Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that often goes undiagnosed initially. Timely detection of SLE is important, because prompt treatment can prevent its many major complications—notably, end organ damage. Here's how to distinguish SLE from other illnesses with similar presentations and how to recognize the complications of undiagnosed SLE, which can progress rapidly and fatally.

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder that can involve multiple organ systems. The presence of antinuclear antibodies (ANA) is a common marker for this disease. In autoimmune diseases such as SLE, the immune system attacks the cells of healthy tissues throughout the body. Genetic, hormonal, and environmental factors (eg, ultraviolet light, infectious viruses, and even use of certain medications) have been implicated in the pathogenesis.1-3

It is estimated that 1.5 million people in the United States and up to 5 million people worldwide have SLE.4 It is nine to 10 times more prevalent in women—especially those of reproductive age—than men and occurs more frequently in African-American, Hispanic, and Asian women than in non-Hispanic Caucasian women.1,2,4-6 Siblings of SLE patients are 30 times more likely to develop the disease, compared to individuals without an affected relative.2 Increased mortality in persons with SLE is attributed to accelerated atherosclerosis, infection, malignancy, and target organ damage, particularly end-stage renal disease.3 Women ages 33 to 45 with SLE are at increased risk (50x greater) for myocardial infarction due to premature atherosclerosis than age-matched women in the general population.7 The life expectancy of SLE patients with renal damage is 23.7 years less than that of the general population.8

Increased awareness of SLE has led to drastic improvements in associated mortality over the past five decades. The survival rate

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in the 1950s was 50% at 2 years, while current rates are about 95% at 5 years and about 90% at 10 years. These improvements likely reflect earlier diagnosis and treatment on the part of well-informed clinicians, as well as more effective treatment.

**SLE MANIFESTATIONS**

SLE can affect any organ in the body with a broad spectrum of clinical manifestations, making it a devastatingly deceptive disease. Disease severity may vary by age, by organ involvement, and over time. Onset may be gradual and mild or rapidly progressive with severe organ involvement. Constitutional manifestations such as fatigue, weight loss, anorexia, and low-grade fever often serve as initial complaints. However, these features are common to a variety of infectious and inflammatory conditions, making early SLE easily overlooked and frequently misdiagnosed.

A mix of manifestations involving the joints, skin, mouth, kidneys, lungs, heart, and nervous system offers clues to the diagnosis of SLE (see Table 1, page 40). Arthritis is the most common symptom, occurring in 85% to 90% of SLE cases. It is typically nonerosive, inflammatory, symmetric or asymmetric, and polyarticular (involving five or more joints) and may be accompanied by constitutional symptoms. The joints most commonly affected are the proximal interphalangeals, metacarpophalangeals (MCP), knees, and wrists. Morning stiffness is a common complaint. Jaccoud arthropathy, which is characterized by reducible, nonerosive joint subluxations (e.g., swan neck deformities, ulnar deviation, boutonniere deformities, and z-shaped thumbs), can be seen in SLE patients. When patients present with articular and constitutional symptoms but lack other typical manifestations of SLE, such as skin rash, appropriate measures—for example, arthrocentesis—should be taken to evaluate for infection.

Cutaneous manifestations are the second most common feature at disease onset, with photosensitivity and malar rash being the most prevalent. Nearly all patients experience skin lesions at some point during the disease course. Diagnostic, or lupus-specific, lesions can be classified into three types: acute, subacute, and chronic.

Acute cutaneous lupus erythematosus (ACLE) is almost always associated with SLE, while subacute cutaneous lupus erythematosus (SCLE) is seen in about 50% of SLE patients. ACLE is usually precipitated by sunlight exposure and includes the classic erythematous, macular, “butterfly” rash located on the malar regions of the face, which may remain for days to weeks. Diffuse or discoid alopecia also may develop in ACLE, along with oral ulcers arising in purpuric necrotic lesions on the palate, buccal mucosa, or gums. Generalized erythematous, papular, or urticarial lesions may affect the face, arms, dorsa of the hands, or “V” of the neck.

