

Systemic Lupus Erythematosus: A Review of the Clinical Approach to Diagnosis and Update on Current Targeted Therapies

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic, complicated and challenging disease to diagnose and treat. The etiology of SLE is unknown, but certain risk factors have been identified that lead to immune system dysfunction with antibody formation and immune complex deposition. This immune system dysregulation causes organ injury, contributing to the variable manifestations and relapsing-remitting course of the disease. Criteria were created to aide in the diagnosis, focusing on clinical manifestations and antibody profiles specific to SLE. Treatment options are limited to a few medications to control the inflammation and decrease organ damage. Continuing investigations into the pathogenesis of SLE has led to new discoveries, making more medications available to treat this difficult disease.

KEYWORDS: systemic lupus erythematosus, antibodies, autoimmunity, treat to target, B-cell depletion and modulation, interferon blocking agents

SLE EPIDEMIOLOGY

SLE is seen worldwide, with incidence and prevalence rates differing geographically. Studies have shown that the incidence rate of SLE around the world is about 1 to 10 per 100,000 person-years, while the prevalence rates range from 20–70 per 100,000 person-years.¹ In the United States (US), the all race incidence was found to be 5.1 per 100,000 person-years² and the prevalence was estimated to be over 300,000 persons.³ SLE predominantly affects women, with a reported peak female-to-male ratio of 12:1 during the childbearing years.² The disease can also be seen in children and the elderly with a narrower gender distribution. Studies have shown racial/ethnic variations, with SLE being more common in non-Caucasian persons, occurring three to four times more often in African-Americans.² In addition to African-Americans, Hispanics and Asians develop SLE more frequently than Caucasians.² In these populations, SLE tends to be more active and severe, with a higher risk of relapses and organ system involvement or damage.⁴ Even with advances in diagnosis and treatment of the disease, the mortality risk in patients with SLE is higher than that of the

general population. For newly diagnosed patients, the 5-year survival rate is over 90% and the 15 to 20 year survival rate is about 80%.¹ Worse outcomes and higher mortality risk correlated with this ethnic disparity, which may be influenced by a lower socioeconomic status as well.⁴

SLE PATHOGENESIS

The etiology of SLE is unknown. Certain risk factors have been identified and shown to contribute to disease susceptibility or activate the immune system causing an inflammatory response, ultimately leading to the development of the disease. Predisposition to SLE is influenced by genetic factors. The female predominance in SLE, may be explained, in part, by the contribution of certain hormones.⁵ Environmental factors, such as smoking, exposure to ultraviolet light, viral infections, and specific medications (e.g. sulfonamide antibiotics) are known to trigger SLE.^{5,6} The pathogenesis of SLE is complex with contribution from many components of the immune system. With the underlying genetic predisposition and in response to various triggers, the balance of the immune system shifts towards reacting against itself, rather than self-tolerance. T and B cells become activated, leading to antibody production and eventual immune complex formation. These complexes circulate and deposit in critical tissues causing organ injury.

SLE DIAGNOSIS

Classification criteria have been derived for SLE, mainly for research purposes, to achieve population homogeneity among research studies. The American College of Rheumatology (ACR) published criteria in 1982, which were revised in 1997 (**Table 1**). The Systemic Lupus Collaborating Clinics (SLICC) international group undertook the evaluation and further revision of the above criteria resulting in a new classification system that is based on clinical and immunologic manifestations (**Table 1**). In an actual clinical practice setting, both criteria were analyzed; it was determined that the SLICC 2012 criteria were more sensitive and may allow patients to be classified with SLE earlier in the disease course.⁷ In the clinical setting, these criteria can be used as an aid in diagnosis, but formal diagnostic criteria for SLE are lacking.

