INR 2-3 is recommended	1b/B
If unprovoked first thrombosis, long-term treatment recommended	2b/B
If provoked first thrombosis, treat as usual	5/D
If provoked first thrombosis with high aPl profile, consider longer treatment	5/D
Patients with APS and recurrent venous thrombosis on warfarin with INR 2-3, consider adding low-dose aspirin or increasing INR target to 3-4 or change to low-molecular-weight heparin	4-5/D
Patients with APS and first arterial thrombosis, warfarin recommended over low-dose aspirin	2b/C
Patients with APS and first arterial thrombosis, warfarin with INR 2-3 or 3-4 recommended	1b/B
Patients with APS and first arterial thrombosis, warfarin with INR 2-3 and low-dose aspirin can be considered	4/C
Patients with APS and recurrent arterial thrombosis on warfarin with INR 2-3, consider adding low-dose aspirin or increasing INR target to 3-4 or change to low-molecular-weight heparin	4-5/D

aPl, antiphospholipid antibodies; APS, antiphospholipid syndrome.

Levels of Evidence: 1a: systematic review of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (and low-quality RCT); 3a: systematic review of case-control studies; 3b: individual case-control study; 4: case series and poor-quality cohort and case–control studies; 5: expert opinion

Grade of Recommendation: A: consistent level 1 studies; B: consistent level 2 or 3 studies, or extrapolations from level 1 studies; C: level 4 studies or extrapolations from level 2 or 3 studies; D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Data from Reference 19.

Patients with antiphospholipid antibodies may also have a false-positive test for syphilis (rapid plasma reagin).[18] Other common manifestations of APS are cognitive impairment, thrombocytopenia, stroke or transient ischemic attack, chorea, migraine, glomerulonephritis, avascular necrosis of bones, heart valve lesions, and livedo reticularis.[82]

It is not clear how to treat pregnant women with antiphospholipid antibodies. Low-dose aspirin (75-100 mg) should be considered during pregnancy for those with a high antiphospholipid profile but no history of thrombosis or pregnancy complications (Level 5/D).[19] Those with no history of thrombosis but who have experienced at least three spontaneous miscarriages before 10 weeks gestation and those with fetal loss at 10 weeks or later should be treated with low-dose aspirin and prophylactic doses of heparin (Level 2b/B). Self-administration of low-molecular-weight heparin may be more convenient for patients. Not only does heparin have anticoagulant effects, but it also has anti-inflammatory and immunomodulating properties and can inhibit complement activation.[86] Hydroxychloroquine should also be considered. Those with a history of delivery before 34 weeks gestation associated with eclampsia or severe preeclampsia or placental insufficiency should receive low dose aspirin alone or with prophylactic doses of heparin (Level 2b/B).[19] If women have recurrent obstetric complications despite receiving aspirin and heparin, clinicians should increase the heparin dose to therapeutic (Level 5/D) or consider adding hydroxychloroquine (Level 4/D) or low-dose prednisolone (Level 4/D) in the first trimester. Pregnant patients with APS and a history of thrombosis should receive low-dose aspirin with therapeutic doses of heparin (Level 4/C).[19] Warfarin is teratogenic and should be avoided during pregnancy, especially during the first trimester.[77] If low-molecular-weight heparin is used, it should be switched to unfractionated heparin 4 weeks before the anticipated delivery date. The heparin should be discontinued at the start of labor or 8 hours before a planned cesarean delivery.[87] All women with APS should receive anticoagulation with prophylactic doses of heparin, low-molecular-weight heparin, or warfarin for 6 weeks postpartum. Women without thrombosis risks may benefit from just 7 to 10 days of low-molecular-weight heparin.[83] Both heparin and warfarin are safe during breastfeeding.[84]

Clinicians can achieve better control of APS by adding hydroxychloroquine, statins, and vitamin D to standard therapy.[84] For patients who do not respond to conventional APS treatment or for whom it is contraindicated, alternative therapies include other platelet inhibitors, corticosteroids, rituximab, and the complement inhibitor, eculizumab. The role of direct acting oral anticoagulants is not clear. They should not be used for patients who are triple antibody positive or those with arterial thrombi.[19] They may be considered for patients with a low risk profile and no history of arterial thrombosis with a difficult to control international normalized ratio on warfarin.[35]

The most severe form of APS is called catastrophic and is associated with widespread thrombosis, multiorgan failure, and high mortality.[83] Any precipitating factors should be investigated and managed.[19] Treatment consists of combination therapy with glucocorticoids, heparin, and plasma exchange or intravenous immunoglobulins. If ineffective, rituximab or eculizumab may be considered.

