RENO AND NONRENA FLARES IN
SYSTEMIC LUPUS ERYTHEMATOSUS:
MEETING THE CLINICAL CHALLENGE

Introduction 3
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Flares and Remissions: 3
The Characteristic Course of SLE
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Clinical Features and Complications of SLE 6
Michelle Petri, MD, MPH
Professor, Division of Rheumatology
Department of Medicine
Johns Hopkins University School of Medicine
Baltimore

Managing Flares I: 8
Treatment Options for Nonrenal SLE Flares
Joan T. Merrill, MD
OMRF Professor of Medicine
University of Oklahoma Health Sciences Center
Head, Clinical Pharmacology Research Program
Oklahoma Medical Research Foundation
Oklahoma City

Managing Flares II: 10
Treatment Options for Renal Flares
Ellen M. Ginzler, MD, MPH
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Chief of Rheumatology
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CME Post-Test and Evaluation 12

TARGET AUDIENCE: This activity has been developed for rheumatologists involved in the care of patients with systemic lupus erythematosus (SLE), including the complications of SLE such as lupus nephritis.

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Renal and Nonrenal Flares in Systemic Lupus Erythematosus: Meeting the Clinical Challenge

Statement of Need: Systemic lupus erythematosus (SLE) is a chronic, inflammatory autoimmune disease that may affect the skin, heart, lungs, blood, kidneys, and/or musculoskeletal system, often beginning with one organ system at the onset of the disease and possibly involving other systems as the disease progresses. Because many of the manifestations of the disease in the various organ systems may mimic the symptoms of a wide range of diseases, the diagnosis of SLE can be a clinical challenge. SLE may be mild or remittent, or in some patients, the symptoms may be severe and life-threatening.

SLE is characterized by flares and remission of disease, and treatment must effectively address the various phases: induction of remission, maintenance of remission, and management of flares. Renal complications—lupus nephritis—develop in 50% of patients with SLE. Unless lupus nephritis is well controlled, the disease can progress to end-stage renal disease, with the need for dialysis and/or organ transplantation.

Clinicians must remain updated on the most recent results of ongoing research on the diagnosis of SLE and its complications, but most particularly on advances in pharmacologic therapy. This program provides practitioners with information of practical clinical use and on therapies currently in clinical trials that may result in treatment advances.

Educational Objectives: At the conclusion of this supplement, the participants should be able to:

- list the signs, symptoms, and clinical impact of SLE.
- outline the clinical course of SLE, the importance of renal and nonrenal flares, and how flares are defined.
- state the treatment options for both nonrenal and renal flares and explain the importance and benefits of early treatment.
- describe the management of nonrenal clinical features of SLE.

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Currently, only three agents are approved by the US Food and Drug Administration for SLE. They are hydroxychloroquine, corticosteroids, and acetylsalicylic acid. Discussion of use of any other agent is considered off-label/investigational.

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INTRODUCTION

Robert Lafyatis, MD, Course Director

Despite the scrutiny of laboratory and clinical investigators, systemic lupus erythematosus (SLE) continues to challenge clinicians and their patients, who number 1.5 million in the United States.1 The precise cause of the disease remains unknown, although research has clearly shown that an autoimmune cascade generates waves of autoantibodies that can induce organ-destructing inflammation at multiple sites in the body.

In the absence of a cure, better patient care has led to improved SLE survival. Since the 1980s, 5-year survival for SLE has increased beyond 90%.2 However, as patients live longer, disease morbidity and treatment-related complications are encountered with increasing frequency. Whereas disease flares and infections are significant contributors to mortality early in the course of the disease, coronary artery disease has emerged as a leading cause of death in patients with long-standing SLE.3

Long-term follow-up of patients with SLE has revealed several distinct disease patterns. True remission is rare, but some patients do have long periods of quiescence. The most common SLE patterns are relapsing/remitting and chronic activity.4 The ability to prevent target organ damage plays a major role in the clinical course and outcome of SLE.5

Clinicians who care for patients with SLE continue to be hampered by a lack of specific therapies. Currently, only three drugs are approved for treatment of SLE: hydroxychloroquine, corticosteroids, and acetylsalicylic acid. Since landmark studies showing its efficacy, cyclophosphamide has become the standard of care for lupus nephritis and also used for other severe disease manifestations. Recently, however, mycophenolate mofetil demonstrated superior activity and a more favorable side-effect profile in a randomized comparison against cyclophosphamide.6

Other agents being evaluated as potential SLE therapies include rituximab, leflunamide, and abatacept. Investigational compounds in various stages of clinical evaluation for SLE include belimumab, epratuzumab, and edratide. The rapid progress in investigating new therapeutics—targeting different aspects of the immune system—will hopefully lead to new treatments of SLE in the near future.

Recently, a panel of experts in the management of SLE discussed the current status of the disease and its treatment options. Their presentations and observations are summarized in the following supplement to Rheumatology News. Readers will find the articles timely, informative, and readily applicable to the care of patients with SLE.

References

FLARES AND REMISSIONS: THE CHARACTERISTIC COURSE OF SLE

Bevra H. Hahn, MD, Chair

The onset of clinical systemic lupus erythematosus (SLE) may be abrupt and occur over a period of a few weeks, or it may take years to evolve. The condition has its genesis in genetic susceptibility, and the number of genes and genetic alterations identified as predisposing continues to increase. For reasons that have yet to be fully explained, SLE has a pronounced female predominance. Various environmental factors contribute to emergence of SLE, including ultraviolet light and infection with Epstein-Barr virus. An abnormal immune response, characterized by SLE autoantibodies, precedes the onset of symptomatic SLE, usually by about 3 years.

