

Long-Term Outcomes in Lupus

Based on a presentation by Michelle Petri, MD, MPH

Presentation Summary

Systemic lupus erythematosus (SLE) can follow an unpredictable course and be either chronic or of a relapsing and remitting form. Current measures used to assess disease activity do little to help physicians predict disease flares or complications that may arise. There are serious musculoskeletal, renal, cardiovascular, and ocular effects associated with SLE and the majority of these adverse consequences are associated with the use of the corticosteroid prednisone in these patients. Pulsed-dose methylprednisone treatment during flares appears to carry less risk than increasing daily prednisone doses. However, medication that can lessen or eliminate steroid use in moderately affected patients is needed.

Systemic lupus erythematosus (SLE) can have an unpredictable course, making it a particularly devastating illness. Patterns of disease activity in SLE can vary from patient to patient. The Physician's Global Assessment (PGA) and modified SLE Disease Activity Index (m-SLEDAI) scales are most commonly used to monitor lupus activity. These instruments often show a "relapsing/remitting" course with lupus, similar to that seen in relapsing/remitting multiple sclerosis, with flares requiring periods of treatment, followed by "quiet" (clinically inactive) periods.¹ Some patients do have long periods of quiescence (remission) lasting several years. However, when an exacerbation does occur, it may manifest with internal organ involvement that may lead to long-term damage or an immediately life-threatening situation.

Therefore, patients require adequate laboratory monitoring throughout periods in which there is no apparent disease activity to facilitate early detection of organ involvement.

SLE may also have a chronic active course in which there is always some disease activity requiring constant medication use. This situation is problematic because currently used lupus medications, including the corticosteroid prednisone, nonsteroidal anti-inflammatory drugs, and immunosuppressive agents, are fraught with long-term adverse effects. The antimalarials, such as hydroxychloroquine, are safer but do require monitoring for ophthalmologic effects. Possible new treatments still under research include prasterone for mild-to-moderate SLE and LPJ-394 for renal lupus.

Predicting Disease Course

Although serologic tests are essential for autoantibodies in making an SLE diagnosis, they may not be the best method of tracking disease activity over time. For example, a longitudinal study of 204 consecutive SLE patients from our institution, who were monitored quarterly for disease activity, found that complement and anti-double-stranded deoxyribonucleic acid (dsDNA) levels (or changes in the levels) could not predict which patients would experience an SLE exacerbation during the 3 months following serologic testing (Table 1).²

To determine whether more frequent serologic testing would be more predictive of disease activity, more than 50 patients included in the original cohort were stud-

ied with monthly instead of quarterly serologic testing for 1 year. Again, serologic parameters were not predictive of an SLE flare at the next month. There was no consistent predictive pattern, with some individual patients experiencing a flare whether anti-dsDNA levels were increasing, decreasing, or staying the same. However, on the actual day the patient presented with a flare, the most common pattern was to detect a decline in the anti-dsDNA level (Table 2).

Normally, clinicians are concerned when an autoantibody level increases. But in lupus, autoantibodies cause inflammation and damage as they are deposited in tissues as immune complexes. Thus, it does make sense that a decrease in serum anti-dsDNA, which could reflect deposition in tissue, occurs at the time of a lupus flare.

It should be emphasized, however, that the decrease in anti-dsDNA was not necessary to diagnose the SLE flares. Each flare was diagnosed on the basis of patient history, physical examination, and routine laboratory testing. These basic tenets of SLE care should be relied on and repeated frequently to diagnose flares and treat lupus patients.