Drug-Induced Lupus

9 Up to 15% of cases of SLE and up to 30% of cases of subacute cutaneous lupus erythematosus can be attributed to drugs.[88] About 15,000 to 30,000 new cases are reported each year in the United States.[11] These are idiosyncratic reactions precipitated by the interplay of genetic predisposition, concurrent illnesses, environmental factors, and other drugs or foods. Various pathophysiologic mechanisms have been proposed for different drugs in inducing lupus. Most drugs are small molecules that can induce an immune response by binding to larger molecules such as proteins, a process called haptenization. Another proposed mechanism is interference with macrophage uptake of apoptotic or necrotic cells, leading to accumulation of self-antigens. A more recently described mechanism is stimulation of neutrophil extracellular traps (NETs; NETosis), a form of neutrophil cell death that also results in self-antigens that stimulate autoreactive T- or B-cells.[89] Other possible mechanisms are dysregulation and hypomethylation of T-cells.[16]

There are no standard diagnostic criteria because the manifestations of drug-induced lupus are so diverse. The diagnosis is based on lupus-like findings in a patient with no history of the disease and the temporal relationship with the drug, including onset at least 1 month after initiation and improvement in symptoms within days to months after the drug is discontinued. The time frame, however, can be variable. The patient will often have laboratory findings such as a positive ANA or anti-histone antibodies, but usually not anti-dsDNA or anti-Sm antibodies.[90]

Many drugs of varied classes have been implicated. The drugs with the highest risk for inducing traditional symptomatic drug-induced lupus are procainamide (20%) and hydralazine (5%-8%), especially with hydralazine doses over 200 mg/day or a cumulative dose of more than 100 g.[90] It is more common in patients who are slow acetylators.[89] The incidence of positive ANAs with these drugs is 80% to 90% and 50%, respectively.[90] Common manifestations include arthralgias, arthritis, and myalgias. Constitutional symptoms such as fever, fatigue, anorexia, and weight loss are common.[11] Other clinical features include rash, pleuritis, pericarditis, and autoimmune hepatitis. Glomerulonephritis, CNS disease, and hematologic

abnormalities are rare in drug-induced lupus.[11] The risk and types of reactions vary depending on the offending drug. Laboratory abnormalities associated with drug-induced lupus include positive ANA and antibodies to histones. Other antibodies such as anti-Sm, anti-dsDNA, and antineutrophil cytoplasmic antibodies (ANCA) may be seen with some drugs. A drug with moderate risk for lupus is quinidine. The incidence of quinidine- and procainamide-induced lupus is declining because of decreasing use of the drugs and use of lower doses. Over 100 drugs of many different classes have been implicated and are considered to be of low risk. Other drugs with well-established links to lupus are minocycline, isoniazid, methyldopa, carbamazepine, and chlorpromazine.[11] A variant of the syndrome is drug-induced subacute cutaneous lupus, which has been most associated with terbinafine and TNF-α inhibitors, but also with calcium channel antagonists, thiazide diuretics, angiotensin-converting enzyme inhibitors, chemotherapeutic agents, phenytoin, carbamazepine, and proton pump inhibitors.[16] The mean age for this syndrome is 59 years; more patients are women, and positive ANA, anti-Ro/SSA, and anti-La/SSB are common, but fewer have anti-histone antibodies than those with drug-induced SLE.[16,89] It may occur after weeks to years of therapy.[89] Chronic cutaneous lupus has been reported with fluorouracil, TNF-α inhibitors, antifungals, and rarely intravenous immunoglobulins.[16] Drug-induced lupus can take weeks to months for skin lesions to resolve after the offending drug has been stopped.[11]

