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Systemic Lupus Erythematosus in Three Ethnic Groups

XVI. Association of Hydroxychloroquine Use With Reduced Risk of Damage Accrual

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Objective. **To examine whether hydroxychloroquine (HCQ) usage is associated with a reduced risk of damage accrual in patients with systemic lupus erythematosus (SLE).**

Methods. **Patients (n = 518) meeting the American College of Rheumatology criteria for diagnosis of SLE and with ≤5 years disease duration at study entry were followed up annually. Socioeconomic, demographic, clinical, and serologic manifestations as well as disease activity (by the Systemic Lupus Activity Measure [SLAM]) and damage (by the Systemic Lupus International Collaborating Clinics damage index [SDI]) were measured. Propensity scores were calculated to adjust for confounding factors affecting treatment assignment. A Cox proportional hazards model was used to compare the risk of developing new damage according to HCQ use at enrollment into the study.**

Results. **Fifty-six percent of the patients were treated with HCQ at the time of study enrollment. Patients who were not treated with HCQ on enrollment had higher SLAM and SDI scores than patients who were treated. Untreated patients were significantly more likely to have major organ involvement such as renal disease ($P < 0.0001$) or central nervous system disease ($P < 0.0025$). Results of unadjusted analysis suggested that treated patients were less likely to accrue damage (hazard ratio [HR] 0.68). With adjustment for differences in treatment assignment, HCQ usage was still associated with a reduced risk of developing new damage, with an HR of 0.68 (95% confidence interval [95% CI] 0.53–0.93) ($P = 0.014$). With adjustment for differences in treatment assignment, HCQ usage was still associated with a reduced risk of developing new damage (HR 0.73 [95% CI 0.52–1.00]) ($P = 0.05$). However, patients receiving HCQ who had no damage at study entry had a statistically significant decrease in the risk of damage accrual (HR 0.55 [95% CI 0.34–0.87]) ($P = 0.0111$), whereas those receiving HCQ who had damage**

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at study entry did not (HR 1.106 [95% CI 0.70–1.74]) ($P = 0.6630$).

Conclusion. **These findings indicate that, after adjustment for propensity to receive HCQ, HCQ usage is independently associated with a reduced risk of damage accrual in SLE patients who had not yet accrued damage at the time of treatment initiation.**

Systemic lupus erythematosus (SLE) is a complex multisystem autoimmune disease of unknown etiology, which is characterized by a waxing and waning course. Disease manifestations are diverse, affecting every organ system in the body; the levels of severity of these manifestations vary from mild to life-threatening (1,2). Although disease activity may be controlled with medication, organ damage may develop over time, as a consequence of the disease itself or medications used to treat it (3–8). Once damage has developed, it predicts the development of additional damage and higher mortality rates (9–13). Several medications that are used to treat active SLE may directly contribute to the development of damage. For example, corticosteroid use is associated with an increased risk of cataracts, myocardial infarction, strokes, osteoporosis, and avascular necrosis (4,14–16). Identification of medications that not only treat disease activity but also prevent damage would be highly desirable. There is accumulating evidence that one such medication is hydroxychloroquine (HCQ) (17–23).

HCQ and several other related medications, originally used for management of malaria, have been used for many decades to treat rheumatic diseases (24,25). In addition to their antimicrobial effects, these antimalarial medications exhibit antiinflammatory, antihyperlipidemic, antithrombotic, and immunomodulatory properties (24,26). HCQ is the most commonly prescribed antimalarial medication for lupus in the US and is useful in the management of mucocutaneous manifestations, arthritis, and mild constitutional symptoms (24). HCQ has many additional health benefits in lupus patients. It has been shown to reduce serum cholesterol levels (18,27–29), protect against osteoporosis in corticosteroid-treated patients (16), and decrease the frequency of lupus flares (30,31). Use of HCQ has also been shown to be associated with lower pulse wave velocity in premenopausal women, suggesting a potential protective effect against future development of major vascular disease (32).

