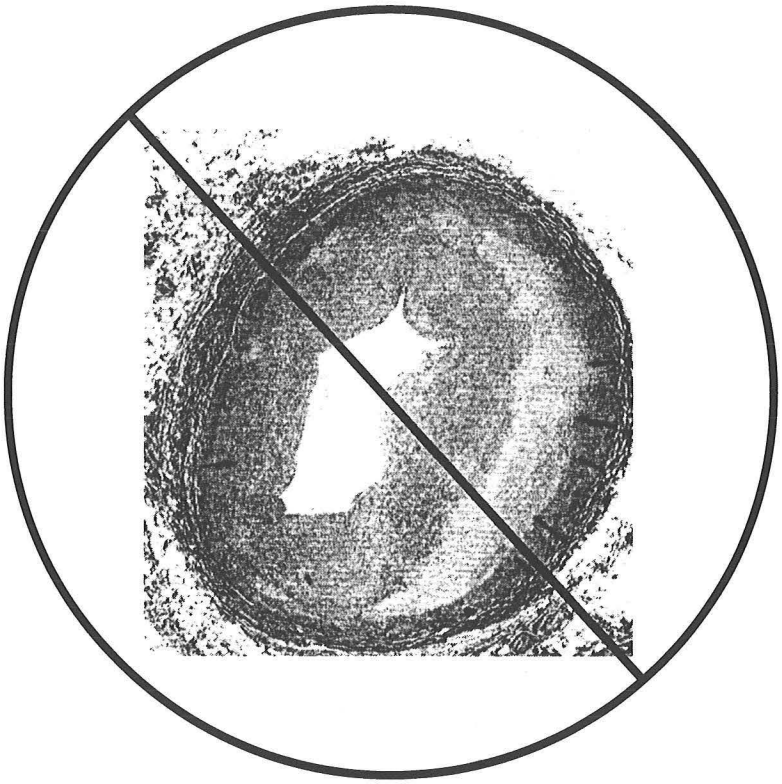
University of Texas Southwestern Medical Center
Internal Medicine Grand Rounds

The Management of Systemic Lupus Erythematosus: an Update

Joel D. Taurog, M.D.

December 21, 2000



This is to acknowledge that Joel D. Taurog, M.D. has disclosed no financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Taurog will be discussing "off-label" uses in his presentation.

Joel D. Taurog, M.D.
Professor of Internal Medicine
William M. and Gay Burnett Professor for Arthritis Research
Rheumatic Diseases Division
Research Interest: Role of HLA-B27 in the spondyloarthropathies

In memory of John L. Decker, M.D., former chief of the Arthritis & Rheumatism Branch, NIH, who passed away in July of this year at the age of 79.

Cover illustration: Atherosclerosis in the left anterior descending coronary artery of a 28 year old woman with systemic lupus erythematosus. From reference 24.

Historical background. The term "lupus" has been used since the Middle Ages to denote certain types of ulcerating skin lesions [1]. The term lupus erythematosus as a characteristic facial lesion emerged in the mid 19th century. The systemic nature of the disease was first recognized by Kaposi in publications of 1869 and 1872, and by Osler in publications of 1895 and 1904, although it is unclear how many of these cases would be called SLE by today's criteria. The main clinical and pathologic features that today are associated with SLE were gradually described over the next half-century, and the major serologic features, including antinuclear antibodies, were characterized in the decades following World War II. The current era of therapy for SLE was inaugurated by the introduction of corticosteroid therapy around 1950. Until the 1940's, lupus was primarily in the province of dermatology and was considered a rare disease. The advent of tests for rheumatoid factor and LE cells in the late '40's, and the introduction of corticosteroid therapy in early 1950's, led to the rapid development of rheumatology as a separate subspecialty and helped to bring the care of patients with SLE into the province of internal medicine.

Mortality in SLE. During the 1950's and '60's, it came to be recognized that corticosteroids were of limited benefit in lupus nephritis, and this led to a search for other agents. The first controlled trials of cytotoxic agents for this disorder were carried out at the NIH in the late 1960's by my mentors Alfred Steinberg and John Decker, and their publications in the early 1970's demonstrated the benefits of this therapy [2, 3]. Since that time, cyclophosphamide and azathioprine have come to be widely used in SLE, and it is fair to say that there have been no comparable breakthroughs in the management of systemic lupus erythematosus in the past 25 years. Nonetheless, mortality rates have declined significantly over the past several decades. In Fig. 1, improvement in 5-, 10-, and 15-year survival of SLE patients in Toronto, Ontario is indicated for series published in 1974, 1985, and 1993, respectively [4].

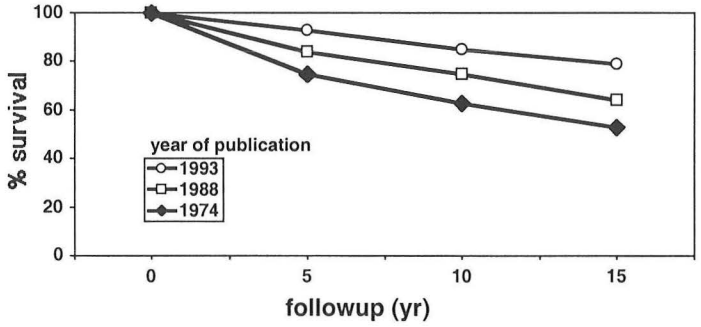


Figure 1. Improved survival in SLE patients followed in Toronto. From [4]. Although survival figures from different centers vary widely, the overall trend in almost all centers has been improvement in survival, and this is best illustrated by these survival data from one center.

Many factors are thought to have contributed to this improvement in prognosis for SLE patients, including improved understanding of disease pathogenesis and clinical course, an increasing number of physicians trained in the care of SLE patients, more widespread use of cytotoxic agents, more judicious use of corticosteroids, more effective antihypertensive and antibiotic agents, improvements in imaging techniques and laboratory evaluation, and rising standards of living, to name just a few. Improvements in prognosis are by no means uniform in different series and populations. In a recent study comparing 288 Caucasian, African-American, and Hispanic SLE patients in Alabama and Texas, poverty was the single strongest predictor of 5 year mortality (OR = 4), with ethnicity *per se* playing no significant role [5]. Moreover, in parts

of the world where access to expertise and/or health care technology is more limited, SLE mortality rates are significantly higher than in the U.S. and Western Europe [6].

In this Grand Rounds, I want to focus on recent literature that addresses the drug therapy of SLE, in terms of both benefits and complications, with the goals of optimizing the current management of SLE patients here at Parkland, mentioning some promising agents that are currently in clinical trials, and suggesting an area where the investigative interests of UT Southwestern internal medicine faculty might be put to good use, namely, the high prevalence of atherosclerotic cardiovascular disease in SLE patients.

Criteria for SLE. Diagnostic criteria for SLE were formulated in 1971 by the American Rheumatism Association and extensively revised in 1982 (the name was changed to American College of Rheumatology in 1988). The 1982 ACR criteria are still the basis for most of the clinical literature on SLE. The criteria were modified slightly in 1997 to take into account the specificity of anti-Sm autoantibodies and to expand the category of anti-cardiolipin antibodies to include all of the serologic and functional manifestations of anti-phospholipid antibodies [7]. The 1997 updated criteria are shown in Table 1.

One anomaly of these criteria has been the restriction of the neurologic manifestations to seizures and pyschosis, since many other manifestations are widely recognized to occur in SLE. In 1999, a multidisciplinary committee convened by the ACR published nomenclature and case definitions for 19 neuropsychiatric lupus syndromes [8]. The syndromes are listed in Table 2. Complete case definitions are available on the ACR website <http://www.rheumatology.org/ar/1999/aprilappendix.html>. This system is intended to expand the neuropsychiatric aspect of the ACR classification criteria. Thus, subjects would be said to have a given neuropsychiatric lupus syndrome if they fulfill the specific syndrome case definition and also meet ≥3 other ACR critieria for SLE. It should be emphasized that all of these classification criteria are intended primarily for classification and reporting, not for strict application to clinical practice.

Measures of disease activity and outcome. Because SLE is a multisystem disease with great heterogeneity of the clinical manifestations and unpredictability of the disease course and outcome, it has been helpful to rheumatologists to develop instruments aimed at objectively assessing disease activity that take into account disease manifestations in the whole array of organ systems that can be affected. Since the late 1980's, a number of instruments have been developed to measure disease activity in SLE. At least six of these have been validated to reflect change in disease activity compared with physician global assessment and changes in treatment, and they have also been validated against each other. These are listed in Table 3. Several studies have shown that these measurements have prognostic significance. An example is given in Figure 2, where patients with a high SLEDAI score upon entry into the Toronto SLE cohort had a significantly poorer longterm survial [10].

Up until recent years, most clinical trials in SLE focused primarily on treating lupus nephritis and thus had the advantage of relatively straightfoward parameters and endpoints to measure, namely, proteinuria, renal function, renal failure, and death. However, recent treatment studies

have aimed more at the overall treatment of SLE. The instruments shown in Table 3, particularly the SLEDAI, are being used in both in randomized clinical trials and in longitudinal

Table 1. Modified 1982 ACR Criteria for SLE

Criterion	Definition or features
Malar rash	Fixed erythema, sparing nasolabial folds
Discoid rash	Scaling, follicular plugging, or atrophy
Photosensitivity	Unusual rash from sunlight
Oral ulcers	Oral or nasopharyngeal ulcers
Arthritis	Nonerosive, peripheral, ≥ 2 joints
Serositis	Pleuritis or pericarditis
Renal disorder	Proteinuria or casts
Neurologic disorder	Seizures or psychosis
Hematologic disorder	AIHA; WBC<4K/μl; lymphocytes <1.5K/μl; plt<100K/μl
Immunologic disorder	anti-dsDNA; anti-Sm; or antiphospholipid antibodies
Antinuclear antibody	Elevated titer of ANA

From [7, 9]

Table 2. Neuropsychiatric syndromes in SLE

Central Nervous System	Peripheral Nervous System
Aseptic meningitis	Acute inflammatory demyelinating polyradioculopathy (Guillain-Barré syndrome)
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Headache	Myesthenia gravis
Movement disorder	Neuropathy, cranial
Myelopathy	Plexopathy
Seizure disorders	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	
Psychosis	

From [8]

Table 3. Instruments for assessing disease activity in SLE

Disease Activity Measurements		Reference
BILAG	British Isles Lupus Activity Group	[11]
SLAM	Systemic Lupus Activity Measure	[12]
LAI	Lupus Activity Index	[13]
SLEDAI	SLE Disease Activity Index	[14]
ECLAM	European Consensus Lupus Activity Measure	[15]
SIS	SLE Index Score	

observational studies, and the advantages and disadvantages of each are gradually emerging [17, 18]. As we will see later, these are being used in clinical trials under the presumption that an effective treatment will cause a measurable and significant change in disease activity. However, these instruments were developed to follow the course in individual patients, and they have been found not to be altogether suitable for comparison of groups of patients to each other. One particularly vexing problem is the variable and unpredictable nature pattern disease activity over time [16] (Figure 3). Some of these, particularly the SLAM, place weight on subjective symptoms of importance to patients, such as fatigue or changes in appearance, that may not directly reflect disease activity or response to therapy. Probably the BILAG is the most useful of

these instruments for clinical trials, but it is quite complex and cumbersome. A new measure of lupus activity, termed RIFLE (Responder Index for Lupus Erythematosus) has very recently been developed specifically for clinical trials that emphasizes the specific response of individual patients to therapeutic intervention [19]. Further refinement and wider validation can expected for this instrument in the near future.

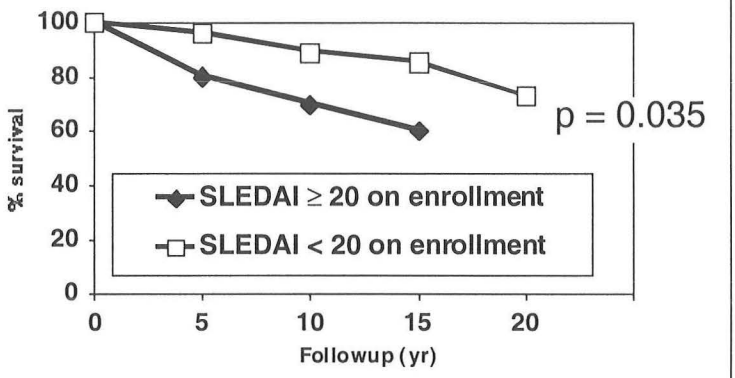


Figure 2. Significant correlation of lupus activity (SLEDAI score), upon entrance into the Toronto cohort, with long term survival. From [10].

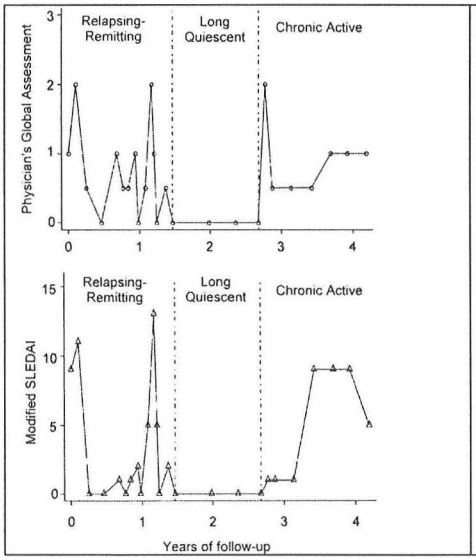


Figure 3. Sample plots of scores on the physician's global assessment (PGA) and modified SLEDAI over time for 1 patient. This patient exhibited 3 patterns of disease activity during the followup period. From [16].

Table 4. SLICC/ACR Damage Index

Organ system	Max. damage score	Organ system	Max. damage score
Ocular	2	Gastrointestinal	5
Neuropsychiatric	6	Musculoskeletal	6
Renal	3	Skin	3
Pulmonary	5	Gonadal failure	1
Cardiovascular	6	Diabetes	1
Peripheral vascular	5	Malignancy	2

From [20, 21]

A complement to the measurements of disease activity, which measure largely reversible events, is the Systemic Lupus International Collaborating Clinics/ACR Damage Index, first published in

1992 [20]. This assesses nonreversible changes, not related to active inflammation, occurring since the onset of the disease (Table 4). It has been validated and shown to be reliable when used by different observers and in a variety of patient populations, it increases over time, and high early scores correlate with a higher mortality rate [21, 22].

