Best Practices in the Treatment and Management of Systemic Lupus Erythematosus (SLE): Addressing Disease Activity and Flares for Improved Clinical and Economic Outcomes

A CME/CNE Approved Activity

JOURNAL of MANAGED CARE MEDICINE

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Best Practices in the Treatment and Management of Systemic Lupus Erythematosus (SLE): Addressing Disease Activity and Flares for Improved Clinical and Economic Outcomes

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By Mail: Jeremy Williams
NAMCP CME Dept.
4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060

Authors:
Dr. Maureen A. McMahon, MD, MS, is associate Clinical Professor in the Division of Rheumatology at the UCLA David Geffen School of Medicine, Los Angeles, CA.
Dr. Daniel J. Wallace MD, FACP, MACR, is a Clinical Professor of Medicine at the Cedars-Sinai Medical Center and the UCLA David Geffen School of Medicine, Los Angeles, CA.
Dr. Gary M. Owens, MD, is the President of Gary Owens Associates.

Learning Objectives:

1. Discuss the impact of uncontrolled systemic lupus erythematosus (SLE) activity on organ damage, mortality, and costs to the healthcare system.
2. Assess disease activity and severity, considering the diverse immunopathology and variable expression of SLE in different patients.
3. Identify patients who may be nonadherent to current SLE therapies that focus on reducing flares and disease activity.
4. Review the safety and efficacy data on current and emerging SLE treatment to control disease activity and prevent or minimize disease flares, drug toxicity, and organ damage in patients with SLE.
5. Communicate effectively with SLE patients and the multidisciplinary team to understand and address the needs of each patient and improve treatment adherence, quality of life, and survival outcomes.
6. Review new options and strategies that may help improve patient adherence and quality of life, including self-administration of treatment.
7. Integrate new evidence into practice to appropriately achieve treatment goals in individual patients with SLE.
8. Address payer- and provider-related barriers to appropriate evidence-based use of BLyS-specific inhibitors.
9. Apply methods to enable optimal cost management of SLE therapies to be realized by multiple stakeholders including managed care organizations.

Faculty Disclosure:
Dr. McMahon has disclosed the following relevant financial relationships, having served on an advisory board for AstraZeneca and GlaxoSmithKline. Both relationships are now terminated.
Dr. Owens has disclosed the following relevant financial relationships, serving on an advisory board or panel for AstraZeneca and serving as a consultant for AbbVie and Roche.
Dr. Wallace has disclosed the following relevant financial relationships, serving on advisory boards for Amgen, Celgene, EMD Serono, Lilly, and Merck and serving as a consultant for Amgen, Celgene, EMD Serono, Lilly, and Merck.

All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacqueline Cole, RN, CPHQ, CMCN; and Jeremy Williams have no relevant financial relationships to disclose.

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Best Practices in the Treatment and Management of Systemic Lupus Erythematosus (SLE): Addressing Disease Activity and Flares for Improved Clinical and Economic Outcomes

Post-Test Questions

1. Which of the following is an accurate statement about systemic lupus erythematosus (SLE)?

   a. It affects over two million people in the U.S.
   b. Eighty-five percent of those affected are female
   c. The highest prevalence of SLE occurs in Caucasions
   d. The peak incidence occurs between 40 and 60 years of age

2. Activation of _____ starts the process of pathogenic autoantibody production and tissue injury in SLE.

   a. Autoreactive T and B cells b. Tumor necrosis factor (TNF)
   c. Various interleukins d. B-lymphocyte stimulator

3. The risk for MI is more than __ times greater for women with SLE aged 35 to 44 compared to age matched controls without SLE.

   a. 5 b. 10 c. 30 d. 50

4. Which of the following may be used in SLE to manage mild disease?

   a. Daily corticosteroids b. Cyclosporine
   c. Nonsteroidal anti-inflammatories d. Belimumab

5. Which of the following is an ACCURATE statement about rituximab use in SLE?

   a. It is FDA approved for lupus nephritis and autoantibody positive disease refractory to steroids.
   b. It produces short-term improvements in measures of disease activity in disease refractory to steroids and/or immunosuppressive drugs.
   c. Most trials found rituximab ineffective in improving disease activity.
   d. The serious adverse effect and costs of rituximab are less than belimumab.