A separate category of drug-induced lupus involves TNF-α inhibitors, such as infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol, and is called TNF-α Antagonist Induced Lupus-like Syndrome (TAILS).[11] These drugs, especially chimeric infliximab, are known to induce autoantibodies. Proposed mechanisms for TNF-α inhibitor-induced lupus are that they induce cell apoptosis, increase the risk for bacterial infection, or suppress T-helper 1 immune response and favor T-helper 2 response. It is common for patients receiving these drugs to develop positive ANAs, anti-dsDNA of the IgM subtype, and extractable nuclear antibodies. Antihistone antibodies are less commonly seen than with other drug-induced lupus. As with traditional drug-induced lupus, the risk of clinical lupus is low compared to the numbers that develop autoantibodies.[90] Rashes and hypocomplementemia are more common features with TNF-α inhibitors than traditional drug-induced lupus.[91] Arthralgias, arthritis, fever, and weight loss are also seen. Renal, hematologic, and neurologic disorders are rare.[11] The underlying diseases being treated with these drugs may be a factor in the development of the observed reactions.

The primary treatment for drug-induced lupus is discontinuation of the implicated drug. Some patients require treatment with corticosteroids or other topical or systemic drugs based on the type and severity of the manifestations. If patients do not improve, a diagnosis of idiopathic SLE should be considered.[11]

Immunizations

Patients with SLE are at increased risk for infections because of immune dysfunction caused by their disease and immunosuppressive therapy. It is important to try to protect patients against these infections, but there are areas of concern regarding the safety and efficacy of vaccines in patients with SLE.[92] SLE cases developing or flaring after vaccine administration have been reported, but the actual risk is low when considering how many people receive immunizations.[93] These reactions may be a response to adjuvants added to increase the immunogenicity of vaccines and could be part of the syndrome called “ASIA—Autoimmune/inflammatory Syndrome Induced by Adjuvants.”[93] Another concern is that immunosuppressed patients may have an impaired response to vaccines such as influenza and pneumococcal as compared with healthy individuals. Revaccination may be needed in some cases.[92] Whenever possible, to achieve the best response, vaccines should be administered when SLE is stable and prior to initiating immunosuppressive medications. Non-live vaccines are considered safe in immunosuppressed patients. It is recommended that SLE patients receive pneumococcal vaccine because they are particularly susceptible to *Streptococcus pneumoniae* infections. They should also receive annual influenza vaccines. Those considered to be at risk should be immunized against hepatitis A and B.[92] Live-attenuated virus vaccines, such as measles–mumps–rubella, varicella, intranasal influenza, and yellow fever, are generally contraindicated in patients receiving immunosuppressive therapy. They should be avoided with consideration of risks versus benefits in patients taking high doses of immunosuppressive drugs. Doses of corticosteroids equivalent to prednisone 20 mg/day or more given for at least 2 weeks, methotrexate at 0.4 mg/kg/week or more, and azathioprine at 3 mg/kg/day or higher are considered immunosuppressive.[92] Measles–mumps–rubella boosters for patients on low-grade immunosuppression at risk for measles may be an exception. Non-live vaccines should preferably be given 2 weeks before starting immunosuppressive drugs if possible.[94] Live vaccines should be given at least 4 weeks before starting immunosuppressive drugs.[92] The recombinant zoster vaccine can be given during therapy with immunosuppressive drugs but should not be given during pregnancy. The same pregnancy delay should be observed for live vaccines and the human papilloma vaccine. The meningococcal serogroup B vaccine should only be given during pregnancy if benefits outweigh risks.[95] B-cell–depleting therapy such as rituximab

suppresses the humoral response to vaccines, so vaccines should be given 6 months after and 4 weeks before the next course of B-cell–depleting therapy.[92] A patient taking a B-cell–depleting therapy who has a high-risk exposure to tetanus should receive passive immunization with tetanus immunoglobulins. Immunosuppressed patients with SLE should receive a third dose of the same mRNA COVID-19 vaccine at least 28 days after the two-dose primary series.[95]