Causes of late mortality: a strikingly high prevalence of coronary artery disease. Over the past several decades, a great deal of information on the natural history of treated SLE has emerged from long term observational studies. In this discussion, I am going to focus on atherosclerotic heart disease as a major cause of mortality in SLE. Interest in this subject dates back to two landmark studies in the mid-1970's. In 1976, Urowitz *et al.* from Toronto reported a striking finding in their cohort of patients [23]. Out of 81 patients, there were 11 deaths. Six of the deaths occurred within a year of the diagnosis. All 6 of these patients had active SLE, most had nephritis, and the major cause of death was infection (Table 5). In contrast, the other five deaths occurred 2.5 to 20 years after onset of SLE, none of the patients had active SLE, and all five deaths were from myocardial infarction. The one patient who died of an MI after only 2.5 years of SLE had had preexisting IDDM for 20 years.

Table 5. Bimodal mortality distribution in cohort of 81 SLE patients

	Age at death (yr)	Sex (F/M)	Duration of SLE	Active SLE	Active nephritis	Sepsis	Myocardial infarction
Early deaths (n = 6)	46±18 (25-75)	4 / 2	3-12 mos	6	5	4	0
Late deaths (n = 5)	42±7 (32-50)	4 / 1	2.5 – 20 yr	1	0	0	5

From [23]

The other landmark study was an autopsy series from the NIH by Bulkley and Roberts [24], in which cardiac findings in 36 corticosteroid-treated SLE patients, average age 32, were compared with autopsy findings in SLE in the presteroid era. Particularly striking was the finding of ≥50% luminal narrowing of at least one of the three major coronary arteries by atherosclerotic plaques in 8 out of the 18 patients who had received corticosteroids for more than 1 year, but in none of the 17 patients who received corticosteroids for less than 1 year, and in none of the 20 historical controls. Four of the 8 patients with narrowed coronary arteries had myocardial infarcts. Although the contributions of concomittant renal disease, hyperlipidemia, hypertension, inflammatory vasculopathy, and diabetes could not be discounted, these authors believed corticosteroid therapy was strongly implicated as a major risk factor in the development of coronary artery disease in SLE patients, most of whom were premenopausal women.

Table 6. Prevalence of coronary artery disease in SLE – compilation of studies

Type of study	Studies (N)	Patients (N)	Modality	% CAD
Autopsy	5	159	Narrowing	38 (10 - 54)
Clinical series	7	1160	MI / Angina	8.5 (2 – 20)
Mortality	13		Deaths attributable to CAD	18* (3 – 45)

*Average of % CAD of 13 different studies, but not adjusted for study size

From [25]

Additional studies over the past two decades have repeatedly documented a high prevalence of CAD in SLE (Table 6 [25]). Four additional autopsy studies were published between 1981 and 1995, and the overall prevalence of CAD in the five autopsy studies was 38% in 159 patients. Angina or myocardial infaction has been described in 8.5% of a total of 1160 patients in seven large clinical series (range 2% to 19.8%). The percentage of deaths in SLE due to CAD has ranged from 3 to 45% in 13 series published between 1976 and 1995, with a median of 15%. (It is interesting that the highest value, 45%, comes from the 1976 study by Urowitz *et al.*, cited above [23], which was a relatively small study). A subsequent (1995) study from Toronto [26], analyzed the cause of death in 124 SLE patients and found that 26.6% were attributable to cardiovascular events (Tables 7-8). Even among the patients with disease duration of 5 years or less, 19% of the deaths were from cardiovascular causes. Overall, 10.5% were from documented myocardial infarction and another 8% were sudden death.

Table 7. Causes of death in 124 SLE patients

Cause of death	Early deaths (≤ 5 yr) (N = 46) (%)	Late deaths (> 5 yr) (N= 78) (%)
Active SLE	26	10
Infections	37	30
Vascular disease	19	32
Organ failure	0	4
Unrelated to SLE	7	13
Unknown/other	11	11

(From [26])

Table 8. Proportion of total mortality attributable to vascular disease

Cause of death	(%)
Myocardial infarction	10.5
CVA	4
Ruptured abdominal aneurysm	0.8
Sudden death	8
Pulmonary embolism	1.6
Congestive heart failure	1.6
Total	26.6

From [26]

In a particularly striking result published in 1997 [27], the age-specific incidence rates of myocardial infarction and angina in 498 lupus patients followed at the University of Pittsburgh were compared with those of 2,208 women in the Framingham Offspring Heart Study for the same period of time (1980-1993) (Table 9). Four MI's were recorded in SLE patients ≤34 years old, compared with none in the control group, and 11 in the patients 35-44 years old, compared with 1 in the control group. In this latter group, the rate of MI in SLE patients was over *50-fold* that of the control group (11 MI's in 1,311 person-years in the SLE group vs. 1 MI in 6,143 person-years in the Framingham subjects). Overall, the prevalence of MI in the SLE patients was 6.5 per 1000 patient-years, over 7-fold higher than in the control group. Hypercholesterolemia, longer duration of corticosteroid use, postmenopausal status, age at SLE diagnosis, and lupus disease duration were the main risk factors in the women suffering from MI, compared with the other patients.

Table 9. Strikingly high rate of myocardial infarction in premenopausal women with SLE

Age	MI / person-years		MI per 1,000 person years		Rate Ratio	95% CI
(yr)	SLE	Framingham	SLE	Framingham		
15-24	1 / 158	0 / 312	6.33	0.00	∞	
25-34	3 / 820	0 / 3,207	3.66	0.00	∞	
35-44	11 / 1,311	1 / 6,143	8.39	0.16	52.4	22 - 98
45-54	3 / 623	10 / 5,125	4.82	1.95	2.5	0.8 – 6.0
55-64	3 / 358	5 / 2,516	8.38	1.99	4.2	1.7 – 7.9
65-74	2 / 252	0 / 216	7.94	0.00	∞	
Total	23 / 3,522	16 / 17,519	6.53	0.91	7.15	

Age-specific incidence of MI per 1,000 person years for 498 women with SLE and 2,208 women from the Framingham Offspring Heart Study, 1980-1993. From [27]

It is of interest that the rate of angina pectoris in these SLE patients was only 2.5-fold that of the rate in the control subjects [27]. Similar discrepancies have been found in other studies. It has been suggested that angina is underdiagnosed in SLE, perhaps being attributed to serositis or musculoskeletal causes. It is also possible that cadiac ischemia in SLE is more often silent than in non-SLE patients. This matter bears further investigation.

In a study based on data from ~10 million hospitalizations in 1991-94 from all of the acute care, non-federal hospitals in California [28], Ward estimated that women with SLE between the ages of 18 and 44 had prevalence rates of acute myocardial infarction, congestive heart failure, and CVA that were, respectively, 8.5, 13.2, and 10.1 fold higher than women in this age bracket without SLE. The results of this novel approach, which was based on 3,851 SLE patients 18-44 years old and was relatively unbiased in terms of ascertainment, confirmed the previous studies showing at least a ~5-10-fold increased risk of atherosclerotic cardiovascular events in premenopausal women with SLE.

Several imaging studies have been carried out to assess the prevalence of atherosclerotic CAD disease in SLE patients. The modalities used have tended to parallel the imaging trends in cardiology, but questions about the specificity of the findings have been raised. Most recently, carotid ultrasound has been used in two studies. Carotid plaque was found in 40% of 175 women with SLE in the Pittsburgh cohort [28a]. In a study from New York, presented in abstract form in Nov 2000 at the annual ACR meeting in Philadelphia, 33% of 87 SLE patients were found to have carotid plaque, compared with 14% of a carefully matched set of 87 healthy controls [29]. These studies are discussed in more detail below in regard to risk factors.

Why is coronary atherosclerosis so common in SLE? Significant attention has been given to identifying the underlying factors for the high prevalence of coronary artery disease in SLE. However, there is considerable complexity to this problem and it has not yet been resolved. As indicated in the following paragraphs, a number of studies have implicated corticosteroids as an apparently independent risk factor. However, it is difficult to sort out the effect of corticosteroid therapy itself from either the severity or the duration of SLE. Moreover, if corticosteroid therapy is itself a risk factor, is it acting through induced lipid changes, insulin resistance, hypertension, obesity, other as yet unidentified metabolic alternations, or some combination of all of these? To what extent does renal disease, with its attendent hypertension, nephrotic syndrome, and associated lipid abnormalities, contribute to CAD in SLE? Let us examine some of the evidence

that has been gathered to attempt to answer these questions. (As extensively discussed in a previous Grand Rounds by Dr. Munford, even subclinical systemic inflammation has itself been implicated as a significant independent risk factor for coronary events [30]. For the purposes of this discussion, I am going to consider the contribution of systemic inflammation as "SLE disease activity.")

Role of corticosteroid therapy as a risk factor for hyperlipidemia and CAD. It is rather surprising how relatively little data has been published on the clinical effects of corticosteroids on lipid metabolism. In SLE patients, several studies have shown a correlation between corticosteroid therapy and elevated triglyceride and LDL levels. In a study from Johns Hopkins, [31] Ettinger *et al.* compared a variety of lipid parameters in SLE patients and matched controls with reference to prednisone treatment (Table 10). None of the patients was acutely ill or had fasting hyperglycemia, serum creatinine ≥1.5 mg/dl, proteinuria, or personal or family history of diabetes, hyperlipidemia, premature CAD, or liver or thyroid disease.

Table 10. Correlation of corticosteroid therapy with hyperlipidemia in SLE

	Prednisone Rx * (n=32)	No Prednisone Rx (n = 14)	Controls (n = 30)
Age (yr)	36±7	30±8	37±10
BMI (kg/M^2)	24±1	25±2	24±2
Race (% Caucasian)	61	71	77
Smoking %	22	36	20
Triglycerides, mg/dl	158±11**	87±9	73±7
Cholesterol	214±9**	170±7	168±6
LDL	130±8**	103±8	94±5
HDL	54±4	50±3	59±2
HDL subfraction 2	9±2**	13±1	18±2
HDL subfraction 3	44±4	36±4	41±2
Apolipoprotein AI	137±7	139±8	146±8
Apolipoprotein E	6±0**	3±1	3±0

*17.4 ± 8.4 mg prednisone per day for 8.3 ± 5.4 yr
**Significantly different from other two groups
From [31]

The patients with SLE had significantly higher levels of triglycerides, total cholestrol, LDL cholesterol, HDL subfraction 2, and apolipoprotein E, compared with controls. All of these were significantly more abnormal in the prednisone-treated group. Prednisone doses correlated significantly with the total plasma cholesterol (r=0.38), LDL (r=0.4), and HDL subfraction 3 (r=0.47). There were no significant correlations between lipid levels and duration of prednisone treatment or duration of disease, or with age or body mass index. This study provided strong evidence for prednisone-associated lipid abnormalities in SLE patients. However, patients were not stratified according to disease severity or duration, and thus it could not be ascertained whether prednisone therapy, disease severity, or both was the most important correlate of dyslipidemia.

A subsequent study from Hopkins by Petri *et al.* [32] of 225 SLE patients looked at the correlation of CAD risk factors with prednisone dose (Table 11). The patients were 38 ± 12 yr old, 93% female, 55% Caucasian, 44% African-American, 1% Asian, with a mean duration of

SLE of 8 ± 7 yr. (Note: this is typical of the racial composition of the Hopkins lupus cohort described by Petri *et al.* in numerous publications).

Table 11. Prednisone dose correlates with cholesterol but no other CAD risk factors in 225 SLE patients

	Average daily prednisone dose (mg)			
	0	0-10	10-20	>20
Number of patients	49	73	58	45
Family Hx premature CAD	43%	44%	41%	36%
Antihypertensive treatment	33	44	45	42
*Total cholesterol >200 mg/dl	46	50	65	66
Obesity (NHANES definition)	33	38	48	34
Smoking (ever)	55	58	55	58
Sedentary life style	67	70	69	74
Diabetes mellitus	2	11	7	7
Mean no. risk factors ± SD	3.2 ± 1.5	3.8 ± 1.3	3.9 ± 1.4	3.7 ± 1.4

*$p < 0.05$
From [32]

Of the conventional risk factors, only hypercholesterolemia (total cholesterol > 200 mg/dl) correlated with average daily prednisone dose. Patients treated with prednisone at any dose had an average of 0.5 to 0.7 more risk factors, compared with the group never treated with prednisone, and this could largely be attributed to hypercholesterolemia. Again, it was not possible in this study to separate prednisone therapy from disease severity, although the lack of association of prednisone dose with antihypertensive treatment suggested that prednisone therapy *per se* was not a direct correlate of severity.

Looking at it the other way, *i.e.*, asking what correlated with hypercholesterolemia, a subsequent longitudinal analysis of 264 SLE patients by Petri *et al.* [33] examined a large set of variables over >3,000 patient visits, using linear regression. The patients were 38 ± 12 yr old, 92% female, 56% African-American, with a mean duration of SLE of 12 ± 8 yr.

Table 12. Estimated effect of various factors on serum cholesterol in SLE (multivariate analysis)

Factor	Effect on serum cholesterol (mg / dl)	p value
Female sex	+23.5 ± 7.8	0.001
Age (per yr)	+0.8 ± 0.2	<0.001
Use of hydroxychloroquine	-8.9 ± 3.4	0.009
Use of diuretics	+8.5 ± 4.9	0.040
Urine protein 2+	+14. 9 ± 6.6	0.012
Urine protein 3-4+	+21.2 ± 6.4	<0.001
Prednisone (effect per mg/d)	+0.75 ± 0.15	<0.001

Not significant: race, smoking, weight, beta-blocker use, urine protein ≤ 1+
From [33]

As shown in Table 12, a number of factors were found to significantly influence serum cholesterol, including, surprisingly, female sex. Each 10 mg of daily prednisone dose was associated with an average increase of 7.5 mg/dl in total serum cholesterol, whereas the use of hydroxychloroquine was associated with a 9 mg/dl decrease in cholesterol. Not surprisingly, diuretic use and higher degrees of proteinuria were also associated with elevations in cholesterol. Each 10 mg change in prednisone dose was also associated with a 1.1 mm Hg increase in mean arterial blood pressure and a 5.5 lb increase in weight. Thus, in this study, prednisone dose

significantly correlated with three conventional risk factors for CAD, cholesterol, blood pressure, and weight, but the changes in the latter two were mild, explaining the lack of significant correlation with the risk factors of obesity and hypertension shown in Table 11.

