CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will recognize some of the issues surrounding the diagnosis and pathology of lupus and the ongoing care of patients with this disease

SUSAN MANZI, MD, MPH*
Associate Professor of Medicine and Epidemiology, Director, Patient Care and Translational Research, Lupus Center of Excellence, University of Pittsburgh School of Medicine and Graduate School of Public Health, Pittsburgh, PA

Lupus update: Perspective and clinical pearls

ABSTRACT

Patients with systemic lupus erythematosus (SLE, lupus) have a markedly better survival rate today than they did 50 years ago, but they face a greater risk of cancer, cardiovascular disease, and osteoporosis at early ages. With better understanding of the immunological mechanisms of the disease, new avenues of therapy are emerging.

KEY POINTS

Lupus is often misdiagnosed. A person may be given a diagnosis based on a positive antinuclear antibody (ANA) test, a finding that alone is not sufficient to establish the diagnosis. In contrast, some patients with lupus may go several years and see numerous physicians before the proper diagnosis is made.

One of the major mechanisms for lupus involves defective clearance of apoptotic cells, which act as a source of self-antigens. Because sun exposure can result in massive cell death of keratinocytes (skin cells), protection from the damaging effects of ultraviolet light plays an important role in the management of lupus.

Patients at any age with SLE should have their modifiable cardiovascular risk factors managed.

Drugs on the horizon for treating SLE inactivate B cells or their actions.

Many questions about systemic lupus erythematosus (SLE, lupus) remain unanswered. Why is this disease so difficult to diagnose even for rheumatologists? Why does lupus tend to develop in previously healthy young women? Why does the disease manifest in so many ways? Why are our current treatments suboptimal?

This article addresses these questions in a brief overview and update of SLE, with an emphasis on clinical pearls regarding prevention and treatment that are relevant to any physician who sees patients with this disease.

WOMEN AND MINORITIES ARE OVERREPRESENTED

Women have a much higher prevalence of almost all autoimmune diseases. SLE has a 12:1 female-to-male ratio during the ages of 15 to 45 years, but when disease develops in either children or the elderly, the female-to-male ratio is only 2:1.

African Americans, Asian Americans, and Hispanics have about a three to four times higher frequency of lupus than white non-Hispanics and often have more severe disease.

WHY IS SLE SO DIFFICULT TO DIAGNOSE?

SLE is frequently overlooked; patients spend an average of 4 years and see three physicians before the disease is correctly diagnosed. Part of the problem is that presentations of the disease vary so widely between patients and that signs and symptoms evolve over time. Often, physicians do not consider SLE in the differential diagnosis.

On the other hand, SLE is also often overdiagnosed. Narain et al[1] evaluated 263 patients who had a presumptive diagnosis of SLE. Only about half of the patients had a confirmed di-

*Dr. Manzi has disclosed that she serves on advisory boards for Abbot, Aspreva, Bristol-Myers Squibb, Centocor, Genentech, Genelabs, and Genzyme corporations, and the US Food and Drug Administration; has served as a consultant for Cellatope and StageMark corporations, holds intellectual property rights to several current and pending patents; and has received grant or research support from Amgen, Aspreva, Bristol-Myers Squibb, Genelabs, Genentech, Human Genome Sciences, and Immunomedics corporations.

Medical Grand Rounds articles are based on edited transcripts from Division of Medicine Grand Rounds presentations at The Cleveland Clinic. They are approved by the author but are not peer-reviewed.

doi:10.3949/ccjm.76a.gr005

agnosis; about 5% had a different autoimmune disease, such as scleroderma, systemic sclerosis, Sjögren syndrome, or polymyositis; 5% had fibromyalgia; 29% tested positive for ANA but did not have an autoimmune disease; and 10% had a nonrheumatic disease, such as a hematologic malignancy with rheumatic disease manifestations. For patients referred by a community rheumatologist, the diagnostic accuracy was better, about 80%.

The traditional classification criteria for SLE[2,3] are problematic. Some criteria are very specific for SLE but are not very sensitive—eg, anti-double-stranded DNA is present in about half of patients with SLE. Others tests, like ANA, are sensitive but not specific—although ANA is present in 95% of patients with SLE, the positive predictive value of the test for SLE for any given patient is only 11%.

Other criteria are highly subjective, including oral ulcers and photosensitivity. These signs may be present in normal individuals who get an occasional aphthous ulcer or who are fair-skinned and burn easily with prolonged sun exposure. It takes a trained clinician to distinguish these from the photosensitivity and oral ulcers associated with lupus.