6. To reduce the risk of retinopathy, hydroxychloroquine should be dosed based on actual body weight rather than ideal body weight and total doses should be less than 5 mg/kg.

   a. True b. False

7. Which of the following is an ACCURATE statement about belimumab?

   a. It blocks the binding of soluble BLyS, a B-cell survival factor, to receptors on B-cells.
   b. Belimumab is FDA approved for the treatment of adult patients with active, autoantibody-positive, SLE as monotherapy.
   c. The subcutaneous formulation is given monthly.
   d. Belimumab is more effective than hydroxychloroquine in reducing flares and overall disease activity.

8. Which of the following has been shown as a benefit of long- term (5 to 7 years) belimumab therapy?

   a. Reduced corticosteroid use b. Reduced severe flare rate
   c. Lower levels of anti-dsDNA autoantibodies
   d. All of the above

9. Which of the following should be a target of therapy in SLE (i.e., treat to target)?

   a. Minimal joint symptoms
   b. Low levels of protein in urine
   c. Low or no disease activity
   d. Reduced risk of cardiovascular disease

10. Which of the following is an accurate statement about medication adherence and persistence in SLE treatment?

    a. The rates of nonadherence with hydroxychloroquine and immunosuppressants are low.
    b. Adherence with hydroxychloroquine has been shown to improve survival
    c. Persistence with therapy is more of a problem than nonadherence.
    d. Achieving hydroxychloroquine levels greater than 1000ng/mL has been shown to improve survival.

Activity Evaluation and Improvement Process

(Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor)

1. Based on the content presented, I am better able to:

   Discuss the impact of uncontrolled systemic lupus erythematosus (SLE) activity on organ damage, mortality, and costs to the healthcare system.

   4 3 2 1

   Assess disease activity and severity, considering the diverse immunopathology and variable expression of SLE in different patients.

   4 3 2 1

   Identify patients who may be nonadherent to current SLE therapies that focus on reducing flares and disease activity.

   4 3 2 1

   Review the safety and efficacy data on current and emerging SLE treatment to control disease activity and prevent or minimize disease flares, drug toxicity, and organ damage in patients with SLE.

   4 3 2 1

   Communicate effectively with SLE patients and the multidisciplinary team to understand and address the needs of each patient and improve treatment adherence, quality of life, and survival outcomes.

   4 3 2 1

   Review new options and strategies that may help improve patient adherence and quality of life, including self-administration of treatment.

   4 3 2 1

   Integrate new evidence into practice to appropriately achieve treatment goals in individual patients with SLE.

   4 3 2 1

   Address payer- and provider-related barriers to appropriate evidence-based use of BLyS-specific inhibitors.

   4 3 2 1

   Apply methods to enable optimal cost management of SLE therapies to be realized by multiple stakeholders including managed care organizations.

   4 3 2 1

2. The activity and presenters were free of bias.

   4 3 2 1

3. The activity was applicable to my position.

   4 3 2 1

4. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

5. Do you plan to change management strategies or patient care in your organization or practice based on the content presented?

   ☐ Yes ☐ No

6. If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?

   _____

   _____

   _____

7. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

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(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF
J. Ronald Hunt, MD

PUBLISHER
Jeremy Williams

JOURNAL MANAGEMENT
Douglas Murphy
Communications Inc.
P.O. Box 71895
Richmond, VA 23255-1895
(804) 387-7580
fax (703) 997-5842

MANAGING EDITOR
Barry Barnum
barry.barnum@douglasmurphy.com

GRAPHIC DESIGN
Douglas Murphy Communications, Inc.

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Maureen A. McMahon, MD, MS; Gary M. Owens, MD; Daniel J. Wallace MD, FACP, MACR

Introduction

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is a chronic, multisystem autoimmune disorder characterized by the production of autoantibodies that result in inflammation and tissue damage.[1] It is a highly heterogeneous disease that is distinguished by flares, spontaneous remission, and relapses. SLE can affect any part of the body but often results in damage to the skin, joints, heart, kidneys, lungs, and nervous system.

SLE affects more than 300,000 people in the United States (U.S.); eighty-five percent of those are female.[2] The highest prevalence of SLE occurs in African Americans, Hispanics, Asians, and Native Americans. SLE affects one in 250 African American women, one in 1,000 caucasian women, and one in 10,000 caucasian men.[3] The peak incidence occurs between 15 and 40 years of age.

Pathophysiology and Presentation

SLE is characterized by production of pathogenic autoantibodies directed against nucleic acids and their binding proteins, reflecting a global loss of self-tolerance and subsequent immune dysregulation.[4] Activation of autoreactive T and B cells start the process of pathogenic autoantibody production and tissue injury. The disease is thought to develop as a consequence of genetic factors, in the setting of environmental triggers and other unknown factors; over 30 genetic loci have been implicated in the pathogenesis of the disease.