The emergence of clinical disease in patients with SLE is associated with inflammation, complement activation, the release of cytokines and chemokines, and activation of proteolytic enzymes. Symptomatic expression of SLE leads to acute and chronic inflammation and chronic oxidative damage that can affect multiple organ systems.

The various predisposing factors involved in the evolution of SLE suggest opportunities to intervene and prevent the emergence of clinical disease. Key stages in the disease process exhibit a dichotomous path of progression. For example, some patients with SLE autoantibodies develop clinical disease and others do not. Some patients with clinical disease have target organ damage and others do not. This dichotomy in disease expression should guide the development of strategies to arrest the disease process.

Recent Epidemiologic Trends

One notable trend in SLE epidemiology has been improved survival, which has been documented in multiple, recently published studies from the United States, Canada, Europe, and Japan (Figure on page 4).15 Throughout the developed world, the 10-year survival among patients with SLE exceeds 90%, and 30-year survival is approximately 70%. Both figures represent dramatic improvement compared to 20 years ago. Deaths from renal disease and infection are declining; although atherosclerosis—a major principal cause of death in patients with SLE after the first decade of disease—is increasing. In addition, the presence of lupus nephritis continues to have an adverse impact on survival.

Factors that predict a poor prognosis in SLE—that is, 10-year mortality of approximately 50%—have been well defined (Table on page 5). These include proliferative forms of nephritis; failure of serum creatinine levels and proteinuria to improve after 6 months of treatment; severe SLE, defined by SLE Disease Activity Index (SLEDAI) score >10 and major-organ involvement; hemolytic anemia; low serum complement; the presence of antiphospholipid antibodies; vascular disease; African American or Hispanic/Texas ethnicity; and poverty.15,20

Classification Criteria for Renal Biopsy

Renal biopsy is recommended in all patients with nephritis if the risk is acceptable. Physicians who request renal biopsies should expect pathologists and nephrologists to follow the most recent update of
the renal biopsy histologic classification criteria developed by the International Society of Nephrology and the Renal Pathology Society. However, the criteria do not address the status of the renal tubules or blood vessels; comments about these aspects of the biopsy should be included in the pathology report because loss of tubules and extensive vascular damage predict a worse prognosis and have implications for therapy.

**Evaluating New Therapies**

Several possible therapies for SLE have entered clinical evaluation within the past 5 to 10 years. Some agents that demonstrated promise nonetheless failed to secure licensing approval. These unsuccessful ventures have revealed aspects of the clinical evaluation process that could be improved. Criticism of SLE clinical trials includes the assertion that current American College of Rheumatology (ACR) diagnostic criteria for SLE are inadequate. For example, development of peripheral neuropathy clearly results from the autoimmune disease but is not a criterion for diagnosis of SLE and, thus, might not be sufficient to enroll a patient in a clinical trial.

A second challenge in the clinical evaluation of new therapies for SLE relates to imperfect patient populations. As an example, patients screened for enrollment in a trial might be seronegative for antinuclear antibodies. Not uncommonly in clinical practice, patients with active SLE no longer have autoantibodies that are diagnostic for SLE. Such heterogeneity poses a dilemma when investigators are considering patients for enrollment in clinical trials.

In addition, data from clinical studies demonstrate a lack of class I evidence from prospective, double-blind, randomized trials that meet the proposed primary outcome. However, it is my opinion that current criteria for diagnosis, disease activity, and damage are adequate to identify highly effective therapies in a properly designed prospective controlled trial.

The ACR recently developed criteria to evaluate the quality of evidence in clinical studies for lupus nephritis. According to the ACR, an effective therapy should demonstrate evidence of a beneficial effect on renal function, protein, and urine sediment, as well as evidence of durability of these effects.

In evaluating therapy for SLE patients with active disease, clinicians should focus on three issues: (1) whether therapy induces acceptable improvement (remission, if possible), (2) whether it maintains improvement, and (3) whether it prevents organ damage.

**Current Therapies**

**Cyclophosphamide.** Cyclophosphamide remains an effective treatment option for SLE. A meta-analysis of clinical trials involving patients with lupus nephritis showed that intravenous (IV) cyclophosphamide reduced mortality by 20% and the risk of end-stage renal disease by 16% compared to prednisone. Moreover, the number needed to treat with an immunosuppressant plus prednisone to prevent one death was 7.6, making that combination highly cost-effective.

Despite its effectiveness, cyclophosphamide’s toxicity potential often leads to side effects that many patients cannot tolerate. Alternative formulations and treatment schedules have been examined with mixed results. Daily oral therapy has proven to be no safer or more effective than monthly IV administration. Limited evidence suggests that administration of cyclophosphamide at lower doses over shorter time intervals might be better tolerated, with no loss of efficacy. Starting patients on cyclophosphamide and then transitioning them to a less toxic immunosuppressant after 6 months is an option that is currently being explored.

Finally, clinical experience with mycophenolate mofetil (MMF) suggests that it may be better and safer than cyclophosphamide both to induce or to maintain improvement in lupus nephritis.

**Azathioprine.** For some time, azathioprine has been viewed as less potent than cyclophosphamide for treatment of lupus nephritis; however, a recent publication might have reopened the debate. A group of Dutch investigators reported that azathioprine plus pulsed methylprednisolone and oral prednisone led to at least as many complete and partial remissions as did cyclophosphamide and oral prednisone. However, after a median follow-up of 5.7 years, more patients on azathioprine had a doubling of serum creatinine; fewer remained relapse-free and/or avoided the combined end point of end-stage renal disease, relapse, and death. Azathioprine was not as good as cyclophosphamide for maintaining remission.