Table 1. Classification Criteria for Systemic Lupus Erythematosus^a

	ACR 1997 ^b	SLICC 2012 ^c
Cutaneous	1. Malar Rash 2. Discoid Rash 3. Photosensitivity 4. Oral or Nasopharyngeal ulceration	1. Acute cutaneous lupus (including malar rash, photosensitive lupus rash) OR Subacute cutaneous lupus 2. Chronic cutaneous lupus (including discoid rash) 3. Oral or nasal ulcers 4. Nonscarring alopecia
Joints	5. Nonerosive arthritis - involving ≥ 2 peripheral joints characterized by pain, swelling or effusion	5. Synovitis - involving ≥ 2 peripheral joints characterized by swelling or effusion or tenderness and ≥ 30 minutes of morning stiffness
Serositis	6A. Pleuritis (pleuritic pain/rub or pleural effusion) OR 6B. Pericarditis (by EKG, rub, or pericardial effusion)	6. Serositis (any of the following) - pleurisy - pleural effusions - pleural rub - pericardial pain - pericardial rub - pericardial effusion - pericarditis by EKG
Renal	7A. Persistent proteinuria (> 0.5g/day or > 3+ dipstick) OR 7B. Cellular casts	7. Renal (any of the following) - urine protein/creatinine (or 24 hour urine protein) > 0.5g/24hr - red blood cell casts
Neurologic	8A. Seizures OR 8B. Psychosis	8. Neurologic (any of the following) - seizures - psychosis - mononeuritis multiplex - myelitis - peripheral or cranial neuropathy - acute confusional state
Hematologic	9A. Hemolytic anemia OR 9B. Leukopenia (<4,000/mm ³ on ≥ 2 occasions) OR 9C. Lymphopenia (<1,500/mm ³ on 2 occasions) OR 9D. Thrombocytopenia (<100,000/mm ³)	9. Hemolytic anemia 10. Leukopenia (<4,000/mm ³ at least once) OR Lymphopenia (<1,000/mm ³ at least once) 11. Thrombocytopenia (<100,000/mm ³ at least once)
Immunologic	10A. Anti-dsDNA OR 10B. Anti-Sm OR 10C. Antiphospholipid Antibody (any of the following) - anticardiolipin antibodies (IgG or IgM) - lupus anticoagulant - false positive syphilis test or > 6 months (confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test) 11. Positive antinuclear antibody	1. Antinuclear antibody 2. Anti-dsDNA 3. Anti-Sm 4. Antiphospholipid antibody (any of the following) - lupus anticoagulant - false-positive RPR - medium or high titer anticardiolipin (IgA, IgG, or IgM) - anti-β ₂ glycoprotein I (IgA, IgG, or IgM) 5. Low complement - low C3, C4, CH50 6. Direct Coombs test
Classification of SLE	- Satisfy four out of the 11 criteria	- Satisfy four of the criteria, including one clinical criterion and one immunologic criterion OR - biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies
Sensitivity¹²	83%	97%
Specificity¹²	96%	84%

Abbreviations: SLICC = Systemic Lupus International Collaborating Clinics; ACR = American College of Rheumatology; SLE = systemic lupus erythematosus; Anti-dsDNA = anti-double-stranded DNA; Anti-Sm = anti-smith antibody; EKG = electrocardiogram; RPR = rapid plasma regain; CH50 = 50% hemolyzing dose of complement

a. Adapted from Epidemiology and Classification of Systemic Lupus Erythematosus. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, eds. *Rheumatology*. 6th ed. Philadelphia, PA: Mosby/Elsevier; 2015:1021-1025

b. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. [letter]. *Arthritis Rheum*. 1997; 40:1725

c. Petri M, et al. Derivation and validation of Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum*. 2012; 64(8):2677-2686

SLE CLINICAL AND LABORATORY MANIFESTATIONS

SLE has a variable, relapsing-remitting course and clinical symptoms vary between patients, depending on which organ systems are affected. The above criteria incorporate the major and common organ systems that can be affected in SLE including skin, mucus membranes, joints, kidneys, brain, lungs, heart and hematologic system (Table 1). Clinical and laboratory surveillance is also important to assess and monitor for the development of any new symptoms or findings. A serious manifestation of SLE, with resultant increased morbidity and mortality, is lupus nephritis (LN). Treatment is based on the findings on a kidney biopsy. Neuropsychiatric involvement is rare but difficult to diagnose. It may not correspond to overall SLE activity. SLE patients may also have comorbidities, further complicating their disease. Atherosclerosis is common, presenting as coronary artery disease (CAD), or cerebral or peripheral vascular diseases. CAD is linked to increased morbidity and mortality, with SLE women aged 35-44 years old being more than 50 times more likely to have a myocardial infarction than women of a similar age without SLE.⁸ Even though traditional cardiovascular risk factors do not fully explain the accelerated rate of atherosclerosis in SLE patients, they should be addressed routinely and modified to prevent further morbidity or mortality.