Finally, a recent study from Hopkins [34], shown in Tables 13 and 14, looked at the role of corticosteroid treatment in irreversible organ damage in SLE, using the SLICC/ACR Damage Index (SDI) shown above in Table 4. The cumulative prednisone dose was calculated for 539 patients, and episodes of high dose prednisone (≥60 mg/day for ≥2 months) and of pulse methylprednisolone (1 gm per day for 1-3 days) were tabulated. Cox proportional hazards models were used to assess association between corticosteroid use and the time that damage following diagnosis of SLE. Separate modeling was done for each damage item. Damage had occurred in 60% of the patients. The mean SDI score was 1.5±2.0, with a median of 1.0 and a range of 0-11. The risk of each damage item was calculated per 36.5 gm cumulative dose of prednisone (equivalent to 10 mg per day for 10 years).

Table 13. Risk of organ damage associated with cumulative corticosteroid dose

Damage item	No. of events	Adjusted RR* (95% CI)	*p*
Osteoporotic fracture	24	1.9 (1.5-2.4)	0.0001
Coronary artery disease	21	1.7 (1.2-2.3)	0.0009
Cataracts	47	1.7 (1.3-2.1)	0.0001
Avascular necrosis	47	1.6 (1.3-2.0)	0.0001
Diabetes mellitus	26	1.5 (1.0-2.3)	0.04
Pulmonary fibrosis	15	1.7 (1.2-2.5)	0.006
Cognitive impairment	30	2.0 (1.2-3.2)	0.007

*Relative risk per each cumulative corticosteroid dose of 36.5 gm of prednisone (equivalent of 10 mg/d for 10 yr), adjusted for age, sex, & race. No significant correlation was found for stroke, hypertension, venous insufficiency, renal failure, deforming arthritis, scarring alopecia, pulmonary hypertension, or malignancy.

From [34]

This finding strongly implicated corticosteroid dose as a separate risk factor for CAD. The fact that no correlation was found with renal failure ($p = 0.2$) suggests that corticosteroid dose is not just a surrogate marker for disease severity. Further evidence along these lines was obtained when the separate relative risks of cumulative prednisone dose, ≥2-month courses of high dose prednisone, and courses of pulse methylprednisolone for each damage item were assessed (Table 14). In this case, the risk of cumulative prednisone dose for CAD was comparable to that of osteoporotic fracture and cataracts, two well-established complications of corticosteroid therapy even in individuals who do not have SLE. Moreover, avascular bone necrosis was found to correlate with high dose prednisone, confirming a number of previous reports that maximum corticosteroid dose, rather than cumulative dose, is crucial in this debilitating complication [35, 36]. These correlations thus lend support to the concept that corticosteroid therapy is a strong risk factor for CAD in SLE, even independent of disease activity itself.

Correlation of lipid abnormalities, corticosteroid therapy, SLE disease activity, CAD, and prognosis. Another study examining the correlation of serum lipid levels with corticosteroid dose and other clinical parameters in SLE patients was reported from Singapore [37]. One hundred consecutive SLE patients were studied. Patients treated with more than 30 mg/day of prednisolone (which is equivalent in potency to prednisone) showed markedly higher levels of

triglycerides and total and LDL cholesterol and markedly lower levels of HDL cholesterol than patients treated with less than this dose (Table 15).

Table 14.

Table 5. Relative risk of damage in SLE associated with cumulative prednisone, high-dose prednisone, and pulse methylprednisolone

Damage item	Cumulative prednisone* Adjusted RR (95% CI)	*P*	High dose prednisone† Adjusted RR (95% CI)	*P*	Pulse methylprednisolone‡ Adjusted RR (95% CI)	*P*
Osteoporotic fracture	2.5 (1.7, 3.7)	0.0001	0.8 (0.7, 1.0)	0.08	1.3 (1.0, 1.8)	0.07
Coronary artery disease	1.7 (1.1, 2.5)	0.008	1.0 (0.8, 1.2)	0.9	1.1 (0.7, 1.8)	0.8
Cataracts	1.9 (1.4, 2.5)	0.0001	0.9 (0.8, 1.1)	0.3	1.0 (0.7, 1.4)	0.9
Avascular necrosis	1.1 (0.8, 1.5)	0.6	1.2 (1.1, 1.4)	0.0002	1.2 (0.9, 1.6)	0.2
Stroke	0.9 (0.5, 1.5)	0.7	1.2 (1.0, 1.5)	0.02	0.9 (0.5, 1.5)	0.7
Diabetes mellitus	1.4 (0.8, 2.4)	0.2	1.0 (0.9, 1.3)	0.5	0.8 (0.4, 1.6)	0.6
Hypertension	1.0 (0.7, 1.3)	0.9	1.1 (0.9, 1.2)	0.3	1.0 (0.8, 1.3)	0.9
Pulmonary fibrosis	1.6 (1.0, 2.8)	0.1	1.1 (0.8, 1.3)	0.7	0.7 (0.3, 1.9)	0.5
Venous insufficiency	1.1 (0.5, 2.1)	0.9	1.1 (0.9, 1.5)	0.4	No events	–
Cognitive impairment/psychosis	1.3 (0.6, 2.9)	0.5	1.1 (0.9, 1.4)	0.3	1.5 (1.1, 2.0)	0.02
Renal failure	1.3 (0.8, 2.1)	0.3	1.0 (0.8, 1.2)	0.7	1.3 (0.8, 2.0)	0.3
Joint deformity/erosion	1.2 (0.8, 1.7)	0.4	0.9 (0.8, 1.1)	0.5	1.3 (0.9, 1.8)	0.1
Scarring alopecia	1.5 (0.9, 2.6)	0.1	0.7 (0.4, 1.1)	0.09	1.2 (0.8, 1.7)	0.4
Pulmonary hypertension	0.7 (0.3, 1.5)	0.4	1.2 (0.9, 1.5)	0.3	1.0 (0.5, 1.8)	0.9
Malignancy	1.1 (0.6, 2.0)	0.8	0.4 (0.1, 2.0)	0.3	1.0 (0.4, 2.5)	0.9

* Adjusted RR = risk ratio associated with a cumulative prednisone dose of 36.5 gm, adjusted for age, sex, race, high-dose prednisone and pulse methylprednisolone. 95% CI = 95% confidence interval.
† Adjusted RR = risk ratio associated with each 2-month exposure to ≥60 mg prednisone, adjusted for age, sex, race, cumulative prednisone dose and pulse methylprednisolone.
‡ Adjusted RR = risk ratio associated with each pulse of methylprednisolone (1,000–3,000 mg intravenously), adjusted for age, sex, race, high-dose prednisone and cumulative prednisone dose.

From [34]

Table 15. Correlation of serum lipids with corticosteroid dose

Parameter	Prednisolone < 30 mg/d (n = 81)	Prednisolone > 30 mg/d (n = 19)	p
	Mean ± SD (mg/dl)		
Total cholesterol	248 ± 96	322 ± 205	<0.05
Triglycerides	204 ± 134	371 ± 395	<0.05
LDL cholesterol	147 ± 82	198 ± 141	<0.05
HDL cholesterol	62 ± 21	49 ± 23	<0.05
TC / HDL ratio	4.5 ± 2.8	8.2 ± 7.9	<0.05

From [37]

However, when patients were stratified into three groups according to serum cholesterol levels, there was a significant correlation of lipid values with renal disease and nephrotic syndrome, as well as with current corticosteroid dose. There was no correlation with disease duration or cumulative corticosteroid dose (Table 16).

These findings suggest that serum lipids tend to reflect the intensity of current disease activity, particularly when that activity involves renal disease. Moreover, when only patients with active disease were considered, after adjusting for prednisolone dose the major factor producing differences in lipid levels was renal disease (Table 17). Overall, this study from Asia (in which serum lipid levels were, surprisingly, considerably higher than in most North American studies) suggests that the severity of disease activity and degree of renal disease with nephrotic syndrome, together with concommitant corticosteroid therapy, are the major risk factors for hypercholesterolemia. The cumulative effect of this activity, whether continuous or episodic, may be a major risk factor for CAD, as suggested by the data in Tables 13 and 14.

Table 16. Serum lipids correlate with disease activity, current prednisolone dose, renal disease, and nephrotic syndrome, but not cumulative prednisolone dose or disease duration

Parameter	Group 1 N = 27	Group 2 N = 38	Group 3 N = 35	p
Female %	96.3	94.7	80	NS
Age (yr)	34±8	31±10	32±12	NS
Chinese %	92	84	80	NS
Total cholesterol	185±31	225±65	362±156	<0.001
Triglycerides	108±31	200±88	375±33	<0.001
LDL cholesterol	93±28	127±47	236±17	<0.001
HDL cholesterol	70±15	61±27	50±15	<0.005
TC / HDL ratio	2.7±0.6	4.1±1.9	8.2±6.1	<0.001
Current anti-hypertensive Rx %	18.5	23.7	34.3	NS
Active SLE %	15	8	54	<0.001
Duration of SLE (mos)	68±61	90±36	68±66	NS
Renal disease %	37	60.5	77	<0.001
Nephrotic %	0	10.5	34	<0.001
Mean current prednisolone mg	9±12	15±16	23.5±22	<0.001
Cumulative prednisolone g	20.5±25.5	20±18	24±22	NS

From [37]

Table 17. Lipid abnormalities correlate in renal disease in patients with inactive SLE

Parameter	Renal disease (n = 33)	No renal disease (n = 31)	p
	Mean ± SD (mg/dl)		
TC	264 ± 112	210 ± 52	<0.05
TG	208 ± 111	143 ± 78	<0.05
LDL	164 ± 100	116 ± 44	<0.05
HDL	64 ± 24	64 ± 16	NS
TC / HDL	4.8 ± 3.5	3.4 ± 1.1	<0.05

Values adjusted for age, current prednisolone dose, and use of beta blockers and diuretics.
From [37]

Disease activity, renal disease, and corticosteroid therapy thus all may be contributing independently and also interdependently to elevated lipid levels in SLE patients. In an attempt to identify the individual contributions of these factors, a study from Brazil [38] examined 36 consecutive female SLE patients under age 50 who had not been treated with corticosteroids or antimalarials for at least three months, and who met a variety of other exclusion criteria (Table 18). A control group of 30 individuals was included without further description.

Compared with controls, patients with inactive disease had significant elevations in triglycerides and VLDL, and significantly lower levels of HDL. Compared with patients with inactive disease and with controls, patients with active disease had even higher levels of triglycerides and VLDL, but *lower* levels of HDL, LDL and total cholesterol. The authors suggested that SLE itself, independent of renal disease or corticosteroid therapy, confers a a pattern of dyslipidemia characterized by elevated VLDL and triglycerides and depressed levels of HDL, and that this pattern is aggravated with disease activity. Overall, 79% of patients with active disease and 29% with inactive disease had HDL levels < 35 mg/dl. When the relationship of lipid levels to SLEDAI was analyzed by regression analysis, significant correlations were seen as shown in Table 19.

Table 18. Active SLE has a specific effect on serum lipids independent of prednisone

Parameter	Active SLE (n = 19)	Inactive SLE (n = 17)	Control (n = 30)
Age (yr)	32±10	34±7	31±5.5
Caucasian %	63	82	80
Weight (kg)	58±8	60±8	60±6.5
Creatinine	0.8±0.2	0.7±0.2	0.8±0.1
Median isease duration (yr)	2.0[§]	7.0	—
SLEDAI	≥6, median 11.0[§]	≤4, median 0	—
TC	148 ± 45*	168 ± 31	170 ± 25
TG	209 ± 165*[§]	109 ± 34*	63 ± 18
LDL	83 ± 32*[§]	104 ± 27	103 ± 20
HDL	26 ± 11*[§]	40 ± 10*	54 ± 14
VLDL	34 ± 16*[§]	22 ± 7*	12 ± 4

Exculsions: corticosteroids or antimalarials for 3 previous months, DM, CAD, liver or thyroid disease, azotemia, proteinuria, alcohol intake, menopause, pregnancy, or lipid raising or lowering drugs
*$p<0.05$ vs. control
[§]$p<0.05$ vs. inactive SLE
From [38]

Table 19. Correlation of lipid levels with disease activity in patients not taking corticosteroids

Parameter	Correlation with SLEDAI	
	r	p
TC	-0.40	0.016
TG	0.48	0.003
LDL	-0.46	0.005
HDL	-0.60	0.0001
VLDL	0.40	0.019

From [38]

Very similar findings were reported in 1988 by others in a group of ten adolescents with SLE [39]. The Brazilian investigators have also very recently reported a two-fold reduction in chylomicron clearance from plasma in SLE patients [40]. When the various studies are considered together, the suggestion emerges that SLE activity itself, without the secondary effects of proteinuria and corticosteroid therapy, produces a pattern of low HDL and LDL, and high VLDL, triglycerides, and chylomicrons. Both proteinuria and corticosteroid therapy substantially elevate LDL and triglyceride levels, without much direct influence on the other parameters. Thus, each of these factors may contribute independently to atherosclerotic disease.

Two recent papers from the group in Toronto have further defined the contributions of hyperlipidemia and of SLE itself to the development of CAD and to mortality. In the first paper [41], they looked at outcomes in 134 patients first seen between 1974 and 1987 within one year of diagnosis. These patients were then divided into three groups: those who had total cholesterol levels below 5.2 mM (200 mg/dl) throughout the first three years that they were followed (normal cholesterol), those who had at least one year of the three during which total cholesterol was consistently <5.2 mM but also had at least one year that contained a reading above this level (variable hypercholesterolemia), and those with at least one elevated level during each of the first three years of followup (sustained hypercholesterolemia) (Table 20).

Table 20. Significant ($p < 0.05$) distinguishing characteristics of SLE patients classified by cholesterol levels during first three years of followup (univariate analysis)

Parameter	Cholesterol levels during first three years (high ≥ 200 mg/dl)		
	Normal (n = 33)	Variably high (n = 47)	Sustained (n=54)
Total cholesterol, mg/dl	156±15	192±17	272±51
Women > 50 yr, %	3	17	29
Renal damage, %	0	2	31
Cardiac disease, %	33	21	44
Steroid treatment (ever), %	61	68	85
Cumulative prednisone dose, g	8±11	9±8	16±11
Months on prednisone (≤36)	15±15	20±15	27±13
Antimalarial treatment, %	79	55	20
Hypertension, %	21	40	72

Parameters that were not statistically significantly different in the three groups included: % with onset > 35 yr of age, % men, % with SLEDAI > 20, % with lung involvement, % with CNS involvement, % with diabetes, and % smoking.