Patients spend an average of 4 years and see three physicians before SLE is correctly diagnosed

Many diseases can mimic SLE

Fibromyalgia frequently presents in women and may include joint and muscle aches, fatigue, and occasionally a positive ANA. ANA may be seen in about 15% of healthy women.

Sjögren syndrome can also present with arthritis, fatigue, and a positive ANA; it is commonly overlooked because physicians do not often think to ask about the classic symptoms of dry eyes and dry mouth.

Dermatomyositis causes rashes that have many features in common with SLE. Even the skin biopsy is often indistinguishable from SLE.

Hematologic problems, such as idiopathic or thrombotic thrombocytopenic purpura, primary antiphospholipid syndrome, and hematologic neoplasms, can cause serologic changes, a positive ANA, and other manifestations seen in SLE.

Drug-induced lupus should always be considered in older patients presenting with SLE-like disease. Now with the use of minocycline (Minocin) and other related agents for the treatment of acne, we are seeing younger women with drug-induced lupus.

PATIENTS ASK 'WHY ME?'

Lupus typically develops in a young woman who was previously healthy. Such patients inevitably wonder, why me?

Lupus is like a puzzle, with genetics, gender, and the environment being important pieces of the puzzle. If all the pieces come together, people develop defective immune regulation and a break in self-tolerance. Everyone generates antibodies to self, but these low-affinity, nonpathologic antibodies are inconsequential. In SLE, autoantibodies lead to the formation of immune complexes, complement activation, and tissue damage.

Genetics plays an important role

Genetics plays an important role but is clearly not the only determining factor. Clustering in families has been shown, although a patient with lupus is more likely to have a relative with another autoimmune disease, especially autoimmune thyroid disease, than with SLE. The likelihood of an identical twin of a patient with SLE having the disease is only 25% to 30%, and is only about 5% for a fraternal twin.

In the first few months of 2008, four major studies were published that shed light on the genetics of SLE.[4–7] Together, the studies evaluated more than 5,000 patients with SLE using genome-wide association scans and identified areas of the genome that are frequently different in patients with lupus than in healthy controls. Three of the four studies identified the same genetic area as important and supported the concept that B cells and complement activation play important roles in the disease pathogenesis.

Although over 95% of cases of SLE cannot be attributed to a single gene, there are rare cases of lupus that may provide important clues to mechanisms of disease. For example a homozygous deficiency of C1q (an early component of complement) is extremely rare in lupus but is associated with the highest risk (nearly 90%) of developing the disease. Deficiencies in other components of the comple-

ment cascade also carry a high risk of disease development.

Investigators discovered that C1q plays an important role in clearing away apoptotic cellular debris. If a person is deficient in C1q, clearance of this debris is impaired. In a person genetically predisposed to getting lupus, the immune system now has an opportunity to react to self-antigens exposed during apoptosis that are not being cleared away.

Even though lupus cases cannot be explained by an absence of C1q, a defect in the clearance of apoptotic cells is a common, unifying feature of the disease.

Immune response is enhanced by environmental factors

Environmental factors, especially sun exposure, are also important. Following sunburn, skin cells undergo massive cell death, and patients with lupus have a huge release of self-antigens that can be recognized by the immune system. Sunburn is like having a booster vaccine of self-antigen to stimulate autoantibody production. Not only does the skin flare, but internal organs can also flare after intense sun exposure.

LUPUS SURVIVAL HAS IMPROVED; DISEASES OF AGING NOW A FOCUS

In 1950, only 50% of patients with SLE survived 5 years after diagnosis; now, thanks to better treatment and earlier diagnosis, 80% to 90% survive at least 10 years.

Early on, patients tend to die of active disease (manifestations of vasculitis, pulmonary hemorrhage, kidney problems) or infection. Over time, cardiovascular disease and osteoporosis become more of a problem. Patients also have a higher risk of cancer throughout life.

Lupus has an unpredictable course, with flares and remissions. But underlying the reversible inflammatory changes is irreversible organ damage caused by the disease itself and, possibly, by treatment. Preventing bone disease, heart disease, and cancer now play more prominent roles in managing SLE.

Increased bone disease

Fracture rates are higher than expected in women with lupus; Ramsey-Goldman et al[8] calculated the rate as five times higher than in the general population. The increased risk of osteoporosis is partly due to treatment with corticosteroids, but it is also likely caused by inflammation from lupus. Even controlling for steroid use, increased bone loss is still evident in patients with SLE.