Autoantibody production is fundamental to the pathogenesis of SLE. These autoantibodies are directed against nuclear or cytoplasmic antigens and are known as antinuclear antibodies (ANA). ANA's are included in the diagnostic criteria (Table 1) and are seen in more than 95% of SLE patients. Other antibodies have been identified that are recognized based on their targeted autoantigens and are collectively known as anti-extractable nuclear antigens (ENA). Anti-double stranded DNA antibody (anti-dsDNA) is highly specific (95% specific) for SLE, especially with renal disease. Anti-Sm antibodies (antibodies against Sm core particles) are unique and highly specific for SLE with renal disease, although seen in only about 20-30% of SLE patients overall. Other antibodies may be seen in SLE, but are not specific for the disease and can be seen in other autoimmune conditions. For example, anti-ribonucleoprotein (anti-RNP) is seen in 30-40% of SLE patients, but is highly associated with mixed connective tissue disease. Anti-Ro (anti-SSA) and anti-La (anti-SSB) are seen in 40% of SLE patients, but have a stronger association with Sjogren's syndrome. Anti-ENA antibodies are used as serologic markers for SLE. Anti-dsDNA antibodies and complement components (C3 and C4) may be used to monitor SLE activity, especially in the setting of lupus nephritis.⁹ Another set of antibodies seen in 30-40% of SLE patients are the antiphospholipid antibodies, which are lupus anticoagulant, anticardiolipin antibodies, and anti- β_2 -glycoprotein 1 antibodies. About 10-15% SLE patients can have antiphospholipid syndrome, manifested by recurrent venous or arterial thrombosis or pregnancy morbidity.⁸

TREAT TO TARGET

Utilization of corticosteroids (CS) in SLE management began in the 1950s and was a major important therapeutic milestone. However, challenges in SLE treatment remain to this day. Retrospective studies have provided evidence that increased disease activity in rheumatologic or autoimmune disorders is related to future organ damage and death.¹⁰ In response to this finding, the "treat to target" strategy to achieve disease remission was established and attainable in rheumatoid arthritis. This concept is gaining momentum in the care of SLE patients with new treatment options available and/or emerging medications in the research pipeline.¹¹ Currently there are only three agents, in addition to CS, that are FDA approved for SLE treatment. The challenge has been to create guidelines for the management and treatment of SLE due to the lack of quality evidence for almost all aspects of SLE, except lupus nephritis.

BASIC THERAPY

Management of SLE patients begins with basic recommendations including avoidance of sunlight and use of high-SPF sunscreen (> 35), with screening and counseling for modifiable cardiovascular risk factors such as cigarette smoking and uncontrolled HTN. Family planning discussions should be considered with SLE patients of reproductive age. Supplementation of calcium and vitamin D is recommended. The general approach to the use of pharmacological agents depends on specific organ involvement and is tailored to other SLE patient characteristics, such as ethnicity and comorbid conditions.

ANTIMALARIALS

Antimalarial medications, such as hydroxychloroquine (HCQ), have proved useful in treating milder manifestations of lupus including dermatitis, arthritis and constitutional symptoms. The exact mechanism of action of antimalarials is unknown. Support for the use of HCQ as background therapy in patients with SLE emerged after a pivotal Canadian study found that HCQ reduced flares in SLE patients compared to subjects in whom the medicine was withdrawn.¹² Subsequent analysis linked HCQ to the reduction of organ damage, thrombosis and improvement in survival. HCQ has been shown to favorably modulate lipid profiles in patients receiving CS.¹³

CORTICOSTEROID TREATMENT IN SLE

Considered the cornerstone of SLE treatment, CS have the major advantage of rapid control of SLE activity, from controlling skin or joint disease, to severe and life threatening complications such as vasculitis and nephritis. CS are often given orally, but for severe life-threatening complications, intravenous forms of CS are usually administered.¹⁴ Short

term use of CS may be necessary and often convenient to control SLE flares, but long-term use is related to significant side effects. Doses of prednisone greater than 10–19 mg a day increase the risk of cardiovascular events 2.4 times compared to daily doses below 9 mg.¹⁵ The risk of long term CS use on skeletal health is well established and will not be addressed here.