In another study involving patients with lupus nephritis, investigators compared MMF, cyclophosphamide, and azathioprine as maintenance therapy after cyclophosphamide induction therapy. All patients received seven monthly IV bolus doses of cyclophosphamide plus corticosteroids and then were randomized to maintenance therapy with quarterly IV cyclophosphamide, daily oral MMF, or daily oral azathioprine for 1 to 3 years. The results showed that MMF was significantly better than IV cyclophosphamide, that azathioprine had a small, but non-significant, advantage over IV cyclophosphamide, and that MMF and azathioprine demonstrated similar efficacy for maintaining improvement.

**Mycophenolate Mofetil.** Oral MMF demonstrated a significant advantage over IV cyclophosphamide in inducing improvement in patients with active lupus nephritis in a recent randomized, controlled clinical trial. The results of that trial are discussed in Dr. Ginzler’s article on page 10 of this supplement.

**Current Therapies in Summary.** Many clinicians today have adopted a standard of care of induction therapy with daily MMF plus corticosteroids, or monthly IV cyclophosphamide plus corticosteroids, until clinical response or 6 months; this should be followed by maintenance therapy.
with daily MMF, daily azathioprine, or possibly quarterly cyclophosphamide.

Proteinuria with or without hypertension should be treated with an angiotensin-converting enzyme (ACE) inhibitor or the combination of an ACE inhibitor and an angiotensin-receptor blocker (ARB).

**Prevention of Organ Damage**

Preventing organ damage attributable to SLE or its therapy is now possible, at least for some organ systems. Cyclophosphamide-induced damage to the ovaries can be prevented by administering the gonadotropin-releasing hormone analog leuprolide, 3.75 mg once a month, 10 to 14 days before each IV dose of cyclophosphamide. A recent nonrandomized study of leuprolide treatment compared to no leuprolide demonstrated ovarian preservation of nearly 100% in women who opted for leuprolide treatment. Treatment with hydroxychloroquine offers the potential for significant, although incomplete, protection against organ damage. Findings from a large prospective cohort study showed treatment with hydroxychloroquine remained protective against damage accrual in patients with SLE who had no evidence of organ damage at baseline.

As previously stated, prevention of renal damage in patients with proteinuria is more likely in those who have good blood pressure control and those who are treated with an ACE inhibitor or an ACE inhibitor plus anARB, whether or not they are hypertensive.

Morbidity and mortality attributable to atherosclerosis continue to increase in patients with SLE. Multiple cardiovascular therapies can help reduce atherosclerotic risk in SLE; these include antihypertensives, ACE inhibitors and ARBs, statin lipid-lowering drugs, and aspirin and antimalarials to reduce clotting potential. In addition, suppression of SLE disease activity affords further protection against atherosclerosis and its complications.

**Infection Prevention.** Infection of any type can pose a serious threat to the patient with SLE. An effective prevention strategy should incorporate immunization and suppression therapies. All patients are potential candidates for immunization against influenza virus and *Pneumococcus*, and human papillomavirus. Splenectomized patients also should consider immunization against *Meningococcus*.

Patients with the following conditions should receive certain types of preventive therapy: *Pneumocystis carinii* pneumonia in highly immunosuppressed patients, recurrent urinary tract infections, and recurrent oral/genital herpes infections.

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**Table. Indicators of Poor Prognosis in SLE**

<table>
<thead>
<tr>
<th>Indicator of Poor Prognosis</th>
<th>Bone Mass and Reducing Complications in SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Cr &gt;1.4 mg/dL</td>
<td>Calcium</td>
</tr>
<tr>
<td>Urinary protein &gt; 2.6 g</td>
<td>Maintenance</td>
</tr>
<tr>
<td>Chronic change on biopsy</td>
<td>Improvement of Glomerular Damage</td>
</tr>
<tr>
<td>Failure of Cr and urinary protein to improve at 6 months of Rx</td>
<td>Prevention of Osteoporosis</td>
</tr>
<tr>
<td>Severe disease: high activity (SLEDAl &gt;10)</td>
<td>Major organs involved</td>
</tr>
<tr>
<td>Cr-creatinine</td>
<td>SLEDAl—systemic lupus erythematosus Disease Activity Index</td>
</tr>
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</table>

**Prevention of Osteoporosis**

Chronic treatment with glucocorticoids can predispose patients to osteoporosis. Bisphosphonate therapy has demonstrated superiority over vitamin D plus calcium for maintaining bone mass and reducing fracture risk in patients on glucocorticoid therapy.

**Summary**

Mortality associated with SLE has declined substantially over the past 20 years, including most of the prominent causes of death. The current standard of care for patients with SLE should focus on achieving three principal therapeutic goals: (1) induction of acceptable improvement and remission if possible; (2) maintenance of the improvement; and (3) prevention of organ damage. IV cyclophosphamide remains an accepted standard of care for patients with lupus nephritis, although recent studies suggest that mycoplhenolate mofetil might be superior with respect to efficacy and tolerability. Patients with SLE also should receive appropriate treatment to prevent organ damage, athroerosclerosis, infection, and steroid-induced osteoporosis.

**References**

Advances in laboratory and clinical research have helped solve some of the mysteries surrounding systemic lupus erythematosus (SLE), but knowledge about many aspects of the condition remains incomplete. For example, clinicians now have at their disposal a variety of objective information to guide their recognition of lupus flares. Yet, the overall status of flare recognition might be likened to the age-old subjective definition applied to objectionable literature or art: I know it when I see it. Similarly, a number of clues have emerged to aid in identifying patients who are more likely to have disease flares, but flares remain difficult to predict. At least two aspects of SLE have become quite clear: (1) true remission rarely occurs and (2) organ system damage frequently occurs. This mix of imprecision and certainty challenges physicians to combine the sciences of medicine and the art of medicine to provide the best care possible for patients with SLE.