[41]

The patients were followed for a mean of 12.4 years (range 2.2 to 23.4), with 8 patients lost to followup (3 in the normal group and 5 in the variable group). CAD events (myocardial infarction, angina, or sudden death) occurred in 1, 3, and 15 patients, respectively, in the three patients groups (3, 6.4 and 28%, respectively) (Figure 4A). The survival probability was significantly higher in the normal cholesterol group, compared with the variable and sustained hypercholesterolemia groups, with 1, 8, and 15 deaths, respectively (Fig 4B). Thus, having even one reading of serum cholesterol >200 mg/ml during the first three years of SLE was predictive of a far worse prognosis than having all readings <200 mg/ml. However, interestingly, at least 14 of the 23 deaths in the sustained and variable groups were from non-vascular events. By multivariate analysis, three factors emerged as predictive of CAD (Table 21), sustained hypercholesterolemia (as defined above), age at onset ≥ 35 years, and lung involvement.

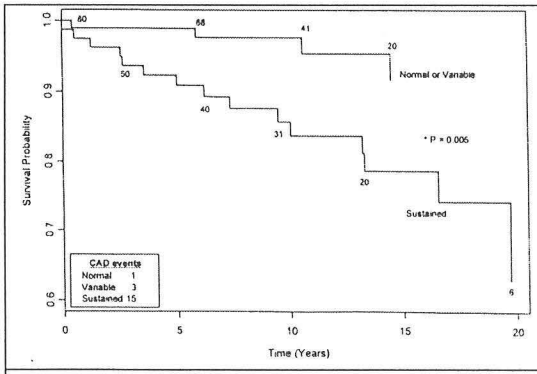


Figure 4A. CAD was significantly more prevalent in the group of patients with serum cholesterol consistently ≥ 200 mg/ml during the first three years of disease. From [41].

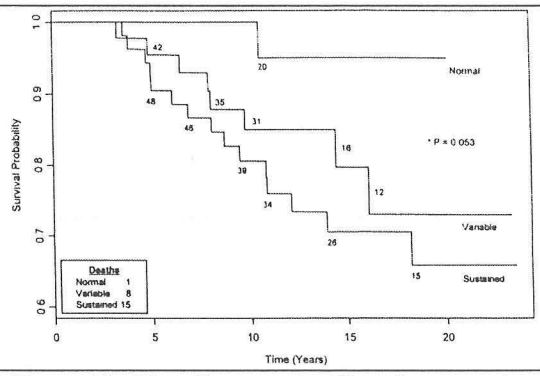


Figure 4B. Mortality was significantly greater in the groups of patients with *any* serum cholesterol reading ≥ 200 mg/ml during the first three years of disease. The one death in the normal group, and at least 14 of the 23 deaths in the other two groups, were from causes other than coronary disease.

The authors did not indicate the factors that predicted variable hypercholestolemia vs. normal cholesterol. However, the factors that predicted sustained hypercholesterolemia vs. normal

cholesterol and vs. variable hypercholesterolemia are indicated in Table 22. Multivariate analysis indicated a positive correlation of cumulative corticosteroid dose, and a negative correlation of antimalarial therapy, with elevated cholesterol levels during the first three years of followup, as well as associations with age of onset, cardiac disease and CNS disease, but by far the strongest correlation was with renal damage (GFR < 50%, proteinuria > 3.5 gm/24 hr, or end stage renal disease).

Table 21. Factors during first 3 years of SLE predictive of subsequent CAD

	Hazards ratio estimate	95% CI	p
Sustained hypercholesterolemia	4.20	1.38 – 12.9	0.005
Age at onset > 35 yr	2.66	1.01 – 7.0	0.042
Lung involvement	3.71	1.45 – 9.5	0.006

From [41]

In another recent study from Toronto [42], 35 SLE patients with CAD (MI or acute coronary insufficiency) were compared for the prevalence of traditional risk factors with 397 non-SLE patients with premature CAD being followed at a cardiology secondary prevention clinic in Montreal. There were 27 women in the SLE cohort and 83 women in the control group. The comparison between these two groups is shown in Table 23.

Table 22. Predictors of sustained vs. normal cholesterol and sustained vs. variable hypercholesterolemia over the first three years of disease by multiple logistic regression

		Odds ratio	95% CI	p
Sustained	Age of SLE onset > 35 yr	6.46	1.70 – 28.7	0.006
Vs. normal cholesterol	Antimalarial therapy	0.08	0.02 – 0.25	<0.001
	Cumulative prednisone dose, per gm*	1.11	1.05 – 1.20	<0.001
Sustained	Antimalarial therapy	0.21	0.07 – 0.59	0.003
Vs. variable	Cardiac involvement	3.17	1.05 – 10.5	0.040
hypercholesterolemia	CNS involvement	3.56	1.20 – 11.6	0.022
	Cumulative prednisone dose, per gm**	1.06	1.01 – 1.12	<0.018
	Renal damage	34.9	4.74 - 777	<0.001

*10 gm prednisone per 3 yr (average of 9 mg/d) associated with OR = 2.95
**10 gm prednisone per 3 yr (average of 9 mg/d) associated with OR = 1.8
From [41]

Table 23. SLE patients with CAD have fewer risk factors than comparable CAD patients without SLE

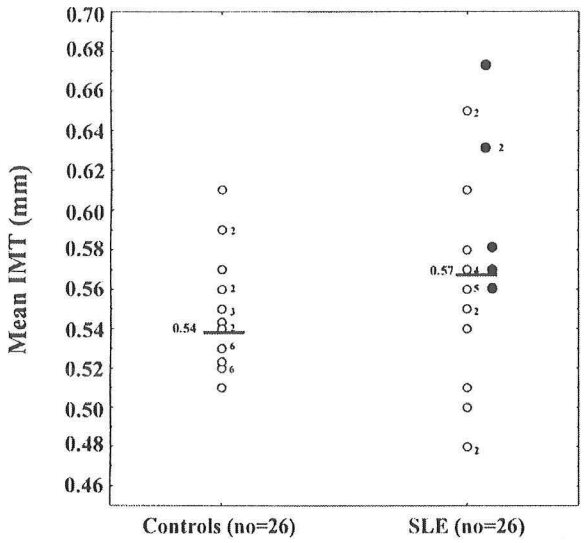
Risk factors in women with CAD (MI or unstable angina)	SLE patients (n = 27)	Control early CAD patients (n = 83)	p
Age at CAD event	50±13	50±7	
BP > 140 or 90 (%)	59	53	
Smoking (%)	48	68	
Hypercholesterolemia (%)	67	77	
Family Hx premature CAD (%)	26	69	$<10^{-4}$
Diabetes mellitus (%)	4	23	0.016
Number of traditional risk factors	2.0 ± 0.8	2.9 ± 1.2	$<10^{-3}$

From [42]

The 8 male SLE patients in the same study were compared with 314 non-SLE males with early CAD. The SLE patients had 1.87±0.83 risk factors, compared with 2.73±0.99 in the controls (p=0.016). These data from both sexes suggest that treated SLE itself constitutes a risk factor for

premature CAD.These data suggest that SLE *per se* or its treatment or both confer an additional whole risk factor equivalent to and independent of the conventional risk factors.

Figure 5. Carotid intima media thickness in SLE patients and controls



Juvenile-onset SLE patients have a higher mean IMT than controls. The dark circles represent the 6 patients with nephrotic range proteinuria. Figure and table from [43].

Table 24.

Table 1. SLE–related and cardiovascular risk factors and results of carotid IMT measurements in SLE patients, according to the presence of NR proteinuria*

	SLE with NR proteinuria (n = 6), mean ± SD	SLE without NR proteinuria (n = 20), mean ± SD	*P*
Age (years)	17.8 ± 4.0	16.8 ± 4.6	0.9
Disease duration (years)	5.9 ± 3.7	5.4 ± 4.3	0.7
Systolic BP (mm Hg)	138 ± 27	113 ± 11	0.02
Diastolic BP (mm Hg)	89 ± 13	72 ± 10	0.007
ESR (mm/hour)	27.7 ± 21.5	19.4 ± 13.5	0.5
C3 (mg/dl)	74 ± 32.5	80 ± 14.4	0.5
C4 (mg/dl)	15.7 ± 7.2	13.9 ± 4.5	0.7
Anti-dsDNA antibody titer	52 ± 69	131 ± 172	0.5
SLEDAI score	14.3 ± 7.3	6.3 ± 4.8	0.01
SLICC/ACR Damage Index score	2.8 ± 1.9	0.25 ± 0.4	0.0001
Cumulative prednisone dose (mg/kg)	1,424 ± 1,122	794 ± 829	0.1
Total cholesterol (mg/dl)	217 ± 59	159 ± 31	0.03
LDL cholesterol (mg/dl)	136 ± 54	87 ± 29	0.04
HDL cholesterol (mg/dl)	56 ± 15	54 ± 15	0.7
Triglycerides (mg/dl)	121 ± 61	91 ± 44	0.2
Apolipoprotein A-I (mg/dl)	140 ± 33	123 ± 26	0.3
Apolipoprotein B (mg/dl)	138 ± 44	90 ± 24	0.02
Fibrinogen (mg/dl)	395 ± 82	299 ± 94	0.04
Mean IMT (mm)	0.61 ± 0.04	0.56 ± 0.04	0.02
Maximum IMT (mm)	0.67 ± 0.07	0.60 ± 0.05	0.02

* SLE = systemic lupus erythematosus; IMT = intima–media thickness; NR = nephrotic range; BP = blood pressure; ESR = erythrocyte sedimentation rate; dsDNA = double-stranded DNA; SLEDAI = SLE Disease Activity Index; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

A recent small Italian study of patients with juvenile-onset SLE used carotid ultrasound to assess intima-media wall thickness (IMT) [43]. There were 26 patients, age 6 to 25 yr, with 0.5 to 13 yr of SLE (mean 5.5). They were compared with 26 age- and sex-matched controls. The SLE patients had significantly higher mean and maximum IMT (Figure 5 and Table 24). The IMT measurements did not correlate with age, disease duration, SLEDAI score, SLICC/ACR DI, laboratory measurements of SLE activity, or cumulative prednisone dose. However, there was a significant correlation with the presence of nephrotic range proteinuria ($p = 0.02$). When the six patients in this category were compared with those without nephrotic range proteinuria, there were significant differences in blood pressure, activity and damage indices, total and LDL cholesterol, apolipoprotein B and fibrinogen (Table 24). Although not statistically significant, the cumulative prednisone dose of the nephrotic range group was nearly twice that of the other patients. These data emphasize the importance of renal disease as a factor in the atherosclerosis of young SLE patients and complement the studies that show older age to be a risk factor even in patients without renal disease.

Finally, the ultrasound study from New York [29], cited above, seemed to indicate that SLE itself is an independent risk factor for atherosclerosis. These investigators compared 87 SLE patients with 87 healthy controls who were matched for age, gender, race, blood pressure, current smoking, and total and HDL cholesterol (Table 25).

Table 25. Carotid plaque and cardiac abnormalities

Parameter	SLE (n=87)	Control (n=87)	p value
Mean age	42	42	
% female	97	97	
Mean blood pressure	112/73	117/74	
Current smokers %	12	13	
Total cholesterol , mg/dl	200	203	
HDL cholesterol, mg/dl	62	58	
Carotid plaques %	33	14	0.002
Vascular pulsatility %	12	14	0.003
LV mass (g/m^2)	85	72	<0.001
LV hypertrophy %	22	6	0.002
LVEF (% ejection)	71	67	<0.001

From [29]

Table 26. Risk factors for carotid plaque

Parameter	Plaque	No plaque	p value
Average age (yr)	50	38	<0.001
LV hypertrophy %	32	10	0.013
Raynaud's %	64	40	0.044

From [29]

The presence of carotid atherosclerosis in the SLE patients was associated with older age, the presence of LV hypertrophy, and Raynaud's phenomenon, but not with blood pressure, lipid profile, smoking habits, family history of myocardial infarction, presence of antiphospholipid antibody or SLE disease duration or severity (SLEDAI) (Table 26). Past or present use of prednisone was associated with a tendency for *less* carotid atherosclerosis (odds ratio=0.44, 95% CI=0.13-1.47). The authors concluded that preclinical cadiovascular disease, as manifested by either carotid atherosclerosis or LV hypertrophy, is significantly increased in SLE patients, unrelated to traditional risk factors or steroid use.

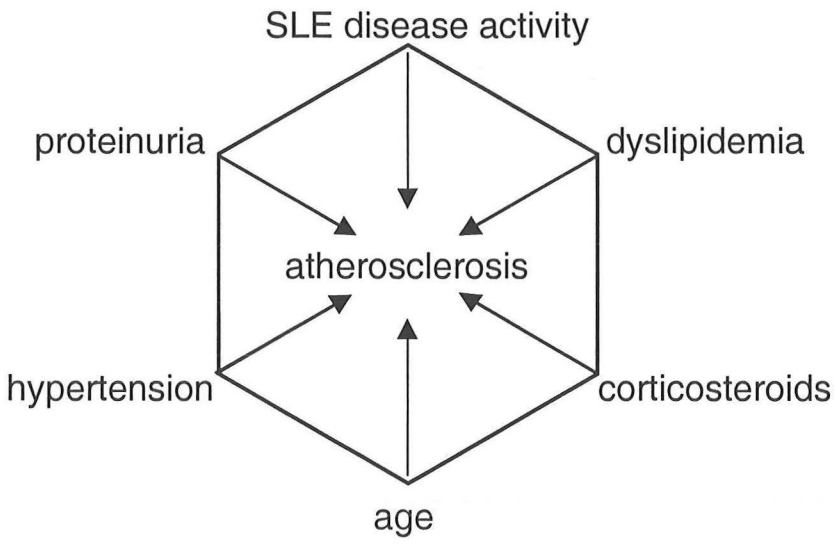


Figure 6. Multifactorial pathogenesis of atherosclerosis in SLE patients. SLE disease activity encompasses both increased risk secondary to systemic inflammation [30] and SLE-specific vascular injury [43a].

Taken together, the available studies suggest that each of the factors we have considered is a separate risk factor for atherosclerosis in SLE patients, with presumably complex interactions between them (Figure 6).

Minimizing the use of corticosteroids in SLE. Given the foregoing, it would seem apparent that care should be taken to confine the cumulative and peak doses of corticosteroids in SLE patients to the minimum necessary to control disease activity. The cumulative dose needs to be minimized to reduce the risk of atherosclerotic disease and osteoporosis, and the peak dose needs to be minimized to reduce the risk of aseptic necrosis of bone (Table 14). In the absence of definitive controlled data, the principles listed in Table 27 are proposed as being widely subscribed to by rheumatologists caring for SLE patients.