SCLE tends to be sudden in onset, with annular
lesions or psoriasiform plaques on the upper trunk, arms, and dorsa of the hands that often coalesce into polycyclic lesions. These subacute rashes are often associated with anti-SSA/Ro antibodies.

Chronic cutaneous lupus erythematosus is usually characterized by skin disease alone. Discoid lupus is the most common type, with circular scaly plaques with erythematous, hyperpigmented rims and atrophic hypopigmented centers that leave scars. It is commonly seen on the face, neck, and scalp.

During the course of SLE, mucous membrane involvement—typically painless oral or nasal ulcers—occurs in 25% to 45% of patients. Oral lesions are most commonly found on the hard palate and buccal mucosa.

Lupus nephritis, perhaps the most dangerous manifestation of SLE, conveys high risk for organ failure, a higher mortality rate compared to patients without renal involvement, and lower life expectancy. Up to 60% of Asians, African Americans, and Hispanics develop renal disease during the course of their illness. The dominant feature is proteinuria, typically accompanied by microscopic hematuria.

Neuropsychiatric SLE (NPSLE) is a clinical manifestation that is poorly understood. An estimated 28% to 40% of NPSLE manifestations develop prior to or synchronous with the diagnosis, and 63% arise within the first year of diagnosis. Mild cognitive impairment is the most common manifestation, reported in up to 7% to 10% of SLE patients. Seizures and psychosis are reported in 7% to 10% of SLE patients, and psychosis—characterized by hallucinations or delusions—in 3.5%.

Cardiac findings are common among SLE patients, with an estimated prevalence of 50%, but are rarely the presenting manifestation. Pericarditis with effusion is the most common cardiac manifestation, occurring in 25% of SLE patients. Advancing atherosclerosis due to chronic inflammation becomes a major cause of mortality in the later years for SLE patients. Compared to the general population, the incidence of myocardial infarction in SLE patients is increased fivefold. Pleuritis is the most common pleuropulmonary manifestation in SLE. Pleuritic chest pain with or without a pleural effusion occurs in 45% to 60% of SLE patients.

DIFFERENTIAL DIAGNOSES

The differential diagnosis for SLE includes rheumatoid arthritis (RA), septic arthritis, mixed connective tissue disease (MCTD), Sjögren syndrome, systemic sclerosis (SSc), polymyositis (PM), fibromyalgia, and drug-induced lupus. Symmetrical, inflammatory, polyarticular arthritis with a predilection for the wrist and MCP joints occurs in both RA and SLE. And, because the initial articular features of SLE are sym-
metric arthralgias, patients with SLE are frequently misdiagnosed with RA. The absence of destructive bony erosions on radiographs and large joint effusions, along with the joint reducibility in SLE, can help distinguish it from RA. Asymmetric arthritis, which can be a presenting feature in both RA and SLE, is more commonly seen in the latter. ANA and rheumatoid factor test results can be positive in both disorders, but antibodies to anti-cyclic citrullinated peptides, with a 95% specificity for RA but absent in SLE, distinguish RA from SLE.1,16

Patients with MCTD display an array of overlapping features of SLE, PM, and SSC, making the diagnosis difficult. Although MCTD can evolve into other connective tissue diseases, such as SLE, it is nonetheless considered a distinct entity. High titers of anti-U1 ribonucleoprotein (anti-U1RNP) antibodies are indicative of MCTD. Anti-U1RNP is rarely detected in SLE and almost never seen in other rheumatic diseases. Typical manifestations of MCTD are Raynaud phenomenon, swollen fingers (referred to as “sausage digits”), and protuberant polyarthritis. Anti-SSA/Ro and anti-SSB/La antibodies, although detectable in SLE patients, are more commonly associated with Sjögren syndrome. In addition, patients with Sjögren syndrome frequently demonstrate signs of keratoconjunctivitis sicca and xerostomia.16