Nonrenal SLE Flares

Three distinct patterns of disease activity have been identified in patients with SLE: flare (relapsing/remitting), chronic activity, and long quiescence. Between 40% and 50% of patients with SLE fall into the relapsing/remitting category, which is characterized by spikes in disease activity followed by obvious declines in activity. The pattern has been demonstrated with multiple types of disease activity indices. In the Johns Hopkins SLE patient population, the incidence of flare is 0.65 per patient-year, and the median time to flare is 12 months.

Equally prevalent is a pattern we have characterized as “chronic activity.” In the Johns Hopkins experience, about half of patients with lupus have some degree of disease activity on an ongoing basis. The physician might tolerate some types of disease activity indices. In the Johns Hopkins cohort, 9 half of patients have accrued organ damage, some types of chronic activity because some of our current treatments, such as prednisone, are too toxic to use in high doses.

Flare Characteristics

Multiple recent studies have identified a variety of environmental triggers of SLE itself and of SLE flares. Documented triggers include exposure to ultraviolet light, certain drugs (including echinacea and granulocyte colony-stimulating factor), smoking, and infections/antibiotic therapy. Unfortunately, these triggers do not uniformly induce SLE flares, so physicians are left to tell their patients that flares are unpredictable.

Flares, both nonrenal and renal, can be prevented with hydroxychloroquine prophylaxis. Every patient with lupus should receive hydroxychloroquine and continue to receive it even after an episode of lupus nephritis has been controlled; continuing the drug can double the rate of complete response with mycophenolate mofetil therapy. Flares can involve multiple organ systems. The most common sites of involvement are cutaneous and musculoskeletal. This observation emphasizes that current treatment of SLE still routinely involves the use of older drugs such as hydroxychloroquine to address cutaneous and musculoskeletal manifestations that do not require immunosuppression.

The utility of serologic tests in the management of SLE has been controversial. Certainly, the presence of anti-dsDNA or low serum complement levels is very useful in helping make the diagnosis of SLE. However, anti-dsDNA antibody levels actually decline on the day that a patient presents with a flare. The levels likely decline because the anti-dsDNA forms immune complexes that are deposited in organs.

At Johns Hopkins, we have evaluated the impact of demographic and serologic factors on the predictive ability of the British Isles Lupus Assessment Group (BILAG) index of SLE disease activity. We identified several factors that can be useful in predicting a patient’s risk of flare during the next year. Statistically significant prognostic factors were African American ethnicity, low levels of complement 3 and complement 4, and anti-dsDNA positivity (Table 1).

In our experience, the presence of these factors doubles the likelihood that a patient will have a flare during the next 12 months.

Long Quiescence/Remission

Long quiescence is the pattern that all clinicians wish for their patients with SLE. Patients in long quiescence have prolonged periods without detectable disease activity. The term “remission” probably should not be used, because disease activity may eventually return. We recently developed a definition of remission that is based on three criteria: no clinical or laboratory disease activity for 2 years, no use of prednisone, and no use of immunosuppressive agents. By this definition, we found that only 3.4% of our patients with SLE at Johns Hopkins achieved remission.

Organ Damage

Avoidance of permanent organ damage is the key to long-term survival in SLE. Data from a Toronto SLE cohort demonstrated a 10-year survival of 93% in patients who had no organ damage at initial presentation compared to 75% in patients who had early organ damage by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology index ($P=0.0002$).

In the Johns Hopkins cohort, half the patients have accrued organ damage, headed by a 25.2% incidence of musculoskeletal injury. Obviously, some types of damage, such as cardiovascular and renal, have greater implications for survival. In our cohort, 10% of patients have cardiovascular damage and almost 12% have renal damage (Table 2).

The use of corticosteroids contributes to much of the organ damage accrued by patients with SLE. The Toronto group found that 75% of organ damage at 15 years could be attributed directly or indirectly to corticosteroid use. Moreover, the route of administration and dosing of corticosteroids influence the risk for and type of organ damage a patient may develop. For example, higher prednisone doses increase the risk of cataract, stroke, venous thrombosis, avascular necrosis, and hypertension. Cumulative prednisone exposure of a patient with SLE influences the risk of cataract, coronary...
artery disease, and osteoporosis. Use of intravenous methylprednisolone increases the risk of only one type of damage: cognitive impairment. This may actually reflect a “bias of indication,” because corticosteroids are frequently used to treat central nervous system lupus flares.

**Cognitive Impairment.** Cognitive impairment has emerged as a major form of organ damage in patients with SLE. As many as 80% of all patients with lupus have some degree of impairment in cognitive function. The underlying mechanisms of cognitive impairment have yet to be determined; but studies in mice have implicated antibodies to N-methyl-D-aspartate receptor, raising the possibility that treatment targeting this might minimize or prevent cognitive impairment. In humans, the factors associated with cognitive impairment seem to differ at the time of diagnosis compared to later in the clinical course. Depression appears to be associated with early lupus, whereas persistent positive anti-phospholipid antibodies are associated with cognitive impairment further along in disease progression.

**Cardiovascular Disease.** Cardiovascular disease is the major cause of death in patients with SLE. A comparison of 498 women with SLE and 2,208 women in the Framingham Offspring Study showed that the SLE patients from 35 to 44 years of age had a 50-fold greater risk of myocardial infarction (MI) than that of the Framingham women in the same age range. Factors associated with MI were older age at SLE diagnosis, longer lupus disease duration, longer duration of corticosteroid use, hypercholesterolemia, and postmenopausal status. In the Johns Hopkins SLE cohort, we have found that predictors of coronary artery disease include older age, higher homocysteine levels, hypertension, diabetes mellitus, renal insufficiency, and lupus anticoagulant. Even after adjustment for conventional cardiovascular risk factors, patients with SLE have an increased risk for atherosclerosis. Using Framingham logistic regression equations, Canadian researchers showed that patients with SLE have a relative risk of 8.3 for MI, 6.7 for cerebrovascular accident, and 5.7 for any cardiovascular event.