Table 27. General principles for minimizing the cumulative and peak doses of corticosteroids in SLE patients

General principles	References
• Most flares of SLE do not involve major organ involvement	[44]
• High dose prednisone is indicated only for major organ involvment	[45]
• 1 mg/kg/d of prednisone *is* high dose (little evidence that more is better)	[45]
• It is uncommon for major organ involvement to be imminently life threatening (hence careful clinical evaluation can be done before starting corticosteroid Rx)	[46]
• Only half of SLE admissions to medical services are for active disease	[47]
• Pulse methylprednisolone gains little or nothing in reducing organ damage over conventional high dose prednisone, compares unfavorably in controlled trials vs. cyclophosphamide, and is associated with considerable toxicity	[48-50a]
• Therapy that is potentially steroid-sparing should be used whenever possible	[51]

Optimizing Therapy for SLE: New Data from Studies of Old Drugs

Antimalarial therapy. Antimalarials (hydroxychloroquine, chloroquine, quinacrine) have been widely used for several decades in the treatment of SLE, especially for cutaneous manifestations, arthritis and arthralgias, constitutional symptoms, and serositis. The mechanism of action is not known, but may be related to inhibition of antigen presentation by MHC class II molecules, inhibition of proinflammatory cytokine production, or up-regulation of apoptosis [52]. Hydroxychloroquine (HCQ, Plaquenil) is the drug most commonly used in the U.S. At maintenance doses of 400 mg/day or less, retinal toxicity is exceedingly rare and preventable with periodic eye examinations [53].

A number of studies have shown that HCQ is beneficial in SLE in reducing symptoms and the frequency of flares. A randomized, double-blind, placebo-controlled study from Canada [54], reported in 1991, looked at 47 patients with stable SLE who had taken HCQ for a mean of 3 years. The patients randomized to discontinue HCQ incurred a 2.5-fold greater risk of a flare over the 6 months of followup, compared with the patients who continued to take the drug, and the time to flare was significantly shorter in the first group. The relative risk of severe flare was 6-fold higher in the group discontinuing HCQ, and five of the six patients withdrawn from the study because of severe disease exacerbation were in the placebo group.

Several other controlled studies have also shown HCQ to be of benefit in SLE in terms of reducing the incidence of flares, reducing disease activity, reducing the incidence of new renal disease, or allowing reductions in corticosteroid dose (Table 28).

Table 28. Controlled studies showing benefit of antimalarials in SLE

Year	No. pts	Drug	Reduced flare rate	Significant reduction of disease activity	Steroid sparing
1975	43	HCQ, C, Q	yes	nt	yes
1991	47	HCQ	yes	nt	no
1994	71	HCQ	no	Reduced arthralgia	no
1995	293	HCQ	nt	Reduced new renal disease	nt
1996	23	C	yes	yes	yes

HCQ = hydroxychloroquine; C = chloroquine; Q = quinicrine, nt = not tested for
From [52]

A number of studies have also documented that HCQ is associated with a more favorable lipid profile in SLE patients. As noted above, Petri *et al.* showed in multivariate analysis that SLE patients taking HCQ had a total cholesterol 9 mg/dl lower than those who had not taken the drug (Table 12), and Rahman *et al.* found antimalarial therapy to be negatively associated with hypercholesterolemia during the first three years of management of SLE (Table 22). In a study from USC [55], two groups of 9 patients each were carefully matched for a variety of pertinent characteristics. One group had been taking HCQ for 4-10 years (mean of 43 months) and the other group had never taken the drug (Table 29). All patients had had multisystem disease in the past, but had minimally active disease at the time of the study. Virtually all categories of fasting serum cholesterol, triglyceride, and apolipoprotein fractions were lower in the HCQ-treated group. Statistically significant differences were seen in all of the categories of triglycerides, in VLDL cholesterol, and in Apo-CIII.

Table 29. Lower lipid levels in SLE patients treated with hydroxychloroquine

Parameter	HCQ Rx'd (43 m, 4-10 y)	Control (Never HCQ Rx)	p
Number of pts	9	9	
Age	30±2	33±3	NS
Wt (kg)	59±3	60±2	"
Pred (mg/d)	7±3	7±2	"
C3 (mg/dl)	93±9	95±3	"
C4 (mg/dl)	18±2	20±3	"
ESR (mm/hr)	27±3	27±5	"
SLAM	2.4±0.7	1.9±0.4	"
Duration (yr)	5.8±1.4	5.1±1.4	"
Race	7H, 1B, 1W	7H, 1B, 1W	"

Fraction	HCQ	Control	p
	mg/dl		
TC	154±7	180±11	NS
TG	74±6	137±12	<0.0003
VLDL-C	8±1	16±2	<0.0004
LDL-C	85±6	97±9	NS
HDL-C	48±4	55±5	NS
VLDL-TG	38±6	82±8	<0.0008
LDL-TG	21±2	33±5	<0.03
HDL-TG	11±2	19±2	<0.003
Apo-AI	122±12	141±15	NS
Apo-B	72±8	85±11	NS
Apo-E	14±1	13±1	NS
Apo-CIII	7.4±0.5	13.0±1.3	<0.002

Exclusions: liver, renal, or thyroid disease; proteinuria, DM, CAD, CA. Pts were all nonsmokers, did not consume EtOH. All with normal menstrual cycles for ≥3 mos before the study. Patients did not take T3, estrogens, anti-BP meds, diuretics, AZA, CTX, fish oil, lipid-lowering agents, ASA. NSAID use was equal in the two groups. All data reported as Mean ± SE.
From [55]

A prospective, placebo-controlled pilot study examining the effect of HCQ on serum lipoproteins was carried out here at UT Southwestern by Arthur Kavanaugh, Margo Denke, and their colleagues [56]. Nineteen female SLE patients from our Parkland clinic were studied, all with stable SLE and prednisone doses ≤ 20 mg/day, and none with proteinuria > 0.5 gm/day, poorly controlled diabetes, treatment with lipid-lowering agents, or any HCQ-intake for ≥ 3 mos.

Table 30. High dose HCQ improves lipid profiles in a controlled trial

Parameter (mg/dl)	Placebo (n=5)	HCQ 400 mg/d (n = 6)	HCQ 800 mg/d (n = 6)
	Mean net change over 3 months		
TC	-6.1	-11.6*	-13.4*
TG	13.6	-9.6	-18.8*
VLDL	1.7	-2.0	-4.5*
LDL	-5.1	-8.9	-11.7
HDL	-2.6	-0.7	2.7
non-HDL	-3.4	-10.9	-16.2*
TC / HDL	-0.1	-0.3	-0.8*
LDL / HDL	-0.1	-0.2	-0.6*

*p < 0.05
From [56]

As shown in Table 30, despite the small group sizes, compared with placebo significant reductions were seen in total and non-HDL cholesterol, triglycerides, and TC/HDL and LDL/HDL ratios in patients treated with high dose HCQ, and similar trends were seen with the lower dose. No changes were found in any of the SLE disease parameters, but these were patients with relatively quiescent disease.

A retrospective study of the large Toronto cohort showed that antimalarials were most effective in reducing serum total cholesterol in patients who were also taking corticosteroids [57]. Initiation of antimalarials in patients already on a stable dose of corticosteroids was associated with an 11% decrease in TC at 3 months and 9% at 6 months ($p \leq 0.004$). In 201 patients taking prednisone alone, mean ± SE TC was 5.63 ± 0.12 mM, whereas in 191 patients taking prednisone and antimalarials, TC was 5.01 ± 0.12 mM ($p=0.002$).

Taken together, these studies convincingly show that antimalarials are beneficial both for SLE disease activity and for the dyslipidemia associated with SLE and concomittant corticosteroid therapy. Several mechanisms for the effect on lipids have been proposed, based on in vitro effects of chloroquine (Table 31). Additional effects that have been ascribed to HCQ that are particularly beneficial in SLE patients include prevention of thrombotic events and reduction of fasting plasma glucose (summarized in [58]).

Table 31. Effects of chloroquine on lipid metabolism in vitro

Inhibits 2, 3 oxidosqualene-lanosterol cyclase
Inhibits lysosomal hydrolysis of cholesterol esters
Stimulates LDL receptor activity
Increases activity of HMG-CoA reductase
Reduces precursors for biliary steroids

From [52]

Methotrexate. Over the past 15 years, low dose methotrexate (MTX) has come to dominate therapy for rheumatoid arthritis. Its long term safety and tolerability are well established. Its efficacy in rheumatoid arthritis has been attributed to a combination of antifolate, antiinflammatory, and immunosuppressive effects. Since 1988, several small, uncontrolled, largely retrospective studies have suggested that low-dose MTX has a useful role in treating SLE [59-64]. It has shown the most promise in treating lupus arthritis and dermatitis, but few studies have shown a steroid-sparing effect. One double-blind, randomized, placebo-controlled trial of MTX in SLE has been reported in a paper from Brazil [65]. Forty-one patients with moderately active disease were randomized to two well-matched groups (Table 32, Figure 7). Patients in the treatment group were given either 15 or 20 mg MTX per wk, depending upon their weight. Thirty-seven patients completed the 6 month study.

Table 32. Double-blind, randomized, placebo-controlled trial of MTX in SLE

	MTX	Control	
Number of patients	20	21	
Number finishing study	18	19	
Mean age	32	30	
Months of SLE	85	80	
Number with joint symptoms at start	17	17	
No. with joint symptoms at end	1	16	p <0.001
Number with skin symptoms at start	12	16	
Number with skin symptoms at end	3	16	p <0.001
SLEDAI (mean at start)	8.7	9.4	
Prednisone dose (mg, mean at start)	17.5	16.4	
Mean Visual Analog Score for pain	5.0	4.7	

From [65]

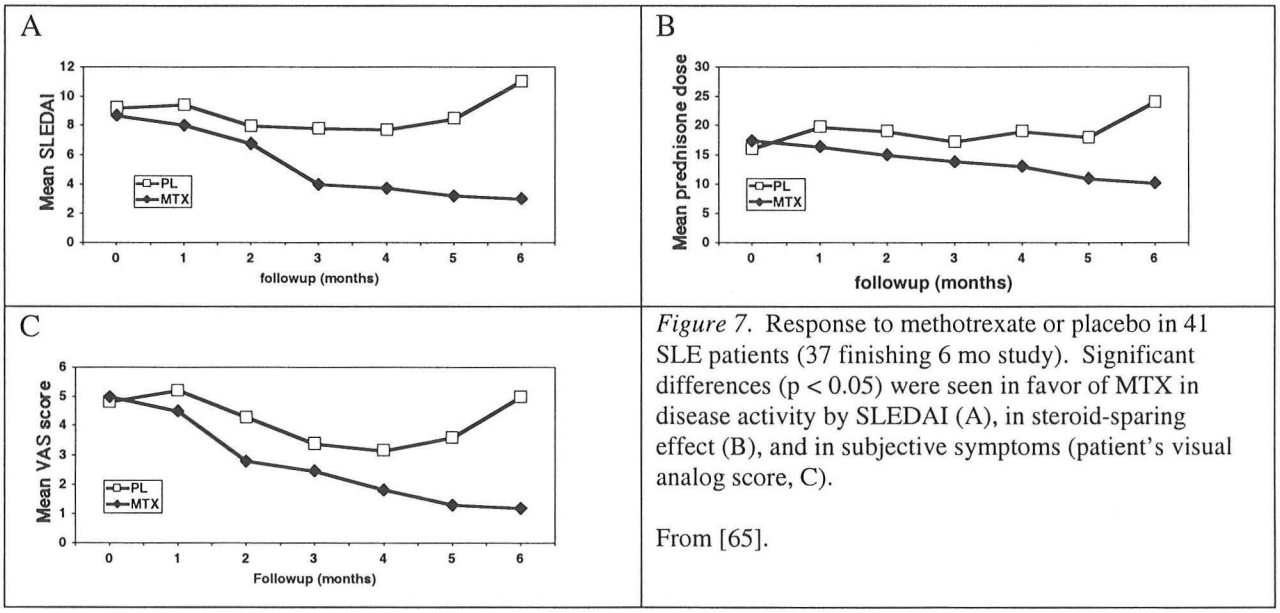


Figure 7. Response to methotrexate or placebo in 41 SLE patients (37 finishing 6 mo study). Significant differences ($p < 0.05$) were seen in favor of MTX in disease activity by SLEDAI (A), in steroid-sparing effect (B), and in subjective symptoms (patient's visual analog score, C).

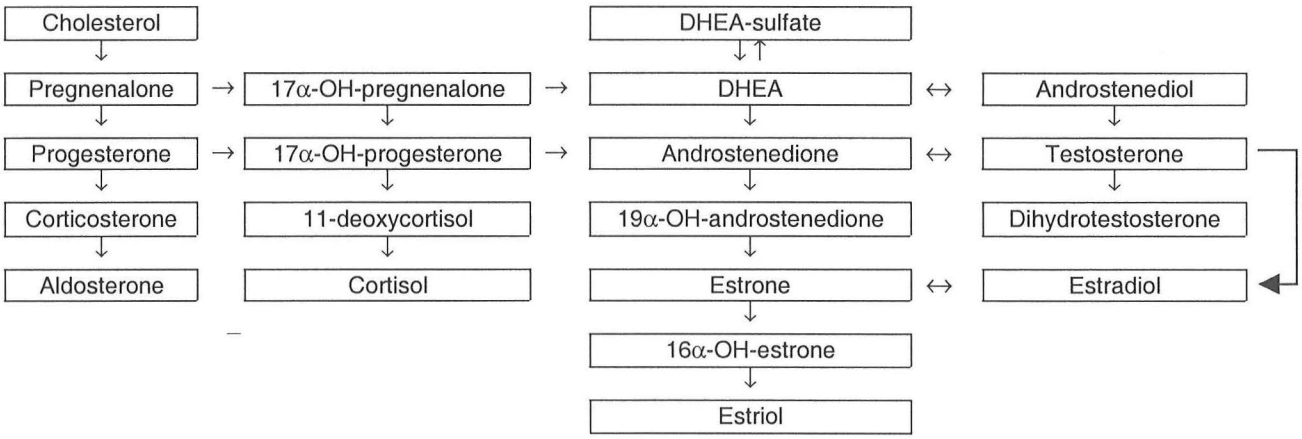
From [65].

There was significant improvement in the MTX treated group in visual analog score for pain, SLEDAI, number of patients with skin or joint symptoms, and reduction of prednisone dose. There were several infections in the MTX group, including one patient who developed

pulmonary TB. Further trials are clearly warranted on the basis of these promising data, although caution regarding infections and the known teratogenicity of MTX will be particularly important in SLE patients.