The clinical features of fibromyalgia include diffuse musculoskeletal pain that readily mimics SLE arthralgias. The 2011 modification of the 2010 American College of Rheumatology (ACR) preliminary diagnostic criteria for fibromyalgia serves as a reliable tool for diagnosing patients with nonspecific, diffuse pain. This 2011 modification includes 19 pain locations and the six self-reported symptoms: fatigue, impaired sleep, headaches, depression, poor cognition, and abdominal pain.18

SSc, also known as scleroderma, is characterized by skin thickening and/or CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia). The presence of anti-Scl-70 and anti-centromere antibodies are noted as well.16

Finally, a suspicion of SLE mandates an evaluation for drug-induced lupus by assessing the patient's exposure to culprit medications, such as hydralazine, procainamide, isoniazid, methyldopa, chlorpromazine, quinidine, minocycline, and tumor necrosis factor inhibitors.1,11 Four key features point toward drug-induced lupus:
- The female-to-male ratio is nearly equivalent.
- Nephritis and central nervous system (CNS) manifestations are not commonly present.
- Anti-double-stranded DNA (anti-dsDNA) antibodies and hypocomplementemia are absent.
- The clinical features and laboratory abnormalities return to baseline once the offending agent is removed.1

Anti-histone antibodies are present in approximately 75% of patients with drug-induced lupus but can also be seen in patients with SLE.11

LABORATORY WORK-UP

Laboratory abnormalities associated with SLE include anemia, leukopenia, lymphopenia, thrombocytopenia, hypocomplementemia, and proteinuria.

SLE can affect any organ in the body with a broad spectrum of clinical manifestations, making it a devastatingly deceptive disease.

A typical work-up includes a routine complete blood count (CBC) with differential, serum creatinine, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urinalysis with microscopy, and serologic ANA titer.1,16,19 A CBC with differential may reveal hematologic abnormalities, such as anemia of chronic disease (most commonly) or autoimmune hemolytic anemia, as well as leukopenia and thrombocytopenia due to circulating autoantibodies.3 An elevated ESR and CRP indicate the severity of the systemic inflammation and/or infection. Urinalysis is effective for detecting lupus with renal disease and may reveal proteinuria due to renal dysfunction.2

A positive ANA titer indicates widespread activation of the immune system targeted against nuclear and cytoplasmic subparticles. The vast majority of patients with SLE will develop a positive ANA with a high titer at some point during the course of their disease.16 The ANA is highly sensitive for SLE (93% to 95%) but lacks specificity (57%).20 The most common tests for ANA are enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay (IFA). ELISA is more sensitive in detecting ANA,
while IFA is the gold standard due to its high specificity. Some laboratories may use immunoassay as a screening tool for ANA and then use IFA to confirm positive or equivocal results. Positive ANA results can be seen in patients with other rheumatologic diseases and in up to 15% of all healthy persons, but with low or borderline titers. For these reasons, ANA testing alone is a poor predictor of SLE.

When either the ANA test results are positive or are negative but a strong clinical suspicion for SLE remains, clinicians should order tests for antibodies to extractable nuclear antigens (ENA panel; see Table 2). Anti-dsDNA and anti-Smith (anti-Sm) antibodies are both specific for SLE, and levels of anti-dsDNA reflect disease activity in many patients. In contrast, anti-dsDNA antibodies are found in fewer than 0.5% of healthy individuals and patients with other autoimmune conditions. Among patients with high levels of anti-dsDNA antibodies and clinically inactive disease, 80% will have active disease within five years after elevated antibodies are detected.

Autoantibodies, including ANA, anti-SSA/Ro, anti-SSB/La, and antiphospholipid antibodies, are usually detectable for many years prior to the onset of symptomatic SLE, while others, such as anti-Sm and anti-U1RNP, appear just months before the diagnosis. Patients with positive ANA results who do not meet criteria for SLE are still at risk for lupus and other autoimmune diseases, because complex autoimmune changes occur years before the diagnosis of SLE. These patients should be followed closely.