Carotid plaque formation is a means of evaluating subclinical atherosclerosis. In a study comparing patients with and without SLE, those with SLE had significantly greater carotid plaque. In patients with SLE, carotid plaque was associated with older age and longer disease duration. Patients with SLE who had more plaque accumulation were less likely to have autoantibodies and had less exposure to prednisone and immunosuppressive agents.

**Malignancy.** Recent studies have shown that malignancy is yet another health threat associated with SLE. In particular, patients with SLE tend to have a higher incidence of lymphoma and to develop aggressive forms of lymphoma. Patients with SLE have an increased risk for all cancers combined, for all hematologic malignancies, for lung cancer, and for hepatobiliary cancer.

**Summary**

Flares are a common feature of SLE in many patients. Flares occur more often in African Americans and in patients who have serologically active disease. Remission is rare. Organ damage is common, and use of corticosteroids to treat SLE plays a major role in the induction of damage. Most patients have some degree of cognitive impairment, which may be autoantibody mediated. Atherosclerosis is a common form of damage associated with SLE and is related to both traditional cardiovascular risk factors and to lupus-specific factors. Patients with SLE have an increased risk of malignancy, particularly aggressive forms of lymphoma.

**Table 2. Fifty Percent of Patients With SLE Have Organ Damage**

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Organ System</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.2%</td>
<td>Musculoskeletal</td>
</tr>
<tr>
<td>15.0%</td>
<td>Neuropsychiatric</td>
</tr>
<tr>
<td>12.8%</td>
<td>Ocular</td>
</tr>
<tr>
<td>11.7%</td>
<td>Renal</td>
</tr>
<tr>
<td>10.4%</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>10.1%</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>7.4%</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>7.4%</td>
<td>Skin</td>
</tr>
<tr>
<td>5.5%</td>
<td>Peripheral vascular</td>
</tr>
<tr>
<td>6.1%</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>2.5%</td>
<td>Malignancy</td>
</tr>
<tr>
<td>1.2%</td>
<td>Premature gonadal failure</td>
</tr>
</tbody>
</table>

**References**

MANAGING FLARES I: TREATMENT OPTIONS FOR NONRENAL SLE FLARES

Joan T. Merrill, MD

Do these widely used agents differ in their clinical activity? Methotrexate has been evaluated in patients with lupus in two randomized clinical trials.7,8 The evidence suggests that the drug is helpful in the management of cutaneous and musculoskeletal manifestations of lupus and that it might be steroid sparing. There is no evidence to indicate that methotrexate has any effect on lupus nephritis.

Azathioprine has been evaluated in multiple randomized trials of patients with lupus nephritis but not in patients with nonrenal SLE.9 Consequently, little evidence-based literature exists to support the clinical use of azathioprine in this population, although rheumatologists frequently use this medication to treat patients with SLE.

MMF has been evaluated in several randomized trials of SLE patients with nephritis.5-11 Case reports indicating MMF’s potential efficacy for treating other manifestations of SLE suggest that this agent may have a broad spectrum of activity. One recent study suggests that opportunities exist in making SLE pharma-cotherapy more effective.12 In this study, cohorts of patients with nonrenal SLE were treated with increasing doses of azathioprine, ranging as high as 3.5 to 4 mg/kg. Assays have now become commercially available to measure the metabolites of 6-mercaptopurine, and this was done in the study to determine if dose-limiting toxicity could be defined with these measures. The results showed that 6 of 10 patients treated with a dose of 3.5 mg/kg had clinical responses, as did both patients who received 4 mg/kg. The optimal response rate with doses up to 3 mg/kg was 31.5%. Although many rheumatologists use this treatment based on good overall clinical experiences, this study suggests that optimal response rates are only achieved at doses that many patients will not be able to tolerate.

Clinical Trials

Several prospective clinical trials have evaluated therapies in patients with nonrenal mild or moderate SLE. One of the most recent compared the antimitobetal clofazamine and chloroquine in 33 patients with cutaneous SLE.7 The results demonstrated equivalent effects on the skin, but the chloroquine group had fewer flares. An important conclusion that can be drawn from this study is that hydroxychloroquine and chloroquine are quite effective for SLE skin disease, and physicians should not hesitate to try higher doses of the drugs before turning to other, potentially more dangerous medications, particularly for long-term therapy.

Other studies have demonstrated variable results with agents such as leflunomide, IDEC 131 (a humanized antibody against CD154), and DHEA. Few studies have evaluated the efficacy of therapies during an SLE flare. Hydroxychloroquine was evaluated in a

Table 1. Lupus Treatment Options1,2

| Potential Rx Adjunct Mild Mod Severe |
|------------------------------------|--------|--------|--------|--------|
| Hydroxychloroquine*                |        |        |        |        |
| Corticosteroids*                   |        |        |        |        |
| ASA,* NSAIDs, anticoag              |        |        |        |        |
| DHEA                               |        |        |        |        |
| Dapsone, thalidomide               |        |        |        |        |
| Azathioprine                       |        |        |        |        |
| Methotrexate                       |        |        |        |        |
| Leflunomide                        |        |        |        |        |
| Mycophenolate mofetil              |        |        |        |        |
| Cyclophosphamide                   |        |        |        |        |
| IVIG/PE                            |        |        |        |        |

*Approved for use by the US Food and Drug Administration. anticoag=anticoagulants; ASA=acetylsalicylic acid; DHEA=dehydroepiandrosterone; IVIG/PE=intravenous immunoglobulin/plasma exchange; Mod=moderate; NSAIDs=nonsteroidal anti-inflammatory drugs.