Dehydroepiandrasterone. DHEA is an androgenic steroid of adrenal origin. Pregnenalone is the rate-limiting precursor, and the pathway for DHEA biosynthesis therefore competes with the cortisol pathway (Fig 8). Most DHEA is produced as the sulfate ester, and free DHEA is converted to DHEA-sulfate in the liver. DHEA has a plasma half life of 15-30 minutes, whereas DHEA-S has a half-life of 7-10 hr. The DHEA/DHEA-S ratio is higher in women. DHEA secretion is stimulated by corticotropin and is suppressed by glucocorticoid administration, but exogenous DHEA does not suppress corticotropin. DHEA is believed to have mild intrinsic androgen effects but it is metabolized to both androgens and estrogens (Fig 8). It is produced in fetal life, then again beginning at adrenarche (age 5-7 yr). Its production peaks in adolescence and begins to decline in the early 30's at a rate of ~2% per year [66-68].

Figure 8. Human adrenocorticoid pathways



From [66]

A number of lines of evidence have suggested that androgen therapy may be of potential benefit in SLE (Table 33). Serum levels of DHEA and DHEA-S are lower in SLE patients than in controls, and the differences do not seem to be explained by either disease activity or corticosteroid therapy [69]. With the in vivo benefit of androgens in general and DHEA in particular in murine SLE and the immunomodulation seen in vitro in human SLE as a rationale, a number of trials of DHEA have been conducted in SLE patients.

Table 33. Rationale for trials of DHEA in SLE

Female predominance of SLE
Abnormally high feminizing estrogen metabolites in SLE
Abnormally enhanced inactivation of testosterone in SLE
Androgens are beneficial in murine SLE models
Low DHEA and DHEA-S levels in SLE, irrespective of activity or treatment
DHEA partially reverses low IL-2 production in vitro by SLE T lymphocytes (murine and human) and decreases IL-4, 5, and 6 production

From [68]

Historically, this compound has been considered an "alternative" medicine, has been used for a wide variety of conditions, and has not been regulated by the FDA. A company in California, Genelabs Technologies, Inc., has recently begun production of the compound under then name GL701, with the generic name Prasterone, and has sponsored the most recent clinical trials.

Much of the early work on DHEA in SLE has been carried out by a group from Stanford. Initially, 8 of 10 patients showed improvement in an open label study of 100-200mg/day [70]. A 3-month double-blind placebo-controlled randomized trial of 200 mg/day in 28 patients with mild to moderate disease (mean SLEDAI scores < 10), there was a significant reduction of flares and improvement in patients' overall assessment [71]. Next, they treated 50 female patients with mild to moderate SLE with 50-200 mg/day DHEA in an open label study [72]. The intention was to treat for a year. Only 42% completed the study (68% at 6 months). Of the dropouts, 30% discontinued for lack of efficacy, 16% because of androgenic side effects (acne, hirsutism, and others). Nonetheless, significant decreases in SLEDAI, prednisone dose, and patient's and physician's global assessment were noted. Serum levels of DHEA, DHEA-S, and testosterone rose markedly.

A second double-blind placebo controlled trial in 21 patients with severe disease (nephritis, serositis, or hematologic abnormalities) was reported in 1999 [73]. Patients were treated with 200 mg/d of drug or with placebo for 6 months, followed by a 6 month open label extension, in addition to their other medications. At 6 months, 7/9 in the treatment group and 4/10 in the placebo group improved ($p < 0.10$), and the mean decrease in the SLEDAI was greater in the treated group ($p<0.07$). DHEA was associated with with significantly less loss of vertebral bone mineral density ($p<0.05$) and with significantly greater decrease in proteinuria (mean 5.0 to 1.35 gm/24 hr in the DHEA group, $p < 0.05$, vs. 5.6 to 3.5 gm/24 hr in the placebo group, p=NS). Unfortunately, the DHEA group has significantly more severe disease at baseline than the control group.

Table 34. Multicenter trial of DHEA shows significant response in patients with active SLE

Patient Population	Variable	GL701	Placebo	p-value
		%	%	
Per-protocol (n=346)	Responders	58	46	0.018
Active SLE (n=265)	Responders	66	49	0.005
Active SLE on steroids &/or cytotoxics (n=165)	Responders	64	44	0.010
Active SLE (n=265)	Flares	24	31	0.201
Active SLE on steroids &/or cytotoxics (n=165)	Flares	26	39	0.056
DEXA (n=37) BMD Change	L-spine BMD	1.8±4.1	-1.8±3.0	0.004
DEXA (n=37) BMD Change	Hip BMD	2.1±4.8	-0.2±2.4	0.080
Per-protocol (n=346)	Acne	33	14	
Per-protocol (n=346)	Hirsutism	16	2	
Active SLE (n=265)	Pt VAS	-7.22	-2.85	0.056

From [74]

Results, shown in Table 34, from a multicenter randomized placebo-controlled trial of the GL701 preparation in 346 patients with mild-to-moderate SLE were reported at the recent ACR meeting [74]. Patients were treated with 200 mg/day or placebo. Patients with active disease showed significant improvements with GL701, compared with placebo. Bone mineral density

improved in the treated group. Acne and hirsutism were common side effects. Four patients died, all in the placebo group. A randomized placebo-controlled 24 wk trial of the GL701 in 119 patients was also reported by a group from Taiwan [75]. The most notable effect was a significantly lower rate of flares in the treated group (18% vs. 34% in placebo group). Overall, the data continue to suggest a likely but modest role for DHEA in SLE.

Newer agents for SLE.

Mycophenolate mofetil. As mentioned above, cytotoxic therapy for lupus nephritis was introduced in the early 1970's. After a decade or more of controlled trials, primarily at the NIH, pulse i.v. cyclophosphamide came to be considered the gold standard [76]. However, this has remained somewhat controversial, with some reports showing equal efficacy with azathioprine [77] and other trials suggesting poor outcome with cyclophosphamide, particularly in African Americans [78]. Toxicity and carcinogenicity from cyclophosphamide are also of continued concern, and safer regimens continue to be sought [79]. It is therefore encouraging that promising results with an apparently less toxic new agent, mycophenolate mofetil (CellCept®) have recently been reported. Mycophenolic acid, the active metabolite, inhibits purine nucleotide synthesis and depletes cells of GTP and inhibits lymphocyte proliferation. It noncompetitively inhibits inducible inosine monophosphate dehydrogenase (INMPDH) expressed in activated lymphocytes. This inhibition depletes these cells of of GMP, GTP, dGTP. GTP depletion has the effect of inhibiting protein glycosylation, which thus reduces adhesion molecule function [80]. Mycophenolate mofetil has proven effective in preventing renal allograft rejection [81]. A randomized controlled trial of this drug in 42 patients with diffuse proliferative lupus nephritis (WHO class IV histology) has recently been published by

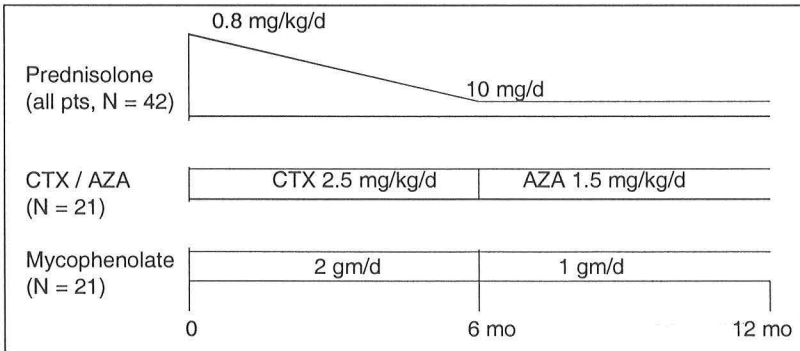


Figure 9. Treatment protocol from [82] comparing mycophenolate with a cyclophosphamide/azathoprine regimen for lupus nephritis.

a group from Hong Kong [82]. The treatment protocol was somewhat unusal by American standards, and is shown in Figure 9. All patients received high dose prednisolone, which was tapered to 10 mg over 6 months. Half the patients also received oral .As shown in Table 35, approximately 80% of patients in each group achieved a complete remission, and most of the rest had a partial remission. Proteinuria decreased significantly and renal function improved. As shown in Figure 10, essentially all of the improvement took place during the first 6 months, so the comparison with regard to induction of remission is with cyclophosphamide, whereas the comparison with regard to maintenance of remission during the second six months is primarily

with azathioprine. It will be of great interest to watch the long term performance of this drug in lupus nephritis, and to assess its efficacy in other severe lupus manifestations.

Table 35. Mycophenolate is effective for SLE nephritis at 12 months

Variable	Mycophenolate (N = 21)		CTX / AZA (N = 21)	
	Baseline	12 mo.	Baseline	12 mo.
Serum C3 (mg/dl)	54	93	46	86
Serum albumin (mg/dl)	2.8±0.6	4.0±0.4	2.8±0.5	4.1±0.3
Urine protein (g/24 hr)	5.8±4.6	0.5±1.1	3.7±1.7	0.2±0.3
Cr Cl (ml/min/1.73 M^2)	86±35	92±21	77±31	82±39
Complete remission %	81 (17/20)		76 (16/19)	
Partial remission %	14		14	
Time to comp. rem. (w)	17±11		22±11	
Time to part. rem. (w)	16±14		14±3	
Treatment failure %	5		5	
Relapse %	15		11	

From [82]

cyclophosphamide for 6 months, followed by oral azathoprine for 6 months. The other half of the patients received mycophenolate mofetil, 2 gm/d for the first 6 months and 1 gm/d for the second 6 months

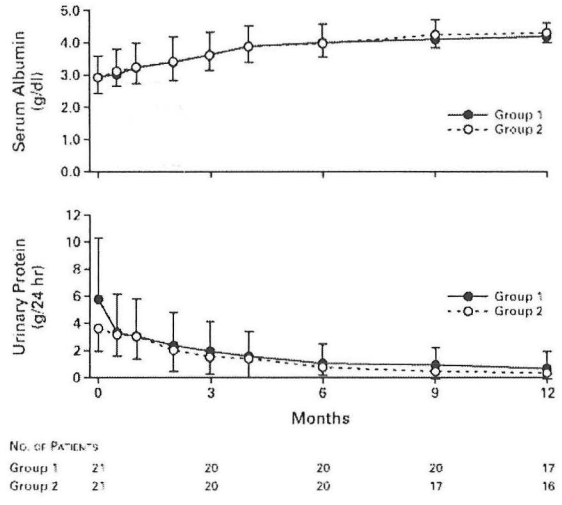


Figure 10. Comparable mprovement in proteinuria and serum albumin during first 6 months of therapy with either mycophenolate mofetil or oral cyclophosphamide (each with high dose prednisolone) in patients with SLE nephritis. Treatment regimens are shown in Figure 10 From [82].

New agents based on the immunopathogenesis of SLE: blocking costimulation. The pathogenesis of SLE is inextricably related to antinuclear antibodies. In recent years, a great deal of information has been obtained regarding the immune mechanisms giving rise to these antibodies. Some of the major advances in our understanding of lupus immunopathogenesis are listed in Table 36. It has become clear that the origin of high affinity IgG anti-DNA antibodies depends upon the processing of nucleosome components by antigen-presenting cells and presentation of peptides from these components to T cells [86, 86a, 86b]. Evidence from both lupus-prone mice and SLE patients suggests that peptides derived from histone proteins are presented to antigen-specific CD4 T cells, which, through the process of intermolecular help,

drive antibody production by B cells specific for a variety of antigens (double-stranded DNA, histone, nucleosomes, and non-histone chromatin). Both B cells and T cells in SLE are abnormally activated and resistant to normal tolerizing signals. Although it is not yet clear what initiates this process, one factor that seems to sustain it is the aberrant expression of the costimulatory molecule CD154 (also referred to as CD40 ligand or CD40L, and formerly gp39) on T cells in SLE patients.

Table 36. Immunopathogenesis of SLE – recent advances

Loss of tolerance to nuclear antigens in both B cell and T cell compartments
Pathogenic anti-nuclear antibodies are high affinity IgG, i.e., antigen-driven (via class switching and somatic hypermutation)
Nucleosomes are major target antigens for both B cells and T cells in SLE
Nuclear antigens are exposed for antigen presentation through processing of apoptotic cells
Lupus patients exhibit abnormally strong T cell-B cell costimulatory signals
Lupus patients exhibit abnormal handling and clearance of immune complexes

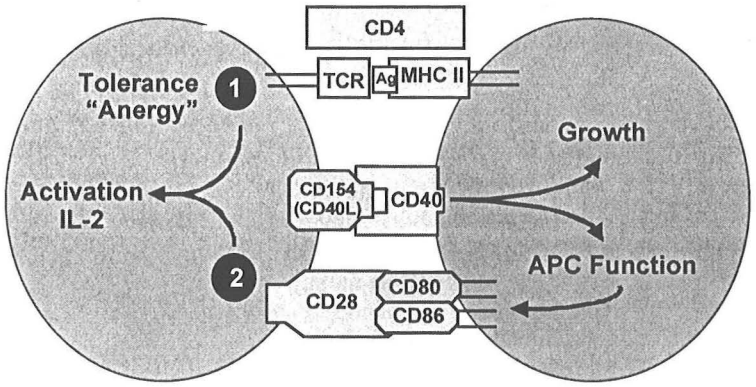


Figure 11. Role of costimulation in T cell-B cell interactions. Signaling of the T cell antigen receptor by B cells (or other APC) provides signal 1, which is stimulatory only in the presence of signal 2, delivered through CD28. Activated T cells, in turn, provide a second signal to antigen-stimulated B cells through CD40 [83, 84].
(Figure provided by Dr. M. Tortoritis, IDEC Pharmaceuticals.)

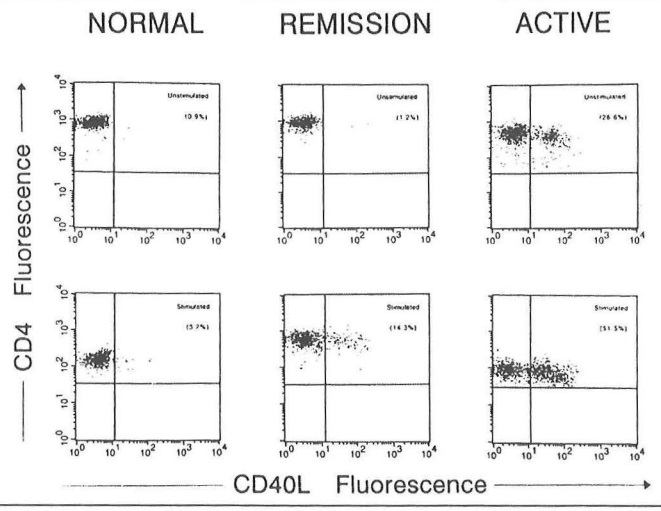


Figure 12. Two color flow cytometry demonstrates excessive expression of CD40L (CD154) on both unstimulated (top panel) and stimulated (bottom panel) CD4 T cells from SLE patients [85].