EVALUATION OF THERAPEUTIC OUTCOMES

10 Patients must be assessed for the activity and extent of lupus and monitored for adverse drug reactions. Monitoring for specific drugs is listed in Table 107-3. Many instruments have been developed and modified over the years to assess SLE therapy in trials. It is difficult to assess SLE therapy because milder forms of the disease may fluctuate, regardless of treatment.[96] Examples of measures of disease activity include the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group (BILAG). The SLEDAI is a measure of global disease activity that scores 24 manifestations as present or not. Modifications include the SELENA (Safety of Estrogens in Lupus Erythematosus National Assessment)-SLEDAI and SLEDAI-2000 (SLEDAI-2K). The SLEDAI-2K modified some of the elements and has been used in recent trials. Another variation is the SLEDAI-2KG that adds a weighted score based on glucocorticoid dose. BILAG measures clinical disease activity in eight organ systems compared to the prior assessment with a score of 0 to 4. The organ domains are given scores of A to E based on severity with A being severe, B moderate, C mild, D no activity, and E no history. An update of this instrument is the BILAG-2004. Individually, these indices were inadequate for showing superiority of new drugs over standard therapy. To overcome this problem, belimumab investigators developed the Systemic Lupus Erythematosus Responder Index (SRI) assessment criteria. The SRI has three components: (a) reduction in disease activity by SELENA-SLEDAI by at least 4 points; (b) no new BILAG A and no more than one new BILAG B score; and (c) less than 0.3 point increase (worsening) in physician global assessment (PGA). The PGA assesses patients' general health status. The BILAG-based Combined Lupus Assessment (BICLA) was used to demonstrate the efficacy of anifrolumab. It is defined as improvement in moderate-severe BILAG-2004 activity, no worsening in global and organ-specific disease activity, and no treatment failure. Other proposed instruments are the S2K RI-50 that measures partial improvement and the Lupus Low Disease Activity State (LLDA).[96] Another important assessment of therapy is health-related quality of life (HRQoL), which may use a patient-reported outcomes tool such as the generic 36-item Health Survey Short Form (SF-36) or one designed for cutaneous lupus.[28]

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) may be used for a more comprehensive assessment of disease activity and damage in cutaneous lupus erythematosus and response to therapy.[96]

A British Society for Rheumatology working group developed guidelines for managing SLE in adults. Patients should regularly be evaluated for SLE manifestations, adverse drug reactions, and comorbidities. Those with active disease should be assessed at least every 1 to 3 months with blood pressure, urinalysis, renal function, anti-dsDNA antibodies, complement concentrations, C-reactive protein, complete blood count, and liver function tests with further testing as warranted. Clinical and laboratory assessments should be performed every 6 to 12 months in patients with inactive disease and no organ damage, and more frequently if abnormalities are found.[97]

CONCLUSION

Much progress has been made in understanding the disease processes that lead to the development of SLE. This has led to the development of new drugs that target those disease pathways. Drug approval has been achieved by designing new tools for the assessment of drug efficacy. Therapeutic success is difficult to show when the "placebo" group is receiving standard treatment that usually includes drugs not approved for management of SLE. Practitioners can increase treatment success by educating patients on the importance of adherence to recommended life-style changes and medication regimens.

ABBREVIATIONS

ACR	American College of Rheumatology
ALMS	Aspreva Lupus Management Study

ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibodies
Anti-dsDNA	anti-double-stranded DNA
aPl	antiphospholipid antibodies
APRIL	a proliferation-inducing ligand
APS	antiphospholipid syndrome
BAFF	B-cell activating factor of the TNF family
BICLA	BILAG-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BLyS	B-lymphocyte stimulator
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CNS	central nervous system
DHEA	dehydroepiandrosterone
DNA	deoxyribonucleic acid
eGFR	estimated glomerular filtration rate
EULAR	European League Against Rheumatism, now European Alliance of Associations for Rheumatology
G6PD	glucose-6-phosphate dehydrogenase
HELLP	hemolysis with elevated liver tests and thrombocytopenia
HRQoL	health-related quality of life
IMPDH	inosine 5-monophosphate dehydrogenase
IL	interleukin
IUD	intrauterine device
La/SSB	antigen La/Sjögren syndrome B antigen
Mesna	sodium-2-mercaptoethane sulfonate
MHC	major histocompatibility complex
MPA	mycophenolic acid