S
ystemic lupus erythematosus (SLE) has a complicated, variable, and unpredictable symptom complex. Pathology may vary between patients, even when they exhibit the same organ involvement. This heterogeneity may be a natural consequence of immune complexity involving myriad potential genetic variations in hundreds of interacting proteins. SLE could represent inevitable consequences of immune versatility linked to species survival, analogous to a bad hand in a game of poker. The heterogeneity that characterizes SLE does not reflect a disordered immune response, but rather an imbalance; therefore, treatment should aim to restore balance, not suppress immunity.

Available Therapies

Few therapies are approved for SLE: hydroxychloroquine, corticosteroids, and acetylsalicylic acid—other agents in use are not approved for SLE. However, in considering the various SLE treatment options, several are available that are reasonably safe and effective, as judged by current standards. Antimalarial therapy with hydroxychloroquine or chloroquine is the most widely used treatment for mild SLE, although corticosteroids and dehydroepiandrosterone (DHEA) are also helpful in some patients. For patients with moderately severe lupus symptoms, a variety of approved and unapproved therapies exist, including corticosteroids, DHEA, dapsone, thalidomide, azathioprine, methotrexate, leflunomide, mycophenolate mofetil (MMF), and cyclophosphamide. Severe lupus can be treated with intravenous immunoglobulin/plasma exchange as well as the drugs used for moderate disease, with the exception of DHEA (Table 1).1,2

Azathioprine, leflunomide, methotrexate, and MMF are moderate-intensity therapies that are widely used in the treatment of SLE. Although these drugs may be considered broadly immunosuppressive, each one, in fact, targets B cells to some degree.1 Azathioprine, methotrexate, MMF, and leflunomide all have antiproliferative effects and influence maturation signals and glycosylation of surface proteins on various immune cells. MMF has a fivefold greater affinity for the type 2 isoform of the inosine monophosphate dehydrogenase enzyme that is selectively expressed in activated lymphocytes. This affinity might result in more potent cytostatic effects on lymphocytes than other cell types.1,4
placebo-controlled trial involving 47 patients.14 Hydroxychloroquine reduced all types of flares compared to placebo, and patients receiving the drug had a relative risk of major flare of 0.43, representing a 57% reduction compared to placebo.

Bijl et al15 evaluated MMF for control of flares in 36 patients with SLE. In this study, the principal clinical objective was to determine whether MMF could prevent flares following a rise in anti-dsDNA antibodies, which has been identified as a marker of impending relapse. Among 10 patients who had a rise in anti-dsDNA, none had a flare over the next 6 months after treatment with mycophenolate, and levels of anti-dsDNA antibodies decreased significantly (P<0.001).

Quality-of-Life Improvement

Several studies have found favorable effects of pharmacologic and nonpharmacologic therapies on various aspects of quality of life, including mental and sexual well-being, overall health-related quality of life, and fatigue. Table 2 lists these studies.

Psychological interventions that have been evaluated in a few studies have demonstrated modest results with strategies such as brief stress management, psychological education in self-efficacy and social support, and brief supportive/expressive group therapy.16-18

Emerging Therapies

New biologic agents may offer potential additions to our therapeutic options for SLE. Rituximab, the anti-CD20 antibody, has been evaluated in a few studies.19-21 In a study of 24 patients with severe SLE, administration of the monoclonal antibody rituximab led to a reduction in B cells in all but one patient. The disease activity index, serum complement 3 levels, and anti-dsDNA levels all decreased significantly. Rituximab was well tolerated, and anti-dsDNA levels, decreased levels of CD27 antibodies, and CD20 antibody depletion and immune reconstitution.20,21

Table 2. Prospective Randomized Studies Involving Quality of Life

<table>
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<th>Rx</th>
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<th>Results</th>
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DHEA = dehydroepiandrosterone; HRQOL = health-related quality of life; MMF = mycophenolate mofetil; QOL = quality of life.

Summary

SLE is a heterogeneous, complicated, and unpredictable disease. These very factors at once dictate a critical need for new treatments and create barriers to drug development. Despite these impediments, treatments for SLE continue to advance.

References

MANAGING FLARES II: TREATMENT OPTIONS FOR RENAL FLARES

Ellen M. Ginzler, MD, MPH

As many as two thirds of patients with systemic lupus erythematosus (SLE) have renal flares,1 which can lead to loss of kidney function, kidney failure, and the need for dialysis. Prompt initiation of immunosuppressive therapy with intravenous (IV) cyclophosphamide can control renal flares but at a potentially significant cost in terms of dollars and toxicity. Effective maintenance therapy is essential to reduce the risk of relapse after a flare has been brought under control. However, the optimal maintenance therapy has yet to be determined. Clinical investigation of mycophenolate mofetil (MMF) has suggested superiority over IV cyclophosphamide for maintaining remission in patients with lupus nephritis. Whether MMF is more effective than other maintenance regimens for long-term preservation of renal function has not yet been established.

Remission and Relapse

Achieving and maintaining remission has emerged as the key to improved patient and renal survival in lupus nephritis. In a study of 86 patients with severe lupus nephritis, Korbet and colleagues2 showed that 37 patients who achieved remission with high-dose prednisone and oral cyclophosphamide or this regimen plus plasmapheresis had a 95% overall survival rate after 5 and 10 years of follow-up, whereas the patients in the study who did not achieve remission had a 69% survival at 5 years, declining to 60% at 10 years. Renal survival remained stable at 94% at 5 and 10 years in the remission group compared to 45% at 5 years and 31% at 10 years in the nonremission group.

The standard National Institutes of Health regimen for lupus nephritis includes six monthly doses of IV cyclophosphamide as induction therapy, implying that remission should be achieved within 6 months. Available data suggest otherwise. For example, Ioannidis et al3 found a median time to remission of 10 months with IV cyclophosphamide, and 22% of patients in their study failed to achieve remission after 2 years. Although the median time to relapse after remission in the Ioannidis study was 79 months, 20% of patients relapsed within the first 18 months.