Figure 11 provides an overview of T cell-B cell interaction. The interaction of CD28 on T cells and CD80 and CD86 on B cells is essential as the second signal for T cell activation (T cell

receptor recognition of MHC molecule plus peptide antigen is the first). In the absence of this costimulatory signal, the encounter of the T cell with MHC plus antigen is toleragenic. Activated T cells transiently express CD154 (CD40L), which delivers a signal to B cells via CD40 that is essential for B cell growth and differentiation, and that prevents apoptosis in germinal center B cells that have encountered antigen. The expression of CD154 is normally transient and tightly regulated. However, in both SLE patients and in mice with SLE-like disease, there is overexpression of CD40L on T cells and also on B cells (Figure 12 [85]). Moreover, SLE patients have elevated serum levels of soluble CD40L [87, 88]. These observations have led to the hypothesis that therapeutic intervention to downregulate CD40L, or to eliminate T cells that overexpress it, might be beneficial in SLE, especially since the abnormality seems to be characteristic of SLE even in patients with inactive disease (Figure 12).

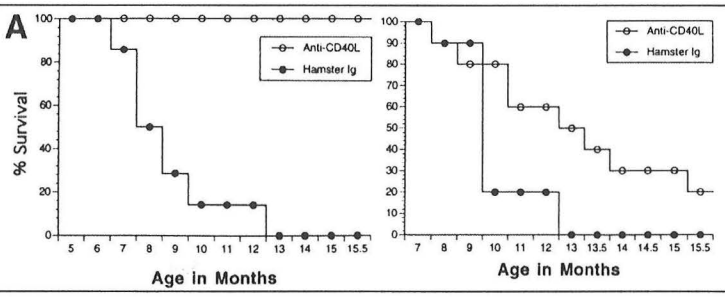


Figure 13. SNF1 mice treated with anti-CD40L antibodies are protected from GN and death even if treatment is started at 5.5 mo (left) when many mice already have early GN. By 7 mo (right), treatment is still partially effective. Hamster Ig is the control Rx. From [89].

Experiments with lupus-prone mice showed that treatment with an anti-mouse CD40L monoclonal antibody could prevent the onset of nephritis and radically prolong survival. More relevant to the treatment of human SLE was the observation that treatment of mice with established nephritis, especially early in its course, could prevent mortality and reverse histologic lesions (Figure 13). This line of investigation has led to clinical trials of anti-CD40L treatment in SLE, and also in several other immunologically mediated diseases. Two companies, Biogen and IDEC Pharmaceuticals, have conducted clinical trials of anti-CD40L therapy with humanized murine monoclonal antibodies. The Biogen trials had to be stopped because of an unusually high incidence of thrombotic events in the treated subjects in several different disease categories. This was unexpected and the reason for it is not known. (However, since CD40L is expressed to some degree on platelets, endothelial cells, and macrophages, it may be a function of the antibody's activity). The IDEC antibody, called IDEC-131, has high affinity for CD154 (ID50 < 1 μg/ml for inhibition of CD154 binding to CD40+ cells). It has no cross reactivity with non-lymphoid human tissues does not activate T cells, endothelial cells or platelets and does not upregulate tissue factor in vitro [90].

The results of a Phase II multcenter randomized double blind placebo-controlled trial of IDEC-131 in 85 patients was presented at the annual ACR meeting in November [90]. The patients had SLEDAI scores between 3 and 12, were on stable therapy, and had not had i.v. cyclophosphamide or pulse corticosteroid therapy for at least 2 months, and did not have rapidly progressive renal disease. The patients were given six i.v. infusions (2.5, 5.0, or 10 mg/kg per dose or placebo) over 16 weeks and evalulated at 20 and 28 weeks. Significant improvement was seen all three treatment doses, but similar improvement was also seen in the placebo group (mean % change in SLEDAI score between 0 and 28 wk: -34, -28, -26, and –29, respectively, for the three drug doses and placebo, with p values of 0.006, 0.001, 0.054, 0.034). The number of

flares and severe flares was not different among the groups, but the median time to flare was almost twice as long in the patients receiving the 10 mg/kg dose (158 days) as in those receiving placebo (85 days). Thus, once again a drug showed promise in a clinical trial, but the improvement in the placebo group was confounding.

DNA as a toleragen. Another approach to treatment of SLE, developed by LaJolla Pharmaceuticals, is based on a strategy of inducing B cell tolerance. The agent, named LJP 394, is a tetramer of four 20 base pair oligonucleotide strands attached to an inert platform. The sequences were chosen for their high affinity for anti-double stranded DNA antibodies found in SLE patients. The rationale of therapy is that the agent will deliver a toleragenic signal to B cells and reduce the production of anti-dsDNA antibodies. The drug has indeed been shown to reduce these antibodies titers in clinical trials [91]. Since anti-dsDNA antibodies are highly associated with nephritis, much of the interest in this agent has been in the treatment of lupus nephritis. The results of a multicenter placebo-controlled trial in 211 patients with lupus nephritis were reported at the recent ACR meeting [92]. Patients received 100 mg LJP 394 i.v. weekly for 16 weeks and 50 mg i.v. intermittently for 60 weeks, or placebo. Renal flares included increases in proteinuria, hematuria, or serum creatinine.

Table 37. DNA toleragen therapy shows promise in nephritis patients with high affinity anti-dsDNA antibodies

Outcome	Pts with high affinity antibody			All patients		
	LJP394	Placebo	p	LJP394	Placebo	p
Number	91	95		105	106	
Renal flares (1st 16 wk)	1	8	0.01	4	9	0.1
Renal flares (18 mos)	7	21	0.002	19	23	0.4
High dose CS or CX (18 mos)	13	34	0.0003	23	38	0.015

From [92]

The subgroup of patients who started the study with high affinity anti-dsDNA antibody showed significant benefit over placebo in terms of reduced renal flares and less need for high dose prednisone or cyclophosphamide.

Hematopoietic stem cell transplantation. Despite therapy with high dose corticosteroids, cyclophosphamide, and other immunosuppressive agents, some patients with SLE fail to respond and continue to have severe active disease. Over the past several years, attempts have been made to treat these desperately ill patients with intensive immunosuppression and bone marrow stem cell rescue. This has been pioneered by a group at Northwestern University, who have recently published their experience with their first seven patients [93]. They selected 9 patients with persistently active SLE despite standard doses of cyclophosphamide, who then underwent stem cell mobilization (Table 38A). Two had to be excluded from transplantation because of infection. The remaining seven patients, with characteristics shown in Table 38B, underwent intensive immunosuppression and autologous stem cell transplantation. All patients suffered fluid overload acutely and there were several infections. Eventually, however, all patients achieved remarkable cessation of lupus activity and clinical improvement (Table 39). No recurrences were seen in 12 to 40 months of followup (median 25 months). Perhaps most encouraging was the apparent resetting of the immune system, with a polyclonal T cell receptor repertoire replacing the previously skewed repertoire and return of serum cytokine levels and activated T cell levels to normal in all of the patients in whom these parameters were measured.

One patient had recurrence of anti-dsDNA antibodies after one year but showed no disease during two more years of followup. Similar results and immune reconstitution have been observed by a group in Berlin [94], but one of their lupus patients relapsed after 14 months. Longterm followup of these patients and experience with additional patients should help determine the role of this radical therapy in managing severe SLE.

Table 38A. Protocol for intensive immunosuppression with stem cell rescue
Mobilize and harvest CD34+ stem cells:
CTX 2 gm/M^2 + 10 μg/kg G-CSF
1 - 10 leukopheresis (15 L)
Immunosuppression, days -6 to -3 with:
CTX 200 mg/kg i.v.
methylprednisolone, 3 gm i.v.
ATG, 90 mg/kg
Reinfuse CD34+ stem cells
Treat with G-CSF and antibiotics

Table 38B. Characteristics of 7 patients undergoing intensive immunosuppression with stem cell rescue	Range/ number
Age (yr)	15 - 51
Disease duration (yr)	<1 - 20
Prednisone dose (mg / d)	40 -80
Total cyclophosphamide dose (g/M^2)	1.4 – 34.6
SLEDAI	17 -37
Proteinuria (g / 24 hr in 5 pts with renal disease	1.5 - 23
≥4 antihypertensive medicines	7 / 7
Low DLCO (7 / 7 pts with low FVC)	6 / 7
Hgb (gm/L)	7 – 10

From [93]

Table 39. Outcomes in 7 patients undergoing intensive immunosuppression with stem cell rescue (12-40 mo. followup)

	Outcome
Remission of SLE	7 / 7
SLEDAI	All ≤ 2
Serum C3	7 / 7 increased
Anti-ds DNA titer	6 / 7 to 0
Serum creatinine	6 / 7 < 2 mg/dl
Proteinuria	5 / 5 decreased
FVC	7 / 7 increased
Prednisone 0 - 5 mg/d	6 / 7
≤1 antihypertensive medicine	6 / 7
Serum IL-4, IFN-γ; CD69+ T cells	4 / 4 normalized
Recovery of polyclonal TCR pattern	3 / 3

From [93]

Conclusions. The past decade has seen great progress in our understanding of SLE and in developing an infrastructure for conducting clinical trials and developing potential new therapies. The high risk of cardiovascular complications casts a long shadow over the long term prognosis of SLE patients. Trials of preventive therapy are urgently needed. It has informally been recommended that SLE patients be managed with the secondary prevention strategy recently proposed for diabetics [95, 96]. Trials of the statin drugs have yet to be carried out and are potentially of great theoretical as well as practical interest. In addition to their cholesterol lowering effect, the antiinflammatory actions of these agents would seem to be ideally suited for use in SLE [97]. Of even greater theoretical interest is the very recently described effect of statins in inhibiting IFN-γ-induced MHC class II expression and antigen presentation to T cells [98]. Meanwhile, in the absence of data from controlled trials, we will need to use them judiciously and with careful monitoring in high risk patients, while trying to minimize unnecessary corticosteroid dosing of all SLE patients and making use of the old, and potentially new, non-steroid agents described here.

BIBLIOGRAPHY

1. Benedek TG: Historical background of discoid and systemic lupus erythematosus. In Wallace DJ, Hahn BH (eds): *Dubois' Lupus Erythematosus*. Baltimore, Williams & Wilkins, 1997, p 3-16.

2. Steinberg AD, Kaltreider HB, Staples PJ, *et al.*: Cyclophosphamide in lupus nephritis: a controlled trial. *Ann Intern Med* 75:165-171, 1971

3. Steinberg AD, Decker JL: A double-blind controlled trial comparing cyclophosphamide, azathioprine and placebo in the treatment of lupus glomerulonephritis. *Arthritis Rheum* 17:923-937, 1974

4. Urowitz MB, Gladman DD, Abu-Shakra M, Farewell VT: Mortality studies in systemic lupus erythematosus. Results from a single center. III. Improved survival over 24 years. *J Rheumatol* 24:1061-1065, 1997

5. Alarcon GS, McGwin J, G., Bastian HM, *et al.*: Poverty is the most important determinant of mortality in a multiethnic cohort of patients with systemic lupus erythematosus (SLE). *Arthritis Rheum*: 43:S131, 2000 (abstract)

6. Gladman DD, Hochberg MC: Epidemiology of SLE. In Lahita RG (ed): *Systemic Lupus Erythematosus*. San Diego, Academic Press, 1999, p 537-550.

7. Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 40:1725, 1997

8. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 42:599-608, 1999

9. Tan EM, Cohen AS, Fries JF, *et al.*: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 25:1271-1277, 1982

10. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J: Mortality studies in systemic lupus erythematosus. Results from a single center. II. Predictor variables for mortality. *J Rheumatol* 22:1265-1270, 1995

11. Symmons DP, Coppock JS, Bacon PA, *et al.*: Development and assessment of a computerized index of clinical disease activity in systemic lupus erythematosus. Members of the British Isles Lupus Assessment Group (BILAG). *Q J Med* 69:927-937, 1988

12. Liang MH, Socher SA, Roberts WN, Esdaile JM: Measurement of systemic lupus erythematosus activity in clinical research. *Arthritis Rheum* 31:817-825, 1988

13. Petri M, Hellmann D, Hochberg M: Validity and reliability of lupus activity measures in the routine clinic setting. *J Rheumatol* 19:53-59, 1992

14. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH: Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 35:630-640, 1992

15. Bencivelli W, Vitali C, Isenberg DA, *et al.*: Disease activity in systemic lupus erythematosus: report of the Consensus Study Group of the European Workshop for Rheumatology Research. III. Development of a computerised clinical chart and its application to the comparison of different indices of disease activity. The European Consensus Study Group for Disease Activity in SLE. *Clin Exp Rheumatol* 10:549-554, 1992

16. Barr SG, Zonana-Nacach A, Magder LS, Petri M: Patterns of disease activity in systemic lupus erythematosus. *Arthritis Rheum* 42:2682-2688, 1999

17. Smolen JS, Strand V, Cardiel M, *et al.*: Randomized clinical trials and longitudinal observational studies in systemic lupus erythematosus: consensus on a preliminary core set of outcome domains. *J Rheumatol* 26:504-507, 1999

18. Strand V, Gladman D, Isenberg D, *et al.*: Outcome measures to be used in clinical trials in systemic lupus erythematosus. *J Rheumatol* 26:490-497, 1999

19. Petri M, Barr SG, Buyon J, *et al.*: RIFLE: Responder index for lupus erythematosus. *Arthritis Rheum* 43:S244, 2000 (abstract)

20. Gladman D, Ginzler E, Goldsmith C, *et al.*: Systemic lupus international collaborative clinics: development of a damage index in systemic lupus erythematosus. *J Rheumatol* 19:1820-1821, 1992

21. Gladman D, Ginzler E, Goldsmith C, *et al.*: The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 39:363-369, 1996

22. Gladman DD, Goldsmith CH, Urowitz MB, *et al.*: The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. *J Rheumatol* 27:373-376, 2000

23. Urowitz MB, Bookman AA, Koehler BE, *et al.*: The bimodal mortality pattern of systemic lupus erythematosus. *Am J Med* 60:221-225, 1976

24. Bulkley BH, Roberts WC: The heart in systemic lupus erythematosus and the changes induced in it by corticosteroid therapy. A study of 36 necropsy patients. *Am J Med* 58:243-264, 1975