African American women with lupus are not exempt. Lee et al[9] found that, after adjusting for body mass, steroid use, thyroid disease, and menopausal status, African American women with SLE had more than five times the risk of low bone mineral density in the spine than white women with the disease.

Increased cancer risk

Patients with SLE have an increased risk of hematologic cancer and possibly lung and hepatobiliary cancers.

Bernatsky et al[10] evaluated cancer risk in an international cohort of patients with SLE from 23 sites. Among patients with SLE, for all cancers combined, the standardized incidence ratio was 1.2; for hematologic cancers the ratio was 2.8; and for non-Hodgkin lymphoma it was 2.4. Surprisingly, although SLE is primarily a disease of women, reproductive cancer rates in patients with SLE did not differ from background rates. Bernatsky et al did not compare rates of cervical cancer, as many cancer registries do not record it. However, studies from the National Institutes of Health indicate that cervical dysplasia is common in patients with lupus.

Everyone generates antibodies to self, but these are normally ineffective

Other interesting findings included an increased risk of hepatobiliary cancer, especially among men with SLE. Lung cancers were also increased, which has been observed in patients with other autoimmune diseases such as scleroderma and polymyositis. Smoking is a strong predictor for developing autoimmune conditions and may play a role in the observed increased cancer risk.

Early and advanced cardiovascular disease

Patients with SLE are at high risk of atherosclerotic cardiovascular disease. At the University of Pittsburgh Medical Center from 1980 to 1993, we compared the incidence of myocardial infarction in nearly 500 women with SLE and more than 2,000 women of similar age in the Framingham Offspring Study.

At ages 15 to 24, women with lupus had a rate of 6.33 per 1,000 person-years; at age 25 to 34, the rate was 3.66 per 1,000 person-years. None of the Framingham women in those age groups had events.

Women ages 35 to 44 with lupus had a risk of heart attack 50 times higher than women in the Framingham cohort, and women in older age groups had a risk 2.5 to 4 times higher.[11]

Subclinical cardiovascular disease is also increased in women with SLE. Asanuma et al[12] used electron-beam computed tomography to screen for coronary artery calcification in 65 patients with SLE and 69 control subjects with no history of coronary artery disease matched for age, sex, and race. Calcification was present in 31% of patients with lupus vs 9% of controls ($P = .002$). Roman et al[13] performed carotid ultrasonography on 197 patients with lupus and 197 matched controls and found more plaque in patients with lupus (37%) than in controls (15%, $P < .001$).

Other data also suggest that women with lupus have advanced cardiovascular disease and develop it early, with most studies finding the greatest relative risk of cardiovascular disease between ages 18 and 45 years.

Sun exposure is like having a booster vaccine for autoimmunity

Traditional risk factors for cardiovascular disease cannot fully explain the increased risk. Many patients with lupus have metabolic syndrome, hypertension, and renal disease, but even after adjusting for these risk factors, patients with lupus still have about a 7 to 10 times higher risk of nonfatal coronary heart disease and a 17 times higher risk of fatal coronary heart disease.[14]

Many investigators are now exploring the role of immune dysfunction and inflammation in cardiovascular disease. A number of biomarkers have been proposed for predicting risk of cardiovascular disease in the general population. The list includes many inflammatory factors that rheumatologists have been studying for decades, including myeloperoxidase, autoantibodies, inflammatory cytokines, tumor necrosis factor alpha, and adhesion molecules, many of which also play a role in autoimmunity.

In our patients with SLE, we found that about 90% had three or more modifiable cardiovascular risk factors that were not being addressed appropriately (unpublished data). Lipid management was the least often addressed by rheumatologists and primary caregivers.

There is reason to believe that lupus patients are a high-risk group that merit aggressive risk-factor management, but no formal recommendations can be made without clear evidence that this approach improves outcomes.

SLE INCREASES THE RISK OF ADVERSE PREGNANCY OUTCOMES

Women with SLE more commonly miscarry and deliver low-birth-weight babies than do other women. A history of renal disease is the factor most predictive of poor pregnancy outcome, and the presence of certain autoantibodies increases the risk of neonatal lupus.

We recommend that women with lupus have inactive disease for at least 6 months before becoming pregnant.