NET	neutrophil extracellular trap
NMDA	*N*-methyl-D-aspartate
NSAID	nonsteroidal anti-inflammatory drug
PGA	physician global assessment
Ro/SSA	antigen Ro/Sjögren syndrome A antigen
RCT	randomized controlled trial
SELENA-SLEDAI	Safety of Estrogens in Lupus Erythematosus: National Assessment-Systemic Lupus Erythematosus Disease Activity Index
SF-36	Medical Outcomes Survey Short Form-36
SLE	systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SPF	sun protection factor
SRI	SLE Responder Index
TAILS	TNF-α inhibitor-induced lupus syndrome
TNF-α	tumor necrosis factor-alpha
TPMT	thiopurine methyltransferase
Treg	T regulatory cell

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SELF-ASSESSMENT QUESTIONS

1. Which of the following individuals would be at the *highest* risk for developing idiopathic SLE?
   A. 20-year-old African American female
   B. 25-year-old White female
   C. 30-year-old Hispanic male
   D. 40-year-old Asian male
2. There is evidence that SLE can be precipitated in a genetically susceptible individual by:
   A. Epstein–Barr virus
   B. Pesticides
   C. Ultraviolet light
   D. All of the above
3. A patient is being considered for a trial of a new drug for lupus. She has a malar rash, oral ulcers, and joint tenderness. The study requires that participants fulfill the 2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus. What is required as an entry criterion to consider

this individual for the trial?

A. Anticardiolipin antibody

B. Proteinuria of 1 g in 24 hours

C. Antinuclear antibodies at a titer of least 1:80

D. White blood cell count of 5,000/mm^3 (5×10^9/L)

4. Patients with SLE should be encouraged to stop smoking. Which of the following has been associated with smoking?

A. Decreased effectiveness of hydroxychloroquine

B. Decreased titers of anti-double-stranded DNA

C. Decreased incidence of hemorrhagic cystitis with cyclophosphamide

D. Decreased cutaneous lupus disease activity

5. Which of the following drugs decreases survival of B-cells by inhibiting B-lymphocyte stimulator?

A. Abatacept

B. Belimumab

C. Rituximab

D. Tocilizumab

6. A 20-year-old African American woman develops Class III lupus nephritis. What is the recommended induction treatment for her disease?

A. High-dose IV cyclophosphamide

B. Low-dose IV cyclophosphamide

C. Mycophenolate mofetil

D. Rituximab

7. A patient with generalized SLE develops severe neurologic manifestations thought to be related to inflammation. Which of the following drugs has the most evidence supporting its use in this situation?

A. Anifrolumab

B. Belimumab

C. Cyclophosphamide

D. Voclosporin

8. A patient has cutaneous lupus on her face and treatment is needed. She is very concerned about her appearance. Which of the following is *most* associated with causing skin atrophy and telangiectasias?

A. Hydroxychloroquine

B. Methotrexate

C. Topical pimecrolimus

D. Topical triamcinolone acetonide

9. A 35-year-old woman who wants to have a baby in the future is found to have SLE. Which of the following drugs has the *greatest* potential to adversely affect fertility?

A. Azathioprine

B. Cyclophosphamide

C. Hydroxychloroquine

D. Mycophenolate mofetil

10. Which of the following drugs used to treat SLE could be started before pregnancy and continued throughout pregnancy with the *least* potential for harm to a fetus?

A. Cyclophosphamide

B. Dexamethasone

C. Hydroxychloroquine

D. Mycophenolate mofetil

11. A patient with definite antiphospholipid syndrome had her first venous thrombosis and was treated for the acute episode. What should initially be used for secondary thromboprophylaxis for this patient?

A. Low-molecular-weight heparin in prophylactic doses

B. Low-dose aspirin

C. Simvastatin

D. Warfarin adjusted to an international normalized ratio (INR) of 2 to 3

12. What manifestation of SLE is common in idiopathic lupus but rare in drug-induced lupus?

A. Arthritis

B. Nephritis

C. Pleuritis

D. Rash

13. A patient is receiving belimumab for treatment of SLE. His immunization history and needs are being assessed. Which of the following vaccines should be *avoided* while he is receiving that drug?

A. Hepatitis B

B. Influenza

C. Yellow fever

D. Pneumococcal

14. A patient who is going to be treated with cyclophosphamide is considered to be at significant risk for hemorrhagic cystitis. Which of the following will *decrease* her chances of developing this complication?