25. Petri M: Detection of coronary artery disease and the role of traditional risk factors in the Hopkins Lupus Cohort. *Lupus* 9:170-175, 2000

26. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J: Mortality studies in systemic lupus erythematosus. Results from a single center. I. Causes of death. *J Rheumatol* 22:1259-1264, 1995

27. Manzi S, Meilahn EN, Rairie JE, *et al.*: Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. *Am J Epidemiol* 145:408-415, 1997

28. Ward MM: Premature morbidity from cardiovascular and cerebrovascular diseases in women with systemic lupus erythematosus. *Arthritis Rheum* 42:338-346, 1999

28a. Manzi S, Selzer F, Sutton-Tyrrell K, *et al.*: Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 42:51-60, 1999

29. Salmon JE, Shanker B-A, Sobel R, *et al.*: Carotid atherosclerosis and left ventricular hypertrophy in SLE are unrelated to traditional cardiovascular risk factors or to steroid use. *Arthritis Rheum* 43:S164, 2000 (abstract)

30. Munford RS: C-reactive protein and cardiovascular risk: the eye of the hippopotamus. *Internal Medicine Grand Rounds* July 6, 2000

31. Ettinger WH, Goldberg AP, Applebaum-Bowden D, Hazzard WR: Dyslipoproteinemia in systemic lupus erythematosus. Effect of corticosteroids. *Am J Med* 83:503-508, 1987

32. Petri M, Spence D, Bone LR, Hochberg MC: Coronary artery disease risk factors in the Johns Hopkins Lupus Cohort: prevalence, recognition by patients, and preventive practices. *Medicine (Baltimore)* 71:291-302, 1992

33. Petri M, Lakatta C, Magder L, Goldman D: Effect of prednisone and hydroxychloroquine on coronary artery disease risk factors in systemic lupus erythematosus: a longitudinal data analysis. *Am J Med* 96:254-259, 1994

34. Zonana-Nacach A, Barr SG, Magder LS, Petri M: Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 43:1801-1808, 2000

35. Zizic TM, Marcoux C, Hungerford DS, Dansereau JV, Stevens MB: Corticosteroid therapy associated with ischemic necrosis of bone in systemic lupus erythematosus. *Am J Med* 79:596-604, 1985

36. Mont MA, Glueck CJ, Pacheco IH, *et al.*: Risk factors for osteonecrosis in systemic lupus erythematosus. *J Rheumatol* 24:654-662, 1997

37. Leong KH, Koh ET, Feng PH, Boey ML: Lipid profiles in patients with systemic lupus erythematosus. *J Rheumatol* 21:1264-1267, 1994

38. Borba EF, Bonfa E: Dyslipoproteinemias in systemic lupus erythematosus: influence of disease, activity, and anticardiolipin antibodies. *Lupus* 6:533-539, 1997

39. Ilowite NT, Samuel P, Ginzler E, Jacobson MS: Dyslipoproteinemia in pediatric systemic lupus erythematosus. *Arthritis Rheum* 31:859-863, 1988

40. Borba EF, Bonfa E, Vinagre CG, Ramires JA, Maranhao RC: Chylomicron metabolism is markedly altered in systemic lupus erythematosus. *Arthritis Rheum* 43:1033-1040, 2000

41. Bruce IN, Urowitz MB, Gladman DD, Hallett DC: Natural history of hypercholesterolemia in systemic lupus erythematosus. *J Rheumatol* 26:2137-2143, 1999

42. Rahman P, Urowitz MB, Gladman DD, Bruce IN, Genest J, Jr.: Contribution of traditional risk factors to coronary artery disease in patients with systemic lupus erythematosus. *J Rheumatol* 26:2363-2368, 1999

43. Falaschi F, Ravelli A, Martignoni A, *et al.*: Nephrotic-range proteinuria, the major risk factor for early atherosclerosis in juvenile-onset systemic lupus erythematosus. *Arthritis Rheum* 43:1405-1409, 2000

43a. Clancy RM: Circulating endothelial cells and vascular injury in SLE. *Curr Rheumatol Reports* 2:39-43, 2000

44. Petri M, Genovese M, Engle E, Hochberg M: Definition, incidence, and clinical description of flare in systemic lupus erythematosus. A prospective cohort study. *Arthritis Rheum* 34:937-944, 1991

45. Quismoro FP, Jr.: Systemic corticosteroid therapy in SLE. In Wallace DJ, Hahn BH (eds): *Dubois' Lupus Erythematosus*. Baltimore, Williams & Wilkins, 1997, p 1141-1162.

46. Lahita RG: The clinical presentation of SLE. In Lahita RG (ed): *Systemic Lupus Erythematosus*. San Diego, Academic Press, 1999, p 325-336.

47. Petri M, Genovese M: Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins Lupus Cohort. *J Rheumatol* 19:1559-1565, 1992

48. Boumpas DT, Austin HA, Vaughn EM, *et al.*: Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 340:741-745, 1992

49. Edwards JC, Snaith ML, Isenberg DA: A double blind controlled trial of methylprednisolone infusions in systemic lupus erythematosus using individualised outcome assessment. *Ann Rheum Dis* 46:773-776, 1987

50. Mackworth-Young CG, David J, Morgan SH, Hughes GR: A double blind, placebo controlled trial of intravenous methylprednisolone in systemic lupus erythematosus. *Ann Rheum Dis* 47:496-502, 1988

50a. Barile LA, Olguin L, Ariza R, *et al.*: Controlled clinical trial of cyclophosphamide vs methylprednisolone in severe neurologic manifestations in SLE. *Arthritis Rheum* 43:S272, 2000 (abstract)

51. Ginzler EM, Aranow C: Prevention and treatment of adverse effects of corticosteroids in systemic lupus erythematosus. *Baillieres Clin Rheumatol* 12:495-510, 1998

52. Petri M: Hydroxychloroquine: past, present, future. *Lupus* 7:65-67, 1998

53. Levy GD, Munz SJ, Paschal J, *et al.*: Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. *Arthritis Rheum* 40:1482-1486, 1997

54. Group TCHS: A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med* 324:150-154, 1991

55. Hodis HN, Quismorio FP, Jr., Wickham E, Blankenhorn DH: The lipid, lipoprotein, and apolipoprotein effects of hydroxychloroquine in patients with systemic lupus erythematosus. *J Rheumatol* 20:661-665, 1993

56. Kavanaugh A, Adams-Huet B, Jain R, Denke M, McFarlin J: Hydroxychloroquine effects on lipoprotein profiles (the HELP trial): a double-blind, randomized, placebo-controlled, pilot study in patients with SLE. *J Clin Rheumatol* 3:3-8, 1997

57. Rahman P, Gladman DD, Urowitz MB, *et al.*: The cholesterol lowering effect of antimalarial drugs is enhanced in patients with lupus taking corticosteroid drugs. *J Rheumatol* 26:325-330, 1999

58. Petri M: Hydroxychloroquine use in the Baltimore Lupus Cohort: effects on lipids, glucose and thrombosis. *Lupus* 5 Suppl 1:S16-22, 1996

59. Boehm IB, Boehm GA, Bauer R: Management of cutaneous lupus erythematosus with low-dose methotrexate: indication for modulation of inflammatory mechanisms. *Rheumatol Int* 18:59-62, 1998

60. Gansauge S, Breitbart A, Rinaldi N, Schwarz-Eywill M: Methotrexate in patients with moderate systemic lupus erythematosus (exclusion of renal and central nervous system disease). *Ann Rheum Dis* 56:382-385, 1997

61. Kipen Y, Littlejohn GO, Morand EF: Methotrexate use in systemic lupus erythematosus. *Lupus* 6:385-389, 1997

62. Rahman P, Humphrey-Murto S, Gladman DD, Urowitz MB: Efficacy and tolerability of methotrexate in antimalarial resistant lupus arthritis. *J Rheumatol* 25:243-246, 1998

63. Ravelli A, Ballardini G, Viola S, *et al.*: Methotrexate therapy in refractory pediatric onset systemic lupus erythematosus. *J Rheumatol* 25:572-575, 1998

64. Wise CM, Vuyyuru S, Roberts WN: Methotrexate in nonrenal lupus and undifferentiated connective tissue disease--a review of 36 patients. *J Rheumatol* 23:1005-1010, 1996

65. Carneiro JR, Sato EI: Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. *J Rheumatol* 26:1275-1279, 1999

66. Derksen RH: Dehydroepiandrosterone (DHEA) and systemic lupus erythematosus. *Semin Arthritis Rheum* 27:335-347, 1998

67. Lahita RG: Dehydroepiandrosterone (DHEA) and lupus erythematosus: an update. *Lupus* 6:491-493, 1997

68. van Vollenhoven RF: Dehydroepiandrosterone in systemic lupus erythematosus. *Rheum Dis Clin North Am* 26:349-362, 2000

69. Lahita RG, Bradlow HL, Ginzler E, Pang S, New M: Low plasma androgens in women with systemic lupus erythematosus. *Arthritis Rheum* 30:241-248, 1987

70. van Vollenhoven RF, Engleman EG, McGuire JL: An open study of dehydroepiandrosterone in systemic lupus erythematosus. *Arthritis Rheum* 37:1305-1310, 1994

71. van Vollenhoven RF, Engleman EG, McGuire JL: Dehydroepiandrosterone in systemic lupus erythematosus. Results of a double-blind, placebo-controlled, randomized clinical trial. *Arthritis Rheum* 38:1826-1831, 1995

72. van Vollenhoven RF, Morabito LM, Engleman EG, McGuire JL: Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months. *J Rheumatol* 25:285-289, 1998

73. van Vollenhoven RF, Park JL, Genovese MC, West JP, McGuire JL: A double-blind, placebo-controlled, clinical trial of dehydroepiandrosterone in severe systemic lupus erythematosus. *Lupus* 8:181-187, 1999

74. Mease PJ, Merrill JT, Lahita RG, *et al.*: GL701 (prasterone, dehydroepiandrosterone) improves systemic lupus erythematosus. *Arthritis Rheum* 43:S271, 2000 (abstract)

75. Chang D-M, Lan JL, Lin HY, Luo SF: GL701(prasterone, dehydroepiandrosterone) significantly reduces flares in female patients with mild to moderate SLE. *Arthritis Rheum* 43:S241, 2000 (abstract)

76. Austin HA, Klippel JH, Balow JE, *et al.*: Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 314:614-619, 1986

77. Nossent HC, Koldingsnes W: Long-term efficacy of azathioprine treatment for proliferative lupus nephritis. *Rheumatology (Oxford)* 39:969-974, 2000

78. Dooley MA, Hogan S, Jennette C, Falk R: Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. Glomerular Disease Collaborative Network. *Kidney Int* 51:1188-1195, 1997

79. Austin HA, Balow JE: Treatment of lupus nephritis. *Semin Nephrol* 20:265-276, 2000

80. Allison AC, Eugui EM: Mycophenolate mofetil and its mechanisms of action. *Immunopharmacology* 47:85-118, 2000

81. Halloran P, Mathew T, Tomlanovich S, *et al.*: Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. *Transplantation* 63:39-47, 1997

82. Chan TM, Li FK, Tang CS, *et al.*: Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. *N Engl J Med* 343:1156-1162, 2000

83. Lenschow DJ, Walunas TL, Bluestone JA: CD28/B7 system of T cell costimulation. *Annu Rev Immunol* 14:233-258, 1996

84. Foy TM, Aruffo A, Bajorath J, Buhlmann JE, Noelle RJ: Immune regulation by CD40 and its ligand GP39. *Annu Rev Immunol* 14:591-617, 1996

85. Desai-Mehta A, Lu L, Ramsey-Goldman R, Datta SK: Hyperexpression of CD40 ligand by B and T cells in human lupus and its role in pathogenic autoantibody production. *J Clin Invest* 97:2063-2073, 1996

86. Datta SK: Production of pathogenic antibodies: cognate interactions between autoimmune T and B cells. *Lupus* 7:591-596, 1998

86a. Lu L, Kaliyaperumal A, Boumpas DT, Datta SK: Major peptide autoepitopes for nucleosome-specific T cells of human lupus. *J Clin Invest* 104:345-355, 1999

86b. Bruns A, Blass S, Hausdorf G, Burmester GR, Hiepe F: Nucleosomes are major T and B cell autoantigens in systemic lupus erythematosus. *Arthritis Rheum* 43:2307-2315, 2000

87. Kato K, Santana-Sahagun E, Rassenti LZ, *et al.*: The soluble CD40 ligand sCD154 in systemic lupus erythematosus. *J Clin Invest* 104:947-955, 1999

88. Vakkalanka RK, Woo C, Kirou KA, *et al.*: Elevated levels and functional capacity of soluble CD40 ligand in systemic lupus erythematosus sera. *Arthritis Rheum* 42:871-881, 1999

89. Kalled SL, Cutler AH, Datta SK, Thomas DW: Anti-CD40 ligand antibody treatment of SNF1 mice with established nephritis: preservation of kidney function. *J Immunol* 160:2158-2165, 1998

90. Kalunian KC, Davis J, Merrill JT, *et al.*: Treatment of systemic lupus erythematosus by inhibition of T cell costimulation. *Arthritis Rheum* 43:S271, 2000 (abstract)

91. Weisman MH, Bluestein HG, Berner CM, de Haan HA: Reduction in circulating dsDNA antibody titer after administration of LJP 394. *J Rheumatol* 24:314-318, 1997

92. Alarcon-Segovia D, Tumlin J, Furie R, *et al.*: SLE trial shows fewer renal flares in LJP 394-treated patients with high-affinity antibodies to LJP 394: 90-05 trial results. *Arthritis Rheum* 43:S272, 2000 (abstract).

93. Traynor AE, Schroeder J, Rosa RM, *et al.*: Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and haemopoietic stem-cell transplantation: a phase I study. *Lancet* 356:701-707, 2000

94. Thiel A, Rosen R, Kimmig S, *et al.*: Longterm follow-up of the immune reconstitution after autologous stem cell transplantation for severe autoimmune diseases. *Arthritis Rheum* 43:S395, 2000 (abstract)

95. Raskin P: Sugar and the heart. *Internal Medicine Grand Rounds* August 3, 2000

96. Rutherford JD: Diabetes and coronary artery disease - therapy and outcomes. *Internal Medicine Grand Rounds* September 7, 2000

97. Maron DJ, Fazio S, Linton MF: Current perspectives on statins. *Circulation* 101:207-213, 2000

98. Kwak B, Mulhaupt F, Myit S, Mach F: Statins as a newly recognized type of immunomodulator. *Nat Med* 6:1399-1402, 2000