Morbidity and Mortality

There is inadequate research on morbidity and mortality in SLE. In one population-based study conducted by

researchers at the Mayo Clinic, data showed that the incidence of SLE has tripled since 1970. These data also showed a disturbing trend in that survival appears to have reached a plateau. Among SLE patients observed between 1980 and 1992, survival 10 years after SLE diagnosis was approximately 80%.³

More than half of SLE patients have evidence of chronic damage to 1 or more organ systems; this damage is a major contributor to both mortality and morbidity (Table 3). This was reflected in our

Table 1. Predictors of Flare—Hopkins Lupus Cohort

Predictors	Probability of Flare Next 3 Months	OR (95% CI)
C3		
No recent change	0.17	1.0
Recent decline	0.18	1.02 (0.77 – 1.55)
Recent increase	0.18	1.13 (0.77 – 1.68)
C4		
No recent change	0.19	1.0
Recent decline	0.15	0.74 (0.47 – 1.17)
Recent increase	0.16	0.92 (0.58 – 1.46)
Anti-dsDNA		
No recent change	0.16	1.0
Recent decline	0.20	1.3 (0.82 – 2.18)
Recent increase	0.20	1.3 (0.79 – 2.22)

CI = confidence interval; dsDNA = double-stranded deoxyribonucleic acid; OR = odds ratio.

Table 2. Decline in Anti-dsDNA (Crithidia) Is Associated with Flare

	Decline (%)	No Decline (%)	Adjusted OR (95% CI)	P Value
PGA	14	12	1.2 (0.7, 2.1)	NS
mSLEDAI	28	16	2.0 (1.3, 3.1)	.0009
mLAI	38	22	2.1 (1.4, 3.3)	.0006
SLAM	15	12	1.4 (0.8, 2.2)	NS
mBILAG	15	12	1.4 (0.8, 2.3)	NS

CI = confidence interval; dsDNA = double-stranded deoxyribonucleic acid; mBILAG = modified British Isles Assessment Group; mLAI = modified Lupus Activity Index; mSLEDAI = modified Systemic Lupus Erythematosus Disease Activity Index; NS = not significant; OR = odds ratio; PGA = Physicians' Global Assessment; SLAM = Systemic Lupus Activity Measure.

Source: Ho et al. *Arthritis Rheum* Submitted for publication.

longitudinal study as well.² However, not all of this organ damage is life threatening, but all is costly in the managed care environment. Furthermore, much of the organ damage observed is a result of or is worsened by lupus treatments, mainly the use of prednisone, rather than just the disease itself.

Musculoskeletal. Approximately 25% of the lupus patients in the Johns Hopkins Lupus Center have had some permanent musculoskeletal damage, with osteoporotic fracture being the most common. Avascular necrosis of the hips, and sometimes of the knees and shoulders, is also seen. Most SLE patients with avascular necrosis will progress to require total joint replacement at a young age, with a second joint replacement being needed during their lifetime. Musculoskeletal damage is largely a result of prednisone use in these patients.⁴

To minimize musculoskeletal damage from steroid-induced osteoporosis, all patients should be advised to take calcium and vitamin D beginning at SLE diagnosis. In addition, bisphosphonates are effective against steroid-induced osteoporosis and can be considered even in premenopausal women with osteoporosis who are not planning a later pregnancy. Bone density scans should be part of routine care for premenopausal women with SLE who are corticosteroid dependent. In postmenopausal women, hormone replacement therapy is effective in steroid-induced osteoporosis, but it should be reserved for women with lupus who do not have antiphospholipid antibodies.

Ocular. Premature cataract is the most common ocular damage in SLE and occurs in about 13% of our patients. Again, cataract formation is a result of prednisone use. A small percentage of patients may experience retinopathy that is directly SLE mediated.⁴ Retinopathy from anti-malarials is rarely seen in our cohort.

Renal. Approximately 12% of our patients will experience renal failure. Fortunately, there are good treatments, including mycophenolate mofetil and intravenous cyclophosphamide, for lupus nephritis when detected early. In most studies, 75% of lupus nephritis patients requiring cyclophosphamide retain renal function, but still 25% will progress to renal failure. Ethnic differences play an important role in renal damage. Two separate studies have shown that African-Americans with renal lupus treated with the same drug regimen as Caucasians will not do as well in terms of ultimate renal function.⁵

It is difficult to track renal dysfunction in SLE because creatinine clearance alone is not an accurate measure of kidney function in patients with proteinuria. Nuclear medicine scans (such as technetium-diethylenetriaminepentaacetic acid) or cimetidine-corrected creatinine clearances are more accurate. Patients with proteinuria or other signs of renal lupus should be considered candidates for angiotensin-converting enzyme (ACE) inhibition therapy. ACE inhibitors are used in diabetes to prevent renal scarring and may be beneficial in lupus as well, although there have been no clinical trials of these agents in SLE patients. It should be noted that ACE inhibitors are contraindicated in pregnancy. Routine monitoring to detect renal insufficiency early is needed and in the future, biologic agents, including tolerogens, may be useful in preventing renal failure in SLE patients.