MAKING THE DIAGNOSIS

Diagnosing SLE may prove problematic because of the remarkable variety of relapsing and remitting clinical features, mimicry of similar conditions, and lack of a simple, definitive diagnostic test. Initial diagnosis of SLE depends on the disease manifestation, published criteria, and exclusion of alternative diagnoses. Confirmation requires careful clinical assessment, based on a thorough medical history and complete physical examination, along with specific laboratory testing. Biopsy results indicative of lupus nephritis in the presence of ANA or anti-dsDNA antibodies also confirm the diagnosis of SLE.

Although created for research purposes, ACR clas-
TABLE 3

Drugs Used for Treatment of Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Use</th>
<th>Common side effects</th>
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<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
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<tr>
<td>Arthritis</td>
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<tr>
<td>Fever, serositis, and arthritis</td>
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<td></td>
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<tr>
<td>Gastritis, nephrotoxicity, fluid retention</td>
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<tr>
<td><strong>Hydroxychloroquine</strong></td>
<td>200-400 mg/d po</td>
<td>Arthritis, skin rashes, fatigue, possible cholesterol reduction, prevention of flares; cornerstone of SLE treatment</td>
<td>Skin hyperpigmentation, retinopathy, myopathy with peripheral neuropathy, and cardiac myopathy (very rare); safe in pregnancy</td>
</tr>
<tr>
<td><em>antimalarial agent</em></td>
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</tr>
<tr>
<td><strong>Glucocorticoids</strong></td>
<td>Low: ≤ 7 mg/d</td>
<td>All symptoms of SLE</td>
<td>Fluid retention, DM, hypertension, acne, myopathy, avascular bone necrosis, osteoporosis, psychosis, hyperlipidemia</td>
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<tr>
<td>Medium: &gt; 7-30 mg/d</td>
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<tr>
<td>High: &gt; 30-100 mg/d</td>
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<tr>
<td>Very high: &gt; 100 mg/d</td>
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<tr>
<td>Pulse: 250 mg/d</td>
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<tr>
<td><em>corticosteroid</em></td>
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<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>Based on BSA and renal function po or IV; Euro-lupus protocol recommends 6 pulses IV of 500 mg q 2 wk</td>
<td>Lupus nephritis and severe SLE</td>
<td>GI toxicity, hair loss, myelosuppression, hemorrhagic cystitis, bladder cancer, gonadal suppression, infertility; contraindicated in pregnancy</td>
</tr>
<tr>
<td><em>cytotoxic agent</em></td>
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<tr>
<td><strong>Mycophenolate mofetil</strong></td>
<td>Up to 3,000 mg/d po</td>
<td>Induction and maintenance therapy in lupus nephritis; moderate-severe SLE</td>
<td>GI intolerance, myelosuppression; contraindicated in pregnancy</td>
</tr>
<tr>
<td><em>immunosuppressive agent</em></td>
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<tr>
<td><strong>Azathioprine</strong></td>
<td>50-150 mg/d po</td>
<td>Systemic features of SLE and maintenance therapy of class 3 or 4 lupus nephritis</td>
<td>GI intolerance, myelosuppression, hepatotoxicity</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>5-25 mg/wk po or SQ</td>
<td>Arthritis or cutaneous disorders without other systemic manifestations</td>
<td>GI intolerance, hepatotoxicity; contraindicated in pregnancy</td>
</tr>
<tr>
<td><strong>Belimumab</strong></td>
<td>3 doses of 10 mg/kg IV at 2-wk intervals and then 10 mg/kg IV q 1 mo</td>
<td>Arthritis, serositis, nephritis, FDA approved in 2011 for SLE patients with active disease despite treatment with standard drugs</td>
<td>Hypersensitivity reaction, GI toxicity, depression, migraine, myalgias, infection</td>
</tr>
<tr>
<td><strong>Rituximab</strong></td>
<td>2 doses of 1,000 mg IV at 2-wk intervals; can be repeated q 6 mo</td>
<td>Active lupus nephritis refractory to conventional drugs</td>
<td>Infusion reaction, infection, progressive multifocal leukoencephalopathy (rare)</td>
</tr>
</tbody>
</table>