The presentation of SLE can be complex, considering the number of organ systems that can be affected by the disease. Exhibit 1 shows the common signs and symptoms of SLE.[5] Manifestations of the disease can range from mild to severe in virtually all organ systems. Arthritis and arthralgias occur in over 90 percent of patients. Most patients have skin and mucous membrane lesions at some point during the course of their disease (e.g. classic butterfly rash, discoid rash, mouth ulcers). Raynaud's phenomenon in SLE is a vasospastic process induced by cold or emotion that occurs in up to 50 percent of patients with SLE. Estimates of vasculitis prevalence from large cohorts range from 11 to 36 percent. Renal involvement is clinically apparent in approximately 50 percent of SLE patients, and is a significant cause of morbidity and mortality. Any structure of the eye can be involved in SLE, with keratoconjunctivitis sicca being the most common manifestation as a result of secondary Sjögren's syndrome. Serious organ or life-threatening complications of SLE include nephritis, thrombocytopenia, cerebritis, thromboemboli, hemolytic anemia, seizures, lupus pneumonitis, alveolar hemorrhage, pulmonary hypertension, and others. Over fifty percent of those with SLE will develop some type of organ-threatening involvement.

In addition to hematologic abnormalities, laboratory features of SLE include findings indicative of autoimmunity. Autoantibodies commonly seen include anti–nuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA), anti-Smith protein (anti-Sm), anti-extractable nuclear antigen to proteins Ro and SSA (anti-Ro/SSA), anti-extractable nuclear antigen to La protein (anti-La/SSB), antibody to ribonucleoprotein (anti-RNP), and antiphospholipid antibodies.

Other Consequences of SLE

In addition to the serious organ or life-threatening complications mentioned previously, there are other consequences of this disease, including accelerated atherosclerosis and bone fractures. Accelerated atherosclerosis is thought to occur secondary to the inflammatory disease process, as seen in rheumatoid arthritis, and the frequent use of corticosteroids can increase the risk for type 2 DM. Compared to the general population, the overall incidence rate of myocardial infarction (MI) is higher in women with SLE.[6] The risk for MI is more than 50 times greater for women with SLE aged 35 to 44, compared to age matched controls without the disease. SLE patients need to be screened early for heart disease and should have risk reduction interventions (smoking cessation, hypertension control, etc.) instituted.

Bone fractures occur in about 12 percent of women with SLE and can have a major impact on quality of life. There is a fivefold increased risk of fracture in SLE women, compared with general population.[7] Those with the highest risk of fracture are older aged at the time of their SLE diagnosis and have a history of longer duration of corticosteroid use.

Mortality Related to SLE

Because of the consequences of SLE, the disease has an impact on mortality. With improved management, especially of kidney disease and infections, survival rates in SLE significantly improved in patients diagnosed from 1980 to 2001, compared with patients diagnosed from 1950 to 1979.[8,9] However, survival is significantly worse than in the general population. Mortality is worse if severe disease or glomerulonephritis is present.[10] There are health disparities in the mortality impact of SLE. African Americans and Texan Hispanics have higher mortality rates, compared with Puerto Rican Hispanics and Caucasians.[11]

Despite improvements in treatment, organ damage accrual rates in SLE are still an issue. In one British cohort, 90 percent of patients had no damage at one year post-diagnosis of SLE; however, by year 10, 50 percent had accrued some damage.[12] Damage accrual was mostly in the neuropsychiatric, renal and musculoskeletal categories, and higher damage scores were associated with a higher risk of death overall. Patients still accrue organ damage even with low disease activity.[13] This may be because most of the therapies, used prior to 2011 for SLE, were not targeting the underlying pathologic issues; additionally, some organ damage may be a complication of treatment, especially chronic corticosteroid use.

Diagnosis

There are two major SLE classification criteria – the American College of Rheumatology (ACR) and the Systemic Lupus International Collaborating Clinic (SLICC).[14,15] The ACR criteria, which many clinicians still use, require four of 11 criteria be present for a definite diagnosis of SLE. These criteria do not include many newer tests that are closely associated with SLE, including complement, Coombs test, or anti-beta2 protein. Other rashes beyond malar rash nor renal biopsy consistent with glomerular nephritis are included in the criteria. To refine the ACR criteria, the SLICC criteria were developed. The SLICC criteria for SLE classification require:

1) Fulfillment of at least four criteria, with at least one clinical criterion and one immunologic criterion or,
2) Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.