ORAL CONTRACEPTIVES AND HORMONE REPLACEMENT

Hormone replacement therapy and oral contraceptives do not increase the risk of significant disease activity flares in lupus. However, women with lupus have an increased risk of cardiovascular disease and thrombosis.

Buyon et al[15] randomly assigned 351 menopausal women with inactive or stable active SLE to receive either hormone replacement therapy or placebo for 12 months. No significant increase in severe flares of the disease was observed, although the treatment group had a mild increase in minor flares.

Petri et al[16] randomly assigned 183 women with inactive or stable active SLE to receive either combined oral contraceptives or placebo for 12 months and found similar rates of disease activity between the two groups.

A weakness of these trials is that women with antiphospholipid antibodies in high titers or who had previous thrombotic events were excluded.

TREATMENTS ON THE HORIZON?

In the past 50 years, only three drug treatments have been approved for lupus: corticosteroids, hydroxychloroquine, and aspirin. Fortunately,

research in autoimmune diseases has rapidly expanded, and new drugs are on the horizon.

Mycophenolate mofetil (CellCept) may be a reasonable alternative to cyclophosphamide (Cytoxan) for lupus nephritis and may be appropriate as maintenance therapy after induction with cyclophosphamide.

Ginzler et al,[17] in a randomized, open-label trial in 140 patients with active lupus nephritis, gave either oral mycophenolate mofetil (initial dosage 1,000 mg/day, increased to 3,000 mg/day) or monthly intravenous cyclophosphamide (0.5 g/m^2, increased to 1.0 g/m^2). Mycophenolate mofetil was more effective in inducing remission than cyclophosphamide and had a better safety profile.

The Aspreva Lupus Management Study was designed to assess the efficacy of oral mycophenolate mofetil compared with intravenous cyclophosphamide in the initial treatment of patients with active class III–V lupus nephritis and to assess the long-term efficacy of mycophenolate mofetil compared with azathioprine in maintaining remission and renal function. It was the largest study of mycophenolate mofetil in lupus nephritis to date. There were 370 patients with SLE enrolled. In the 24-week induction phase, patients were randomized to receive open-label mycophenolate mofetil with a target dose of 3 g/day or intravenous cyclophosphamide 0.5 to 1.0 g/m^2 in monthly pulses. Both groups received prednisone. Response to treatment was defined as a decrease in proteinuria (as measured by the urinary protein-creatinine ratio) and improvement or stabilization in serum creatinine.

The results (presented at the American College of Rheumatology Meeting, November 6–11, 2007, in Boston, MA) showed that 104 (56%) of the 185 patients treated with mycophenolate mofetil responded, compared with 98 (53%) of the 185 patients treated with intravenous cyclophosphamide (P = .575). The study therefore did not meet its primary objective of showing a superior response rate with mycophenolate mofetil compared with cyclophosphamide. There was no difference in adverse events. It is this author's opinion that having an agent that is at least as good as cyclphosphamide in treating lupus nephritis is a major step forward.

Mycophenolate mofetil can cause fetal harm and should not be used during pregnancy. It is recommended that the drug be stopped for 3 to 6 months before a woman tries to conceive.

New drugs target B cells

Many new drugs for lupus target B cells.

Rituximab (Rituxan) is a monoclonal antibody that depletes B cells by targeting the B-cell-specific antigen CD20. It has been studied for treating lupus in several open-label studies that altogether have included more than 400 patients.[18–21] Regimens included either those used in oncology for treatment of lymphoma or those used in rheumatoid arthritis, coupled with high-dose corticosteroids and cyclophosphamide. In early studies, nearly 80% of treated patients entered at least partial remission, and 25% to 50% are still in remission more than 12 months later.

The first randomized controlled trial of rituximab vs placebo was recently completed and presented at the American College of Rheumatology meeting, October 24–28, 2008, in Boston, MA. The EXPLORER trial (sponsored by Genentech) included 257 patients with moderate to severe disease activity. The results showed that there was no difference in major or partial clinical response (based on a change in the British Isles Lupus Assessment Group index) in those on rituximab (28.4%) vs placebo (29.6%) at 12 months (P = .97). Overall, adverse events were balanced between the groups. It is this author's opinion that the bar for "response" was set very high in this study, considering that all patients who entered were fairly sick and received significant doses of corticosteroids that were tapered over the course of the trial.

Up to 90% of patients survive at least 10 years after diagnosis of SLE

B-cell toleragens, which render B cells incapable of presenting specific antigens, are also of interest.