Classification criteria for SLE, published in 1982 and revised in 1997, have been used for more than 30 years to diagnose lupus (see www.rheumatology.org/Practice-Quality/Clinical-Support/Criteria/ACR-Endorsed-Criteria). In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) group revised the 1997 ACR classification criteria to address major flaws and to improve clinical precision. According to SLICC, a definitive diagnosis requires the presence of at least four of 17 criteria, including at least one clinical and one immunologic criterion. The SLICC revisions have resulted in fewer misclassifications and provide greater sensitivity but lower specificity in the identification of SLE in comparison to the 1997 ACR criteria. To date, no one set of criteria allows for early diagnosis of SLE.

MANAGEMENT OPTIONS

Treatment must be tailored to the patient’s specific organ system involvement. Effective therapy hinges on controlling symptoms and reducing underlying inflammation. Four classes of drugs are used: NSAIDs, antimalarial drugs, corticosteroids, and cytotoxic drugs (see Table 3, page 43). Most patients benefit from NSAIDs to alleviate minor arthritis and arthralgia symptoms, but the risk for peptic ulcers and nephrotoxicity should be addressed; this may require the concomitant use of gastroprotective agents such as proton pump inhibitors. Antimalarials are effective for musculoskeletal symptoms that do not respond to NSAIDs and for cutaneous rashes. The current antimalarial drug of choice is hydroxychloroquine (200 to 400 mg/d po), which has been shown to control SLE manifestations by reducing and preventing disease flares. It is well tolerated and can be used for the duration of treatment. Patients should be informed that this drug’s onset of action is one month. In rare cases, this drug can cause retinal toxicity; therefore, SLE patients receiving hydroxychloroquine should be referred to an ophthalmologist for a baseline eye examination and yearly assessments to monitor for this rare adverse effect.

Low-dose corticosteroids, such as oral prednisolone or methylprednisolone, are employed when NSAIDs and antimalarials fail to control arthritis or cutaneous SLE eruptions. Major systemic manifestations that occur during a disease flare—such as severe arthritis, hemolytic anemia, glomerulonephritis, alveolar hemorrhage, pericarditis, pleurisy, or CNS involvement—necessitate high-dose IV corticosteroids in conjunction with immunosuppressive agents. These high-dose glucocorticoids should be gradually withdrawn as soon as remission is achieved. Long-term suppressive therapy with oral corticosteroids in addition to other agents is often needed to preserve organ function.

The major adverse effects of long-term glucocorticoids are osteoporosis, hypertension, hyperlipidemia, glucose intolerance, and susceptibility to infection. It is recommended that patients taking prednisolone 7.5 mg/d or more undergo a bone mineral density scan every two years. Those with T scores below –2.5 should be prescribed bisphosphonates.

Immunosuppressive agents, such as cyclophosphamide, mycophenolate mofetil, and azathioprine, are used in conjunction with corticosteroids or when syndromes are resistant to corticosteroids. Collaboration between primary care, rheumatology, and nephrology is advisable for patients requiring immunosuppressive or disease-modifying pharmacologic agents.

Two new treatments for SLE are the immunologic agents belimumab and rituximab. Belimumab, a monoclonal human antibody, is the first medication in the past 50 years that has been approved by the FDA for antibody-positive SLE patients with active lupus unresponsive to standard treatment. Rituximab is an anti-CD20 monoclonal antibody, approved by the FDA for non-Hodgkin lymphoma, chronic lymphocytic leukemia, and RA, and is now considered an option for SLE refractory to conventional treatment regimens. The efficacy of belimumab and rituximab, and the spectrum of indications for their use, are still under study, but these new therapeutic agents hold promise for the treatment of patients with refractory SLE.