Exhibit 2 compares the two criteria.[14,15]

The SLICC criteria have higher sensitivity and similar specificity compared to the ACR criteria and result in fewer misclassifications.[15]

Exhibit 1: Common Signs and Symptoms of Lupus

- Painful or swollen joints and muscle pain
- Unexplained fever
- Rashes, most common in sun exposed areas
- Chest pain upon deep breathing
- Unusual loss of hair
- Raynaud's phenomenon
- Sensitivity to the sun
- Edema in legs or around eyes
- Mouth ulcers
- Swollen glands
- Extreme fatigue

Economic Costs of SLE

An analysis of seven published studies between 2000 and 2010 showed variable costs by disease severity.[16] Mean annual direct costs of SLE patients ranged from $13,735 to $20,926. The costs of those with and without nephritis ranged from $29,034 to $62,651 and $12,273 to $16,575. Pharmaceutical costs comprised 19 to 30 percent of total expenditures, with inpatient costs accounting for 16 to 50 percent and outpatient costs accounting for 24 to 56 percent of overall costs. One study found the average unadjusted cost per mild, moderate, and severe flare, respectively, was $909, $1,539, and $17,059; most of the flare costs were for medical expenditures rather

Exhibit 2: SLICC/ACR Comparison[14,15]

SLICC Clinical Criteria	ACR Criteria
1. **Acute cutaneous lupus** including lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash in the absence of dermatomyositis **or subacute cutaneous lupus** (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias).	1. **Malar Rash** 2. **Photosensitivity**
2. **Chronic cutaneous lupus** including classical discoid rash localized (above the neck) or generalized (above and below the neck) hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chillblains lupus, discoid lupus/lichen planus overlap.	3 **Discoid Rash**
3. **Oral ulcers:** palate, buccal, tongue or nasal ulcers in the absence of other causes, such as vasculitis, Behcets, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods.	4 **Oral Ulcers**
4. **Non-scarring alopecia** (diffuse thinning or hair fragility with visible broken hairs) in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia	**N/A**
5. **Synovitis:** Involving two or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness.	5 **Arthritis**
6. **Serositis:** Typical pleurisy for more than 1 day or pleural effusions or pleura rub Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day or pericardial effusion or pericardial rub or pericaritis by EKG In the absence of other causes, such as infection, uremia, and Dressler's pericarditis	6. **Pleurisy or Pericarditis**
7. **Renal:** Urine protein/creatinine (or 24-hr urine protein) representing 500 mg of protein/24 hr or red blood cell casts.	7. **Renal Disorder**
8. **Neurologic:** seizures, psychosis, mononeuritis multiplex (in the absence of other known causes such as primary vasculitis), myelitis peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection, and diabetes) acute confusional state (in the absence of other causes, including toxic-metabolic, uremia, drugs).	8. **Neurologic Disorder**
9. **Hemolytic anemia**	9. **Hematologic Disorder**
10. **Leukopenia:** (< 4000/mm^3 at least once) (in the absence of other known causes such as Felty's, drugs, and portal hypertension) OR Lymphopenia (< 1000/mm^3 at least once) (in the absence of other known causes such as corticosteroids, drugs, and infection).	
11. **Thrombocytopenia:** (<100,000/mm^3) at least once in the absence of other known causes such as drugs, portal hypertension, and TTP.	
SLICC IMMUNOLOGIC Criteria	**ACR Criteria**
12. **ANA** above laboratory reference range	10. **ANA**
13. **Anti-dsDNA** above laboratory reference range, except ELISA: Twice laboratory reference range	11. **Immunologic Disorder**
14. **Anti-Sm**	
15. **Antiphospholipid antibody:** any of the following: lupus anticoagulant , false-positive RPR medium or high titer anticardiolipin (IgA, IgG or IgM) anti-b_2 glycoprotein I (IgA, IgG or IgM)	
16. **Low complement** C3, C4, CH50	
17. **Direct Coombs test** in the absence of hemolytic anemia	

than pharmaceutical.[17] The frequency and cost of flares increased with disease severity.

Work loss and reduced productivity are also common consequences of SLE. In one trial, mean annual productivity costs (lost hours of productive work) for participants of employment age was $8,659.[18] Another trial found that by four years of follow-up, 57 percent, 34 percent, and 38 percent of those with thrombotic, musculoskeletal, and neuropsychiatric manifestations, respectively, had stopped working, as had 42 percent of those with increased disease activity.[19]

Treatment

In 1965, corticosteroids, methotrexate, azathioprine and cyclophosphamide were available for treating SLE, and little progress was made until 2011. Numerous immunosuppressants and biologics indicated

for other autoimmune or inflammatory diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease have been introduced in recent years; however, none of these are indicated for SLE. Lupus has had an unacceptably high morbidity and mortality rate with past management, and better, more targeted therapies are needed. A biologic, belimumab, was FDA approved in 2011 for SLE and will hopefully continue improving morbidity and mortality.