FROM OTCS TO CHEMOTHERAPY

In addition to antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs) and traditional agents used for rheumatoid arthritis, such as methotrexate, have been used to control mild to severe arthralgias and arthritis. Immunosuppressive drugs such as azathioprine (AZA) in doses of 2-2.5mg/kg/d may be used as steroid sparing agents to treat the various manifestations of SLE. For the most life threatening SLE organ manifestations such as neuropsychiatric, LN, pulmonary hemorrhage and systemic vasculitis, high-dose or pulse steroids as the initial treatment are being used, usually followed by high potency steroid sparing agents. Cyclophosphamide (CYC), an alkylating agent, has emerged as the gold standard medication for the management of lupus nephritis after an NIH study which showed that SLE patients on CYC had better renal survival than patients on CS alone.¹⁶ The dose and regimen for CYC was standardized since the NIH experience, but based on the Euro-lupus trial, the lower dose of CYC can be safely used in selected populations, without compromising its efficacy.¹⁷ CYC is used as induction therapy to further decrease inflammation and decrease disease activity. Due to its significant toxicity, most SLE patients are managed with maintenance medications that include AZA or mycophenolate mofetil (MMF) to reduce the frequencies of flares.¹⁴ Nearly 25 years since the publication of the pivotal NIH study of the use of CYC for the management of LN, MMF proved to be non-inferior and for some populations, non-Caucasians, even superior to CYC as an agent for induction of remission of LN.¹⁸

B-CELL DEPLETION OR MODULATION

B cells play a central role in the pathogenesis of active lupus through cytokine production, presentation of self antigens, activation of T cells and antibody production. Better understanding of B cell function in SLE pathology directed investigators to conduct trials of rituximab (RTX) for the treatment of severe SLE. RTX is a chimeric mouse/human monoclonal antibody (mAb) against the CD20 antigen on B cells, rapidly decreasing B cells, hence reducing inflammation. The important study of the utilization of RTX in lupus nephritis did not meet the primary end point of reduction in proteinuria; despite reducing the level of complements and dsDNA.¹⁹ Critics of the study point to possible faulty study design (small number of patients, use of high dose of steroids, short study time) as a reason for not reaching

statistical significance. Further, the suboptimal response to RTX may be related to immune complex-mediated advanced kidney injury rather than antibody production related damage. Still, “off label” RTX is used as a second-line agent in lupus complications like neuropsychiatric SLE and vasculitis in addition to its proven efficacy in idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AHA). The most common side effects of RTX are related to post infusion complete blood count (CBC) abnormalities. Epratuzumab is another B cell therapy targeting the CD22 molecule on B cells. CD22 is responsible for B cell activation and function. This anti-CD 22 agent, that modulates B cell response, has entered late phases of clinical trials with promising preliminary data.²⁰ Epratuzumab was first studied in trials which ended prematurely due to shortage of the drug. Data analysis showed that epratuzumab may decrease disease activity in SLE, but the authors were unable to draw definitive conclusions. Another trial, studying the same molecule, showed improvement in most areas of SLE activity, from mucocutaneous to renal and neuropsychiatric manifestations. Headache and nausea were the most common side effects.²¹

TARGETED THERAPIES

BLyS (a B lymphocyte stimulator) is responsible for B cell survival in some SLE patients and is targeted by belimumab, a new FDA-approved drug. This fully human mAb binds to BAFF (B-cell activating factor) receptor on mature B cells decreasing their activation, antibody secretion and possibly preventing T cell activation as well. Belimumab was found to be beneficial in patients with SLE-related dermatitis, mucositis and arthritis, but was not specifically studied in LN. In one clinical trial, a subgroup of patients with elevated dsDNA and low C3 and C4, benefited from this medication the most.²² Belimumab may constitute a viable, but expensive, option to treat SLE patients who are not responding or intolerant to first line therapies. It has an acceptable safety profile.

INTERFERON BLOCKING AGENTS

Interferon α (INF) has been linked to accelerated disease activity and is the main target of antimalarial therapy in SLE.²³ INF α blocking therapies entered phase II clinical trials and show promising results in moderate to severe SLE.²⁴ Preliminary data presented in abstract form in 2014 showed promising results with sifalimumab, mAb against INF α . This INF inhibitor reduced baseline moderate to severe SLE mucocutaneous involvement, as well as decreased arthritis and fatigue scores. It did not improve serological markers of active disease, such as dsDNA and complement levels. For this medication, the overall safety data was acceptable, with infections and headache as the most commonly reported adverse effects. Novel studies capitalize on INF γ with INF γ gene expression seen in peripheral blood of subjects with

autoimmune disorders, such as SLE. A recent randomized controlled trial of a mAb against INF γ (molecule AMG 811) used in subjects with mild to moderate SLE showed dose dependent modulation of INF gene expression and reduction of the inflammatory protein linked to the prediction of future flares and level of disease activity.²⁵

CONCLUSION

SLE remains a challenging disorder that requires an interdisciplinary approach with a team of health-care providers to diagnose, manage and tailor treatment to individual patient needs. Continued dedication and research into the pathogenesis of SLE to identify specific immunologic targets for potential therapies, will bring more exciting new medications and hope to SLE patients to better control this difficult and unique disease.