Other studies have demonstrated wide variation in relapse rates and time to relapse. In one of the larger studies conducted to evaluate relapse in treated lupus nephritis, the relapse rate was 45% and the median time to relapse was 36 months (18 months in partial responders).4 Several predictors of renal flares in patients with lupus nephritis have been well documented. Of note, virtually all studies that specifically evaluated the timing of therapy showed that a delay in instituting treatment is as important in predicting renal flares as the time required to achieve a remission.

One recent study5 highlighted the role of duration of therapy in achieving a remission and predicting relapse. Patients who did not flare were treated for a median of 57 months compared to 30 months of treatment for patients who had flares (P<0.009). Moreover, patients who did not have flares continued treatment for a median of 24 months after they achieved remission, compared to 12 months in the group that had flares (P=0.02).6

Several considerations are involved in distinguishing between worsening of a patient’s prior renal status and the occurrence of a flare. The clinician first must establish the patient’s initial presentation of lupus nephritis, which usually can be determined from the medical record. Second, the patient’s remission status after a flare must be characterized, beginning with the determination of whether the patient achieved a complete response or had stabilization of abnormalities. (For example, if the patient had a complete response, how was that defined? Did the definition go beyond clinical and immunologic parameters and include repeat biopsies?) Third, it must be determined whether the patient has persistent serologic activity without changes in clinical status, which suggests a poorer treatment outcome and greater likelihood of relapse. Finally, it must be determined whether the patient has had deterioration of renal function in the absence of immunologic or clinical exacerbation of renal disease that would suggest a flare.

Need for Therapy Alternatives

Cyclophosphamide has been shown to induce remission in patients who have active lupus nephritis. However, the drug has several disadvantages that have driven the search for effective alternatives. Cyclophosphamide is associated with myriad toxicities affecting multiple organ systems. Racial and ethnic differences in response to the drug clearly exist. Studies also have documented socioeconomic differences in outcomes of treatment with IV cyclophosphamide.6,7 Emergence of Mycophenolate Mofetil

MMF is a reversible inhibitor of inosine monophosphate dehydrogenase, a rate-limiting enzyme in purine synthesis. MMF has selective effects on lymphocytes, including inhibition of B- and T-cell proliferation, antibody formation, and expression of adhesion molecules and other cytokines. The drug is approved for prevention of transplant rejection. Data from murine models of lupus suggest that MMF improves survival and helps preserve renal function.8,9

Several factors provide a rationale for use of MMF to treat lupus nephritis. As noted above, a clear need exists for a cyclophosphamide alternative that is just as effective but safer. Unlike a new drug still in development, MMF has been commercially available for more than a decade, during which time its clinical activity and side-effect profile have been well defined. Soon after MMF became available, anecdotal reports suggested efficacy in patients with lupus nephritis unresponsive to steroids and IV cyclophosphamide.

Early Studies. Preliminary clinical comparisons against cyclophosphamide provided reason for optimism about MMF as a potential alternative therapy for lupus nephritis. In one study,10 42 patients with class IV lupus nephritis were treated with oral cyclophosphamide or MMF. Both therapies were associated with about an 80% response rate and similar toxicity profiles. Investigators in another preliminary clinical trial11 treated 46 patients with biopsy-proven diffuse proliferative lupus nephritis with IV cyclophosphamide or MMF. MMF led to greater improvement in proteinuria, urinary red blood cell counts, anti-DNA titers, and renal biopsy results and was associated with fewer adverse reactions.

Multicenter Trial. Concurrent with the publication of these studies, the US Food and Drug Administration (FDA), through the agency’s Orphan Products Program, supported a multicenter, randomized clinical trial to compare MMF, 3 g/day, and monthly IV cyclophosphamide in escalating doses up to 1 g/m2, as induction therapy for lupus patients with an active flare of class III, IV, or V lupus nephritis.12 The trial was designed to test the hypothesis that MMF has equivalent efficacy with superior toxicity/tolerability compared to IV cyclophosphamide.

The trial involved 140 patients who...
were treated in an open-label study design for 24 weeks. The results showed that 16 of 71 patients in the MMF group achieved complete remissions compared to 4 of 69 patients randomized to cyclophosphamide (P = 0.005). When complete and partial remissions were combined, 37 of 71 patients treated with MMF responded to therapy versus 21 of 69 in the cyclophosphamide group (P = 0.009).

Because of evidence of poorer absorption of the drug in African Americans, the study protocol called for a higher target dose of MMF than that used in any previous studies. Gastrointestinal (GI) side effects were common but did not result in study withdrawal: nausea, vomiting, and bloating were controlled in most cases by gradual dose escalation or treatment with a proton pump inhibitor. Diarrhea was more common with MMF than with IV cyclophosphamide, but most episodes were mild and self-limited. Infections occurred less often with MMF than with cyclophosphamide. One patient in the MMF group developed a severe rash that recurred on rechallenge and led to discontinuation.

The principal conclusions of the study were that MMF was more effective and better tolerated than was IV cyclophosphamide for induction therapy of lupus nephritis.

**Other Studies.** In another recent study, 44 patients with proliferative lupus nephritis were randomized to MMF, 2 g/day, or monthly IV cyclophosphamide, 0.75 to 1.0 g/m2, for 6 months. The total response rate (complete and partial remissions) was similar in both treatment groups (58% with MMF, 52% with cyclophosphamide), but a greater proportion of patients achieved complete remissions with MMF (26% vs 12%). Adverse events were similar in the two treatment groups.