    A. Alkalinization of urine

    B. Cholestyramine

    C. Folic acid

    D. Mesna

15. Eye examinations are recommended for patients receiving:

    A. Belimumab

    B. Cyclophosphamide

    C. Hydroxychloroquine

    D. Mycophenolate mofetil

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** SLE occurs most frequently in women of reproductive age, especially in non-White females. It is most common in those of African origin. See the "Epidemiology" section for more information.

2. **D.** Many environmental factors such as viruses, chemicals, and light can trigger SLE. See the "Etiology" section for more information.

3. **C.** Classification criteria are used to qualify subjects for trials. The EULAR/ACR criteria require that subjects have an ANA titer of at least 1:80 to even consider the other classification criteria. See the "Clinical Presentation" section and Table 107-1 for more information.

4. **A.** Smoking decreases the effectiveness of certain drugs (such as hydroxychloroquine and belimumab), increases cutaneous lupus disease activity, and increases the risk of some adverse drug reactions. Smokers are more likely to have elevated titers of anti-double-stranded DNA. See the "Etiology" and "Nonpharmacologic Therapy" sections for more information.

5. **B.** Belimumab inhibits B-lymphocyte stimulator. Rituximab also affects B-cells but through a different mechanism. See the "Biologic Agents" section under "Pharmacologic Therapy" for more information.

6. **C.** The usual induction treatment for Class III lupus nephritis is cyclophosphamide or mycophenolate mofetil. Low-dose IV cyclophosphamide was shown to be effective in White patients with Western or Southern European backgrounds. African American patients respond less well to cyclophosphamide and may respond better to mycophenolate mofetil. Cyclophosphamide can affect fertility, especially in high doses. Rituximab was not shown to be effective in controlled studies of lupus nephritis but can be tried if other treatments fail. Mycophenolate mofetil would be the best choice for initial induction therapy for this patient. See the "Pharmacologic Therapy" section and Fig. 107-3 for more information.

7. **C.** The EULAR recommendations for the management of neuropsychiatric lupus include cyclophosphamide for treatment of various manifestations. Patients with severe active CNS lupus were excluded from the primary anifrolumab and belimumab studies, although those drugs show promise in some studies. See the "Pharmacologic Therapy" and "Biologic Agents" section for more information.

8. **D.** Topical corticosteroids can cause skin atrophy and telangiectasias. To avoid that, the lowest effective potency and duration should be used. Triamcinolone acetonide is considered to be mid-potency. The low-potency fluocinolone acetonide or hydrocortisone creams would be preferred if a corticosteroid is to be used for the face. See the "Pharmacologic Therapy" section for more information.

9. **B.** Cyclophosphamide is associated with ovarian failure and infertility. This is especially of concern in older women who wish to conceive. See the "Pregnancy and Contraception" section under "Special Populations" for more information.

10. **C.** Hydroxychloroquine is considered safe during pregnancy and can help prevent SLE flares. Cyclophosphamide and mycophenolate mofetil are considered teratogenic. Dexamethasone is a fluorinated corticosteroid. It crosses the placenta and should only be used for treatment of the fetus. See the "Pregnancy and Contraception" section under "Special Populations" for more information.

11. **D.** This patient requires full anticoagulation. See Table 107-4 for more information.

12. **B.** Features of traditional drug-induced lupus include arthritis, pleuritis, and rash. Nephritis is rare. See the "Drug-Induced Lupus" section under "Special Populations" for more information.

13. **C.** Live vaccines should be avoided in patients taking biologic agents. Yellow fever is a live-attenuated virus vaccine. The other choices are inactivated vaccines. See the "Immunizations" section under "Special Populations" section for more information.

14. **D.** Although mesna is only approved for prevention of ifosfamide-induced hemorrhagic cystitis, it is also used with cyclophosphamide. See the "Immunosuppressive Drugs" section under "Pharmacologic Therapy" and Table 107-3 for more information.

15. **C.** Hydroxychloroquine can cause retinal toxicity. This can be minimized with appropriate monitoring. See the "Antimalarials" section under "Pharmacologic Therapy" and Table 107-3 for more information.