References

1. Pons-Estel, GJ et al. Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum.* 2008;39:257-268
2. Danchenko, N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. *Lupus.* 2006;15:308-318
3. Helmick CG et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States Part I. *Arthritis Rheum.* 2008; 58(1):15-25
4. Gonzalez LA, Toloza SM, Alarcon GS. Impact of race and ethnicity in the course and outcome of systemic lupus erythematosus. *Rheum Dis Clin N Am.* 2014; 433-454
5. Tsokos, GC. Systemic Lupus Erythematosus. *NEJM.* 2011; 365:2110-21
6. Petri M, Allbritton J. Antibiotic allergy in systemic lupus erythematosus: a case-control study. *J Rheumatol.* 1992;19:265-9
7. Ines L et al. Classification of systemic lupus erythematosus: systemic lupus international collaborating clinics versus American college of Rheumatology criteria. A comparative study of 2,055 patients from a real-life, international systemic lupus erythematosus cohort. *Arthritis Care Res.* 2015; 67(8):1180-1185
8. Lisnevskaja L, Murphy G, Isenberg D. Systemic lupus erythematosus. *Lancet.* 2014; 384:1878-88
9. Leffler J, Bengtsson AA, Blom AM. The complement system in systemic lupus erythematosus: an update. *Ann Rheum Dis.* 2014; 73:1601-1606
10. Lopez R, Isenberg D, et al. Lupus disease activity and the risk of subsequent organ damage in a large patient cohort. *Rheumatology (Oxford)* 2012;51 (3):491-498
11. VanVollenhoven RF, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;00:1-10
12. Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in SLE. *NEJM* 1991; 324:150-154
13. Petri M. Hydroxychloroquine use in the Baltimore Lupus Cohort: effects on lipids, glucose and thrombosis. *Lupus* 1996 (5) Suppl. 1 S16-S22
14. Hahn B, Grossman J. American College of Rheumatology Guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res* 2012, (6) 64:797-808
15. Magder LS, Petri M. Incidence of and risk factors for adverse cardiovascular events among patients with systemic lupus erythematosus. *AM J Epidemiology* 2012;176:708-719
16. Austin A, Klippel J. Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. *NEJM.* 1986;314:614-619
17. Houssiau FA. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum.* 2002;46(8):2121
18. Appel GB. and co. for ALMS Study Group. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009 May;20(5):1103-12
19. Rovin B. (LUNAR Investigator Group), Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum.* 2012; 64(4) 1215-1226
20. Wallace D. Efficacy and safety of epratuzumab in patients with moderate/severe flaring SLE: results from two randomized, double blind controlled, multicentre studies (AALEVIATE) and follow up. *Rheumatology* 2013;52;1313-1322
21. Wallace D. Efficacy and safety of epratuzumab in patients with moderate/severe flaring SLE: results from EMBLEM, a phase IIb, randomized, double blind controlled, multicentre study. *Ann Rheum Dis* 2014; 73:183-190
22. VanVollenhoven R. Belimumab, a BLYS-specific inhibitor, reduces disease activity and severe flares in seropositive SLE patients: BLISS-76 study. *Ann Rheum Dis* 69(Suppl. 3): 74
23. Sacre K. Hydroxychloroquine is associated with impaired interferon-alpha and tumor necrosis factor-alpha production by plasmacytoid dendritic cells in SLE. *Arthritis Res Ther* 2012; 14(3):R155
24. Khamashta M. Safety and Efficacy of Sifalimumab, an Anti IFN-Alpha Monoclonal Antibody in a Phase 2b Study of Moderate to Severe Systemic Lupus Erythematosus (SLE); [late breaking abstract no14]; 2014 ACR/AHRP Annual Meeting
25. Welcher A. Blockade of INF γ normalizes INF-regulated gene expression and serum CXCL10 levels in patients with SLE. *Arthritis Rheum.* 2015;67(10):2713-2722

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