The approach to the treatment of lupus depends on the type and the severity of disease. General recommendations for all patients include sun protection, proper diet and nutrition, exercise, smoking cessation, appropriate immunizations, and management of comorbid conditions and cardiovascular (CV) disease risk factors. The European League Against Rheumatism (EULAR) released recommendations for the treatment of SLE in 2007; the ACR has developed guidelines for managing lupus nephritis and is currently developing guidelines for SLE in general.[20,21]

Nonsteroidal anti-inflammatories (NSAIDs) are used to decrease joint swelling, joint pain, fever, and inflammation of the heart and pleura, and they are often effective for those with milder disease. The major adverse effects include gastrointestinal upset and bleeding, fluid retention, increased CV risk, renal toxicity, hypertension, and hepatic toxicity.

Hydroxychloroquine (Plaquenil®), an agent used in the past to prevent and treat malaria, has a central role in the long-term treatment of every patient with lupus at a dose of 200 – 400 mg daily because it has been shown to reduce flares and prolong survival.[22] As early as World War II, it was found to be effective for lupus-related arthritis, fatigue, rashes, and mouth sores. It may interfere with T-cell activation and inhibit cytokine activity and is also thought to inhibit intracellular toll-like receptors. Adverse effects include macular damage to the eyes and muscle weakness. To reduce the risk of retinopathy, guidelines from the American Academy of Ophthalmology recommend that this medication be dosed based on actual body weight rather than ideal body weight and that doses be below 5 mg/kg.[23] Unfortunately, 38 to 50 percent of patients are overdosed.[24,25]

Patients with serious or life-threatening problems such as nephritis, lung or heart involvement, and central nervous system symptoms need more aggressive treatment. This may include high-dose corticosteroids, such as prednisone and immunosuppressants in addition to hydroxychloroquine and NSAIDs. The long-term adverse effects of corticosteroids are numerous; therefore, the lowest doses possible should be used for daily therapy. The ACR guidelines for managing lupus nephritis recommend high-dose corticosteroids for induction and low-dose daily corticosteroids in combination with other immunosuppressants for maintenance in some cases.[21]

Immunosuppressants used in severe SLE, particularly if lupus nephritis or central nervous system disease are present, include azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil. Although studied and frequently used for the disease, none of these agents are specifically FDA approved for treating SLE. Adverse effects include myelosuppression, hepatotoxicity, and renal dysfunction.

Biologics for Treatment of SLE

Biologics are also used in SLE to more specifically target the underlying pathophysiology of autoimmunity. Several uncontrolled observational studies have reported efficacy of rituximab (Rituxan®), a B-cell-depleting chimeric monoclonal antibody, in the treatment of SLE patients, with and without lupus nephritis, who have failed to respond to standard treatment.[26-28] A systematic review of SLE patients with active disease refractory to steroids and/or immunosuppressive drugs assessed the efficacy and safety of rituximab on non-renal outcomes and found short-term improvements in measures of disease activity.[29] Two randomized trials found that rituximab did not provide any significant benefit, compared with controls.[30,31] Both comparator groups in these trials were receiving high doses of glucocorticoids in addition to immune suppression; thus, the efficacy of rituximab may have been diluted. Rituximab is not currently FDA approved for treating SLE, and its role in SLE remains controversial.

Tocilizumab (Actemra®), an interleukin-6 antagonist; abatacept (Orencia®), a selective T- cell costimulation modulator, and anti-tumor necrosis factor (TNF) agents have also been studied for SLE treatment. These agents are all FDA approved for rheumatoid arthritis treatment, but they are not approved for treatment of SLE.

Belimumab

The first biologic specifically developed for treating SLE is belimumab (Benlysta®), a human monoclonal antibody that inhibits B-lymphocyte stimulator (BLyS).[32] Belimumab blocks the binding of soluble BLyS, a B-cell survival factor, to receptors on B cells. BLyS is a member of the TNF ligand superfamily and contributes to B-cell proliferation and differentiation. Levels of BLyS are elevated in some patients with SLE, and it may play a role in the pathogenesis of lupus by promoting the formation and survival of memory B cells and plasmablasts making autoantibodies.