HELPING PATIENTS LIVE WITH SLE

Patients with SLE have a higher mortality rate, as well as a lower quality of life, compared to the general population. Initial diagnosis of SLE depends on the disease manifestation, published criteria, and exclusion of alternative diagnoses.

In patients with SLE, initial diagnostic criteria for SLE, published in 1982 and revised in 1997, have been used for more than 30 years to diagnose lupus (www.rheumatology.org/Practice-Quality/Clinical-Support/Criteria/ACR-Endorsed-Criteria). In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) group revised the 1997 ACR classification criteria to address major flaws and to improve clinical precision. According to SLICC, a definitive diagnosis requires the presence of at least four of 17 criteria, including at least one clinical and one immunologic criterion. The SLICC revisions have resulted in fewer misclassifications and provide greater sensitivity but lower specificity in the identification of SLE in comparison to the 1997 ACR criteria. To date, no one set of criteria allows for early diagnosis of SLE.

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Patients with SLE have a higher mortality rate, as well as a lower quality of life, compared to the general population.
population. The major contributors to a decreased quality of life are fatigue, mood disturbances (eg, depression), and chronic pain. Practitioners should advise SLE patients to participate in support groups and psychotherapy to alleviate the anxiety and depression associated with this chronic disease.

For patients with long-standing disease, accelerated atherosclerotic cardiovascular disease adds to morbidity and mortality. For this reason, obesity, hypertension, hyperlipidemia, and smoking are targets for intervention. Lifestyle modifications—such as exercise, smoking cessation, a healthy diet with low saturated fat, stress avoidance, and adequate rest—are recommended.

Avoiding overexposure to sunlight, by using sunscreen with an SPF of at least 30 and wearing sun-protective clothing, is essential for management of cutaneous lupus. Yearly influenza vaccination is appropriate, as are other immunizations (eg, pneumococcal vaccine).

Advise women of childbearing age with SLE that lupus flares result in a high risk for miscarriage. All women should undergo yearly cervical cancer screening.

Patients taking long-term glucocorticoids should adopt bone-protective behaviors, including quitting smoking, limiting alcohol intake, partaking in weight-bearing exercise, and consuming dietary calcium and vitamin D. Patients taking these drugs should avoid live virus vaccines. Those on immunosuppressive therapy should be warned about the hazardous adverse effects of glucocorticoids.

MONITORING AND FOLLOW-UP
Collaborative efforts between primary care providers and several types of specialty providers can facilitate coordinated interventions in the long-term management of lupus. Rheumatologists are experts in making therapeutic decisions for SLE.

Patients being treated for SLE require routine monitoring to assess disease activity and detect flares. The European League Against Rheumatism (EULAR) guidelines recommend that monitoring include assessment for new clinical manifestations, routine laboratory tests, and immunologic assays, chiefly anti-dsDNA, anti-Sm, and serum complement levels, coupled with one of the validated global activity indices, such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

A routine office visit with a physical examination and laboratory testing for CBC with differential, basic metabolic panel, and urinalysis every three months is recommended for patients with stable disease; patients with uncontrolled SLE may require weekly visits. Patients taking immunosuppressive drugs should be provided with adverse-effect profiles alerting them to toxicity symptoms and require frequent laboratory monitoring for potential toxicity.

CONCLUSION
Advances in immunologically targeted serologic tests have shed more light on the underlying pathogenesis of SLE, which in turn has led to improvements in disease detection and monitoring of complications, as well as advances in therapy. Although SLE cannot be cured, emerging therapies targeting different mechanisms of SLE offer hope for patients diagnosed with this complex disease.

Find the posttest for this activity at www.clinicianreviews.com/cecme-activities.html

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