Cardiovascular Morbidity. Accelerated atherosclerosis is the major cause of cardiovascular morbidity and mortality in SLE. It is likely that lupus itself leads to initial vessel inflammation and the dam-

Table 3. Distribution of Damage (%)

25.2	Musculoskeletal	7.4	Gastrointestinal
15.0	Neuropsychiatric	7.4	Skin
12.6	Ocular	5.5	Peripheral vascular
11.7	Renal	6.1	Diabetes
10.4	Pulmonary	2.5	Malignancy
10.1	Cardiovascular	1.2	Premature gonadal failure

age is then compounded by chronic prednisone use, which is associated with hyperlipidemia, weight gain, and hypertension.⁴ In our cohort, 10% of SLE patients have had angina or myocardial infarction. The prevalence of atherosclerosis is greater when noninvasive screening studies, such as carotid duplex or helical computed tomography, are used. Patients with renal disease are at greater risk of cardiovascular damage, because hyperlipidemia and hypertension are associated with renal dysfunction as well.⁶

About half of SLE patients have antiphospholipid antibodies, which are associated with both hypercoagulability and coronary artery disease. Stroke is also associated with antiphospholipid antibodies (anticardiolipin and the lupus anticoagulant).⁷ Antiphospholipid antibody syndrome usually presents with venous or arterial thromboses, miscarriage and/or intrauterine growth retardation, or thrombocytopenia.⁸ Assays to detect antiphospholipid antibodies should be part of routine testing in SLE patients; however, good quality assays are sometimes not available.

In a retrospective study, we showed that hydroxychloroquine is protective against thrombotic events in SLE patients.⁹ In addition, a recent study showed that

women diagnosed with antiphospholipid antibody syndrome following miscarriage were less likely to experience a subsequent thrombotic event if they were maintained on low-dose aspirin therapy.¹⁰

Elevated homocysteine, which is a risk factor for both thrombosis and atherosclerosis, is found in one third of SLE patients. SLE patients should routinely undergo homocysteine level testing. The effects of elevated homocysteine are fortunately easy to combat with folic acid therapy.⁶

Because of the high risk of accelerated atherosclerosis in SLE patients, a carotid duplex, an ultrasound test of the carotid arteries, should be considered in women with SLE who have been maintained on prednisone therapy.⁶ Alternatively, a helical computed tomography scan to detect coronary calcification could be considered, because of its greater sensitivity.

Diabetes. Because prednisone causes weight gain, SLE patients with a family history of type 2 diabetes are more likely to develop the disorder with treatment. After an SLE patient is diagnosed with comorbid diabetes, aggressive diabetes management is indicated, along with reduction of corticosteroids to the minimum required dose.

Table 4. Damage in Systemic Lupus Erythematosus

Damage Item	Cumulative Prednisone	Highest Prednisone Dose	IV Methylprednisone
Cataract	1.1 (1.0, 1.2) <i>P</i> = .03	2.9 (1.5, 5.5) <i>P</i> = .001	NS
Cognitive impairment	NS	NS	1.5 (1.1, 2.1) <i>P</i> = .009
Stroke	NS	3.5 (1.4, 8.8) <i>P</i> = .008	NS
Coronary artery disease	1.7 (1.2, 2.4) <i>P</i> = .002	NS	NS
Venous thrombosis	NS	4.2 (1.2, 15.4) <i>P</i> = .03	NS
Osteoporosis	1.9 (1.4, 2.6) <i>P</i> = .0001	NS	NS
Avascular necrosis	NS	4.2 (2.2, 8.0) <i>P</i> = .0001	NS
Diabetes mellitus	NS	2.4 (0.9, 6.0) <i>P</i> = .007	NS
Hypertension	NS	1.6 (1.0, 2.6) <i>P</i> = .05	NS

NS = not significant.