Belimumab is FDA approved for the treatment of adult patients with active, autoantibody-positive

SLE who are receiving standard therapy. It has been studied only as an adjunct to standard therapy rather than as a replacement monotherapy. It was initially available as an intravenous infusion given at two-week intervals for the first three doses and at four-week intervals thereafter. A subcutaneous self-injection formulation was approved in 2017 and is given as 200 mg once weekly.[33]

Two year-long Phase III trials were conducted for FDA approval; both trials used doses of 1 mg/kg and 10 mg/kg. These trials enrolled SLE patients if they had Safety of Oestrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA–SLEDAI) scores of 6 or higher, were seropositive for ANAs and/or anti-dsDNA at two independent time points, and had received standard care for at least 30 days. Belimumab plus standard therapy significantly improved the SLE responder index (SRI) response rate (~50% vs 39%), reduced disease activity (~52% vs 41%) and severe flares (reduced by 35%), and was generally well tolerated, compared to placebo.[34, 35] A similarly designed trial conducted in Asia found that the SRI response rate was higher with belimumab versus placebo (53.8% vs 40.1%; $P = 0.0001$).[36] Patients in the belimumab group had a 50 percent lower risk of experiencing a severe flare. If the baseline prednisone dose was greater than 7.5 mg/day, there was a significant reduction in steroid use favoring belimumab (P=0.0228).

Long-term data (5-6 years) from ongoing open-label portions of trials used to get FDA approval of belimumab are showing 87.6 percent of patients have no organ damage accrual.[37] High-risk patients with pre-existing organ damage also had low accrual (81.5%). Both findings suggest a favorable effect on future damage development.

The efficacy of belimumab appears to increase over time. Severe flares occurred in 19 percent with placebo and 17 percent with belimumab during the first year, with the annual rate declining to 2 percent to 9 percent during years two to seven of belimumab therapy.[38] Anti-dsDNA autoantibodies in patients positive for them at baseline had a progressive decline of 40 percent to 60 percent from baseline over two to seven years of treatment with belimumab. Corticosteroid use decreased over time, with a 50 to 55 percent reduction in median dose during years five to seven. Reduced corticosteroid use should have a tremendous impact on the development of osteoporosis and type 2 diabetes.

The most commonly reported adverse effects with infusion of belimumab are nausea, diarrhea, pyrexia, bronchitis, insomnia, extremity pain, depression, and migraine. Skin reactions are the most common adverse effect with subcutaneous injection. In trials, serious infections occurred in about 6 percent of all belimumab patients and in about 5 percent of placebo patients.[39]

Rates of treatment discontinuation owing to any adverse effect were lower in the belimumab patients (6.2% vs 7.1% for placebo).[39] Infusion reactions were the most common reason for discontinuing belimumab therapy (1.6%).

The efficacy of belimumab has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide, thus use is not recommended in these situations.

Overall, belimumab has shown modest efficacy in SLE treatment without significant side effects. The advantage to this agent may be the long-term benefits of reduced autoantibodies, flares, and corticosteroid use. It would be very helpful to determine if any subgroups of patients, in particular, benefit from its use and whether it might work better in combination with another therapy or as monotherapy. The UK National Institute for Health and Care Excellence (NICE) assessment recommends belimumab as an add-on treatment option for active autoantibody-positive SLE in adults only if there is evidence for serological disease activity (defined as positive anti-double-stranded DNA and low complement) and a SELENA-SLEDAI score of greater than or equal to 10 despite standard treatment.[40] Furthermore, the assessment recommends treatment with belimumab should only be continued beyond 24 weeks if the SELENA-SLEDAI score has improved by 4 points or more.

Investigational Agents

Many different biologic and small molecule therapies will likely be coming to market for SLE treatment in the next five to 10 years. Agents targeting T cells, B cells, complement, various interleukins, toll-like receptors, and Janus kinase are all under investigation for SLE and specifically for lupus nephritis. For example, atacicept modulates the biological functions of B cells through BLyS and a proliferation-inducing ligand (APRIL) by binding to and sequestering them, thus preventing them from activating their receptors. Atacicept treatment showed evidence of efficacy in SLE, particularly in those with serologically active disease or high disease activity.[41] Several therapies already FDA approved for other diseases are also under investigation. These include toclizumab (Actemra ®), ustekinumab (Stelara®), tofacitinib (Xeljanz®), and baricitinib (Olumiant®).