Other experimental drugs target the soluble cytokine BLyS, which normally binds to a B-cell receptor and prolongs B-cell survival. It may also be possible to inhibit costimulatory pathways (which are normally important for inducing activation, proliferation, and class-switching of B cells) with the use of cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin inhibitor (CTLA4Ig) and

anti-CD40 ligand.

The results of a 12-month exploratory, phase II trial of abatacept (Bristol-Myers Squibb) in patients with SLE and active polyarthritis, serositis, or discoid lesions were presented at the American College of Rheumatology meeting in 2008. The primary and secondary end points (based on an adjudicated British Isles Lupus Assessment Group index) were not met. There were no differences in adverse events. Post hoc analyses of other clinical end points and biomarkers suggested that abatacept may have benefit in lupus. Further studies are under way.

Downstream blockade may also be useful, with drugs that inhibit inflammatory cytokines, particularly interferon alfa. This is now being tested in clinical trials.

REFERENCES

1. **Narain S, Richards HB, Satoh M, et al**. Diagnostic accuracy for lupus and other systemic autoimmune diseases in the community setting. Arch Intern Med 2004; 164:2435–2441.
2. **Tan EM, Cohen AS, Fries JF, et al**. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–1277.
3. **Hochberg, MC**. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997; 40:1725.
4. **Hom G, Graham RR, Modrek B, et al**. Association of systemic lupus erythematosus with C8orf13 BLK and ITGAM ITGAX. N Engl J Med 2008; 358:900–909.
5. **Kozyrev SV, Abelson AK, Wojcik J, et al**. Functional variants in the B cell gene BANK1 are associated with systemic lupus erythematosus. Nat Genet 2008; 40:211–216.
6. **International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), Harley JB, Alarcón-Riquelme ME, Criswell LA, et al**. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet 2008; 40:204–210.
7. **Nath SK, Han S, Kim Howard X, et al**. A nonsynonymous functional variant in integrin alpha(M) (encoded by ITGAM) is associated with systemic lupus erythematosus. Nat Genet 2008; 40:152–154.
8. **Ramsey-Goldman R, Dunn JE, Huang CF, et al**. Frequency of fractures in women with systemic lupus erythematosus: comparison with United States population data. Arthritis Rheum 1999; 42:882–890.
9. **Lee C, Almagor O, Dunlop DD, et al**. Association between African-American race/ethnicity and low bone mineral density in women with systemic lupus erythematosus. Arthritis Rheum 2007; 57:585–592.
10. **Bernatsky S, Boivin JF, Joseph L, et al**. An international cohort study of cancer in systemic lupus erythematosus. Arthritis Rheum 2005; 52:1481-1490.
11. **Manzi S, Meilahn EN, Rairie JE, et al**. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997; 145:408–415.
12. **Asanuma Y, Oeser A, Shintani AK, et al**. Premature coronary artery atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003; 349:2407–2415.
13. **Roman MJ, Shanker BA, Davis A, et al**. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med 2003; 349:2399–2406. Erratum in: N Engl J Med 2006; 355:1746.
14. **Esdaile JM, Abrahamowicz M, Grodzicky T, et al**. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001; 44:2331–2337.
15. **Buyon JP, Petri MA, Kim MY, et al**. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 2005; 142:953–962.
16. **Petri M, Kim MY, Kalunian KC, et al; OC SELENA Trial**. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 2005; 353:2550–2558.
17. **Ginzler EM, Dooley MA, Aranow C, et al**. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med 2005; 353:2219–2228.
18. **Anolik JH, Barnard J, Cappione A, et al**. Rituximab improves peripheral B cell abnormalities in human systemic lupus erythematosus. Arthritis Rheum 2004; 50:3580–3590.
19. **Looney RJ, Anolik JH, Campbell D, et al**. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose escalation trial of rituximab. Arthritis Rheum 2004; 50:2580–2589.
20. **Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA**. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthritis Rheum 2002; 46:2673–2677.
21. **Cambridge G, Stohl W, Leandro MJ, Migone TS, Hilbert DM, Edwards JC**. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment: relationships with B cell depletion, circulating antibodies, and clinical relapse. Arthritis Rheum 2006; 54:723–732.

***ADDRESS**: Susan Manzi, MD, MPH, University of Pittsburgh Arthritis Institute, Biomedical Science Tower, South Wing, Room 722, 3500 Terrace Street, University of Pittsburgh, Pittsburgh, PA 15261; e-mail sxm6+@pitt.edu.*