MMF was compared with IV cyclophosphamide and azathioprine as maintenance therapy after IV cyclophosphamide induction in patients with proliferative lupus nephritis (Figure). The study involved 59 patients who were followed for as long as 30 months after response for as long as 30 months after response for as long as 30 months after response for as long as 30 months after response for as long as 30 months after response. For the primary end point of freedom from renal relapse, MMF proved superior to IV cyclophosphamide (P = 0.021) and equivalent to azathioprine. Hospitalization, amonorrhea, infection, and GI side effects occurred less often with MMF and azathioprine than with cyclophosphamide.

Follow-up data from one of the preliminary clinical studies suggested that early relapse occurred more often with MMF than with oral cyclophosphamide. In that trial, the MMF dose was decreased after 6 months, and patients on oral cyclophosphamide were switched to azathioprine. In response to this observation, the MMF dose was tapered more gradually, and, after follow-up for an average of 63 months, the flare rate was similar in the two treatment groups.

**Unresolved Issues**

Several questions related to MMF therapy for lupus nephritis remain to be answered. With regard to induction therapy, the potential value of continuing therapy in patients who do not respond by 6 months has not been determined. In the clinical arena of MMF maintenance therapy, issues involving the optimal duration of therapy, dose reduction in responding patients, and MMF maintenance after IV cyclophosphamide have not been resolved. Whether MMF is superior to other potential maintenance regimens with regard to long-term renal preservation also has not been established.

**Emerging Therapies**

Several FDA-approved drugs are being used off-label and investigationally for the treatment of lupus nephritis. They include rituximab, abatacept, and leflunomide. In addition, several investigational agents will be evaluated in upcoming clinical trials, including belimumab, epratuzumab, and daridrate.

**Summary**

Renal flares are common in patients with lupus nephritis. Therapy that achieves a complete remission reduces the likelihood of flares. IV cyclophosphamide has been the standard of care for treating lupus nephritis, but toxicity has fueled a search for safer alternatives. Various medications are being used off-label for treatment of lupus nephritis, and their efficacy and safety have not yet been established. In addition, a number of investigational agents, particularly biologics, will be evaluated in clinical trials involving patients with lupus nephritis.
Rheumatology News® Renal and Nonrenal Flares in Systemic Lupus Erythematosus: Meeting the Clinical Challenge

CME Post-Test

Instructions: On the answer sheet, darken the circle of the one answer to each question that is true. To obtain credit, you must have 70 percent or more of the answers correct. For participants who pass the test, please allow 4 weeks after returning the post-test and evaluation form to receive your certificate. Completed answer sheets/program evaluations should be returned as indicated on the form. Credit is available through February 15, 2008. Non-US physicians can claim CME credit for this program.

Estimated time to complete: 1 hour.

1. The clinical course of systemic lupus erythematosus (SLE) usually evolves over how many years?
   A. A critical 5-year period of adolescence
   B. A 10-year period from adolescence to early adulthood
   C. A period of 20 to 40 years
   D. The clinical course is unpredictable
2. Which of the following factors predicts a poor prognosis in SLE?
   A. Proliferative nephritis
   B. Development of severe disease
   C. Presence of antiphospholipid antibodies
   D. No improvement in creatinine/proteinuria after 6 months of treatment
   E. All of the above
3. Which of the following drugs is approved for treatment of SLE?
   A. Hydroxychloroquine
   B. Cyclophosphamide
   C. Mycophenolate mofetil
   D. Azathioprine
4. Treatment for SLE should aim to:
   A. Suppress an overactive immune system
   B. Restore balance to the immune system
   C. Normalize lymphocyte counts
   D. Reduce inflammation
5. Which of the following is/are the most common disease pattern of SLE?
   A. Skin and kidney
   B. Musculoskeletal and kidney
   C. Kidney and cardiovascular
   D. Skin and musculoskeletal
   E. All of the above
6. The two most common target organ systems of SLE are:
   A. Proliferative nephritis
   B. IV cyclophosphamide and MMF as induction therapy for lupus nephritis showed that:
   A. IV cyclophosphamide remains the most potent drug therapy available for lupus nephritis
   B. IV cyclophosphamide and MMF are equally effective and tolerated
   C. MMF is better tolerated and more effective than IV cyclophosphamide
   D. MMF is too toxic for chronic treatment of SLE
   E. None of the above

Answer Sheet

1. A B C D D
2. A B C D D
3. A B C D D
4. A B C D D
5. A B C D D
6. A B C D D
7. A B C D D
8. A B C D D

Please provide the address to which you would like your certificate mailed:
First Name ____________________________ MI ____________________________
Last Name ____________________________
Specialty ____________________________ Check one: [ ] MD [ ] DO [ ] RN [ ] NP [ ] PA [ ] Other [ ]
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Program Evaluation

1. How would you rate this activity overall? (5=excellent, 1=poor; please circle one) 5 4 3 2 1
2. In your opinion, did you perceive any commercial bias? [ ] Yes [ ] No
3. Do you plan on making any changes in your practice as a result of this activity? If yes, please explain.
   [ ] Yes [ ] No
4. Do you feel each of the following objectives was met? [ ] Yes [ ] No [ ] Partially [ ] N/A
   • list the signs, symptoms, and clinical impact of SLE.
   • outline the clinical course of SLE, the importance of renal and nonrenal flares, and how flares are defined.
   • state the treatment options for both renal and nonrenal flares and explain the importance and benefits of early treatment.
   • describe the management of nonrenal clinical features of SLE.
5. Do you feel that the information in this activity was based on the best evidence available? If no, please explain.
   [ ] Yes [ ] No [ ] Partially [ ] N/A
6. Please suggest topics for future activities.
7. Please rate the content of this activity. (5=excellent, 1=poor; please circle one)
   7a. Timely, up-to-date? 5 4 3 2 1
   7b. Relevant to your practice? 5 4 3 2 1
8. General comments: ____________________________

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