Medication Nonadherence

Medication nonadherence is a problem in SLE, as

Exhibit 3: FDA Guidance for Industry on Developing Medicinal Products for SLE Treatment

- Two adequate and well controlled trials are needed; Superiority trials with open label extension preferred.
- The trials should be randomized controlled trials of one year's duration; patients should fulfill ACR criteria for SLE.
- Patients should be stratified by severity.
- BILAG-2004 is preferred disease activity index. SLEDAI, ECLAM, and SLAM are acceptable.
- Guidance defines major clinical response; partial clinical responses, remission, reduction in flare, increase in time to flare.
- Steroid use variability should be minimized and sparing effects defined.
- Patient reported outcome measures should be evaluated.
- Biomarkers are potentially applicable.

in other chronic diseases. U.S. Medicaid data from 2000 to 2006 for adults aged 18 to 64 years with SLE found 79 percent of those taking hydroxychloroquine and 83 percent taking immunosuppressants were nonadherent.[42] There were higher rates of emergency room visits and hospitalizations in those with nonadherence, compared to those who were adherent.[42] Another trial found 39 percent nonadherence with prednisone, 51 percent with hydroxychloroquine, and 43 percent with immunosuppressants.[43]

Hydroxychloroquine nonadherence is associated with an increase in flare rates and adherence is associated with increased survival. Risk factors for nonadherence in this trial were single status, low education level, complicated medication regimens, limited comprehension of physician explanations, and medications dosed more than once daily. Other determinants of nonadherence include depression and rural residence.[44] Persistence with therapy is also an issue. In a systematic review of 11 "real-world" observational studies, up to 33 percent of patients discontinued therapy within five years.[44] No specific data on belimumab adherence or persistence have been published to date.

One strategy to improve outcomes in SLE and medication adherence is to monitor medication serum levels. Measurement of drug or metabolite concentrations has been shown in a number of studies to identify under- and over-dosing, predict efficacy, and detect non-adherence to therapy, with positive associations between optimum drug or metabolite levels and improved outcomes.[45] Hydroxychloroquine levels greater than 1,000ng/mL are associated with lower flares and levels greater than 600ng/mL are associated with renal protection.[46] Mycophenolic acid steady state levels less than 3mg/L correlate with flare risk in non-renal lupus.[47] One hour post dose levels of mycophenolate greater than 13 mg/L are associated with better outcomes in lupus nephritis.[48]

Improved communication with patients and decision making aids can also help improve adherence.[49] Overall, medication adherence and persistence support are necessary to help patients achieve optimal outcomes.

Assessing Clinical Effectiveness in Trials

In 1999, the first efforts to better define outcomes in SLE trials were published. The FDA has since established guidance for SLE trials (Exhibit 3). Since 2005, 20 medications for SLE drugs have failed in Phase II/III trials to meet their primary endpoint using the FDA guidance document. There are various reasons why the trials failed, including the medication did not work or was not safe, the trial design was flawed, a poor choice of a primary outcome measure was selected, the trial was badly implemented due to complex logistics, certain factors discouraged enrollment, poor site selection (geographical bias), poor choice of concomitant medications allowed or disallowed, artificially mandated use of steroids and tapering that are not used in clinical practices, and inadequate assessment instruments. There is concern among clinicians and researchers that many medications which possibly could be effective are not making it to market because of poor trial design or the use of the wrong outcome measures.

The British Isles Lupus Assessment Group-2004 (BILAG-2004) is the FDA preferred disease activity index and includes 86 items in one of nine organ domains (musculoskeletal, mucocutaneous, cardio-

Exhibit 4: Consensus Definition of Lupus Low Disease Activity State[52]

Domain and Items
Disease Activity
1. SLEDAI-2K ≤ 4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity.
2. No new features of lupus disease activity compared with the previous assessment.
3. SELENA-SLEDAI physician global assessment (PGA scale 0 - 3) ≤ 1.
Immunosuppressive Medications
4. Current prednisolone (or equivalent) dose ≤ 75mg daily.
5. Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs.

respiratory, renal, neuropsychiatric, hematologic, constitutional, gastrointestinal, and ophthalmic). The resulting scores for each organ domain can be A through E, where A is very active disease, B is moderate activity, C is mild stable disease, D is resolved activity, and E indicates the organ was never involved during the last 30 days. This scale is intended and validated to demonstrate clinical activity, but it was not developed for use in clinical trials. It also has other shortcomings, including poor central/site scoring correlations, it is time consuming to understand definitions in the instrument, and English language proficiency is required. Even though 86 factors are included, Raynaud's disease is not and the scale is weighted toward gastrointestinal and eye findings, which are seen in less than 1 percent of patients. Other FDA acceptable disease activity assessment tools include the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), the Systemic Lupus Activity Measure (SLAM), and the European Consensus Lupus Activity Measurement (ECLAM).