Source: Reference 4.

Corticosteroid Complications

Although clinicians recognize the adverse effects of corticosteroid therapy, about 90% of SLE patients in most academic centers require some prednisone to prevent life-threatening lupus complications and to improve quality of life. Prednisone confers numerous benefits early in the course of lupus, but over time, the damage from both the disease and prednisone use increases.⁴

For moderate-to-severe lupus flares, pulsed methylprednisone for 3 days can minimize the need for high daily doses of prednisone and therefore reduce long-term damage. Although cognitive impairment is increased in patients who have received pulse methylprednisone, some clinicians believe this may simply reflect the common use of this therapy for central nervous system-SLE. Increased daily prednisone in the range of 40 mg for lupus flares is associated with later cataracts, strokes, and avascular necrosis and also increases the risk of diabetes and hypertension. Even small daily doses of 5- to 10-mg prednisone carry increased risk of cataracts, osteoporosis, and coronary artery disease over the years (Table 4).⁴

Pregnancy Complications

Pregnant SLE patients are at higher risk for disease flares and have more pregnancy complications than the general population. Lupus is more likely to flare during pregnancy and even without a disease flare, patients with antiphospholipid antibodies are at greater risk of miscarriage or placental insufficiency leading to preterm birth, growth retardation, and placental failure.¹¹

Most women with lupus have normal fertility, although patients who have received cyclophosphamide may have premature gonadal failure. However, about 90% of patients can have a successful pregnancy, even though additional treatment for flares may be needed and low-dose aspirin and heparin injections may be required to suppress the action of antiphospholipid antibodies.¹¹

Infants born to lupus patients are more likely to be premature; at Johns

Hopkins Hospital prematurity averages about 3 to 4 weeks.¹² This may lead to some neonatal intensive care admissions. In addition, more women with SLE are likely to have complications at the time of birth (such as preeclampsia) and therefore are more likely to require caesarian sections. Because SLE patients are often immunosuppressed, there can also be an increase in wound infections postpartum.

... DISCUSSION HIGHLIGHTS ...

Dr. Abu-Samrah: Does steroid psychosis occur as a result of prednisone use in these patients?

Dr. Petri: Steroid psychosis can occur when doses of prednisone in excess of 20 mg are used. If lupus requires continued treatment, other immunosuppressive drugs can be used.

Dr. Wallace: I find that when I have to refer patients for a bone density scan, it is difficult to have it done. This is partially because these women have no symptoms of osteoporosis and they have to make a separate appointment and take another day off work. If I had preauthorization, I could have it done while they were in my office for the consult.

Dr. Abu-Samrah: This really should be done by the primary care physician because the risk of osteoporosis with prednisone use is known to every practicing physician. Perhaps this is a problem in physician education.

Dr. Petri: This is also a problem of patient education. There is a higher level of awareness of osteoporosis among postmenopausal women, whereas most women with SLE are premenopausal. This is a national challenge. However, treatment is inadequate, even when started, because studies have shown that most women stay on bisphosphonates for only about 3 months.

Dr. Vega: At what point would you test for homocysteine in SLE. From diagnosis or only after a flare?

Dr. Petri: I recommend that we should test all SLE patients, because in our center, more than 30% have elevated homocysteine. However, the interval at which the testing should occur is unclear—our research fails us in that area. Obviously, it should be done in anyone who is developing renal disease because their homocysteine will rise as their creatinine does. Again, physician education is needed because no one thinks of testing for cardiovascular risk factors in young women.

Dr. Mansi: I think we are in agreement that it is a matter of physician education. We try to convince our primary care physicians to treat the lupus patient as if she is diabetic. If they have angina—they should be taken seriously and have cardiac catheterization regardless of age, there should be complete fasting lipid panels done, and the goal should be a lower low-density lipoprotein cholesterol below 100 mg/dL. Vigilance is required with all these risk factors in these patients.

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