Assessing Therapy Effectiveness in Clinical Practice

There is no universally used outcome tool for assessing therapy effectiveness in clinical practice. Determining the appropriate therapeutic regimen requires an accurate assessment of both disease activity and severity, and a clear understanding of the patient's response to previous and ongoing therapeutic interventions. There are generally three patterns of disease to consider: intermittent disease flares (or relapsing and remitting disease with periods of disease quiescence in between flares), chronically active disease in terms of patterns of organ involvement, and quiescent disease. In clinical practice, disease activity and severity are assessed using a combination of clinical history, physical examination, laboratory and serologic studies as well as organ-specific tests.[50] Biomarkers for assessing response to treatment are under study.[51]

Treating to low or no disease activity is becoming routine in rheumatoid arthritis, but no comparable goal has been commonly used for SLE treatment. A consensus definition of lupus low disease activity state (LLDAS) has been developed and preliminary validation demonstrates its attainment to be associated with improved outcomes in SLE (Exhibit 4).[52] In the initial validation study in 191 patients followed for a mean of 3.9 years, patients who spent greater than 50 percent of their observed time in LLDAS had significantly reduced organ damage accrual, compared with patients who spent less than 50 percent of their time in LLDAS ($p = 0.0007$) and were significantly less likely to have an increase in SDI of ≥1 (relative risk 0.47, 95% CI 0.28 to 0.79, $p = 0.005$).[52] Another trial found that patients who spent at least two consecutive years in LLDAS had significantly less damage accrual compared with patients never in LLDAS ($p = 0.001$), and were significantly less likely to have an increase in SDI.[53]

Reductions in disease activity scores have been shown to correlate with reduced health care resource utilization (HRU) and costs. SLEDAI score reductions of 4 points result in 10 percent reductions of HRU and 14 percent of costs over a 30-day

period. Reductions of 8 points led to 19 percent reductions of HRU and 26 percent of costs; 10 point reductions were associated with HRU reductions of 23 percent and costs by 31 percent.[54] Annualized reductions in disease activity scores were associated with annualized cost reductions, ranging from $2,485 to $5,679.[54] This analysis only focused on short-term effects and did not determine the potential benefits of low disease activity on costs related to long-term organ damage prevention or comorbidities, but these are likely to be substantial.

Payer Challenges

Treatment of inflammatory conditions, including lupus, is the largest category of specialty spending. According to Express Scripts, inflammatory conditions have been the most expensive specialty therapy class for several years.[55] Management of belimumab and any subsequently approved biologics is driven by category cost concerns.

Because belimumab is a specialty drug which costs $35,000 to $40,000 annually, most payers manage it with prior authorization. Typical prior authorization features in initial authorization include medically necessary for the treatment of adults (aged 18 years or older) with active SLE and positive autoantibody test (may require specific titers), must be receiving standard therapy comprising any of the following (alone or in combination): antimalarials, corticosteroids, immunosuppressives (excluding intravenous cyclophosphamide), and NSAIDs. Ongoing authorization typically requires documentation of improvement in disease activity following treatment with belimumab, indicating a therapeutic response and no evidence of severe renal disease, or active central nervous system lupus.

Management of biologic use is still about determining the right therapy for the right patient, while being fiscally responsible. In addition to prior authorization, management strategies include step therapy through non-biological immunosuppressants before biologicals, preferred biological agents, if there is more than one choice, limited prescribing of biologicals to appropriate specialists, guideline-based management, and managing site of service. Now that a subcutaneous formulation of belimumab is available, plans may prefer it over the use of intravenous infusion as a lower cost option.

Conclusion

SLE is characterized by a significant increase in morbidity and mortality. Patient medication nonadherence is a major reason for disease flares and poorer outcomes. Current metrics for measuring lupus activity are in need for improvement. Clinical design is evolving and new methods of clinical ascertainment will lead to the successful introduction of biologics and targeted therapies over the next five years. The novel disease-modifying drug, belimumab, when combined with standard of care, has the potential to delay disease progression and improve clinical outcomes.

Author Bios

Maureen A. McMahon, MD, MS is Associate Clinical Professor in the Division of Rheumatology at the UCLA David Geffen School of Medicine, Los Angeles, CA.

Daniel J. Wallace MD, FACP, MACR is a Clinical Professor of Medicine at the Cedars-Sinai Medical Center and the UCLA David Geffen School of Medicine, Los Angeles, CA.

Gary M. Owens, MD is the President of Gary Owens Associates.

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