In the present investigation, we sought to examine the impact of HCQ use on the accrual of damage in patients participating in the LUMINA (LUpus in MInorities, NAture versus nurture) study, a longitudinal study of outcome in lupus patients. Since HCQ is traditionally used for the treatment of mild-to-moderate lupus manifestations and is not used as primary treatment for major organ system involvement such as renal or central nervous system disease, a traditional multivariable regression technique comparing damage accrual between HCQ users and nonusers would lead to unreliable estimates of risk, due to confounding by indication. Patients with milder disease, who are typically treated with HCQ, would naturally accrue less damage compared with those with severe multiorgan involvement. To address this concern regarding nonrandom treatment assignment, we used propensity score analysis (33) to adjust for potential known confounding factors that may influence the accrual of damage. To our knowledge, propensity score analysis has not been used previously to examine the impact of medications on a lupus cohort. Ultimately, a randomized controlled trial would be the ideal way to determine whether HCQ is truly protective against damage accrual. However, such a trial is not feasible given the widespread use of HCQ and the long-term followup necessary to adequately address this question.

PATIENTS AND METHODS

Study population. LUMINA is a longitudinal study of outcome in SLE patients from the University of Alabama at Birmingham, the University of Texas Health Science Center at Houston, the University of Texas Medical Branch at Galveston, and the University of Puerto Rico Medical Sciences Campus. The cohort, study visits, and variables have been described in detail previously (34). Briefly, patients of defined ethnicity (Hispanic, African American, or Caucasian) who met at least 4 components of the American College of Rheumatology (ACR) criteria for SLE (35) and who had disease duration of $\leq$5 years at study enrollment were eligible to participate. After providing informed consent, patients completed a series of questionnaires and underwent physical examination and serologic testing. Demographic, socioeconomic, clinical, and immunologic data were obtained at the baseline visit (time 0), every 6 months for 1 year, and then annually thereafter. At time 0 and each subsequent visit, all available medical records were reviewed.

Definitions of variables. The demographic characteristics recorded were age, sex, and ethnicity. Clinical variables included ACR criteria manifestations and other manifestations attributable to lupus, including Raynaud's phenomenon, arterial and/or venous thrombotic events, biopsy-proven renal disease, vasculitis, central nervous system manifestations, and cardiac disease. Immunologic variables included the presence of autoantibodies (antinuclear antibodies by indirect immunofluorescence [IIF], anti–double-stranded DNA antibodies by IIF against *Crithidia luciliae*, anti-Sm, anti-Ro/SSA, anti-La/

Table 1. Demographic, socioeconomic, clinical, and serologic characteristics in SLE patients who were and those who were not treated with HCQ at the time of enrollment (time 0)*

Variable	HCQ use at time 0 (n = 291)	No HCQ use at time 0 (n = 227)	*P*
Age at time 0, years	37.9 ± 12.5	35.1 ± 12.6	0.0132
Female, %	90	88	NS
Ethnicity, %			<0.0001
Hispanic (Texas) (n = 105)	16	26	
Hispanic (Puerto Rico) (n = 73)	53	43	
African American (n = 190)	32	22	
Caucasian (n = 150)	34	9	
Have medical insurance, %	18	27	0.0074
Highest education level, years	13.1 ± 3.1	12.6 ± 3.1	0.0317
Below poverty line, %	32	35	NS
Disease duration at time 0, years	1.4 ± 1.3	1.5 ± 1.3	NS
Clinical manifestations, %			
Arthritis	83	71	0.0019
Pleuritis or pericarditis	40	52	0.0034
Pulmonary disease	9	10	NS
Renal disease	25	53	<0.0001
Immune-mediated cytopenias	77	85	0.0275
CNS involvement	32	45	0.0025
Myositis	9	19	0.0014
Fibromyalgia	4	2	NS
No. of ACR criteria met	5.4 ± 1.3	5.6 ± 1.3	NS
SLAM at time 0	8.2 ± 4.3	11.6 ± 7.0	<0.0001
SDI at time 0	0.6 ± 0.9	1.07 ± 1.5	<0.0001
Anti-dsDNA antibodies	25	32	0.0158
HLA–DRB*08	8	14	0.0074
Hospitalizations due to SLE, %	32	35	NS
ER visits due to SLE, %	22	37	0.0003
IBQ total at time 0	18.5 ± 6.7	18.7 ± 6.6	NS
Corticosteroid use, %	90	88	NS
Azathioprine use, %	12	16	NS
Cyclophosphamide use, %	5	27	<0.0001

* Except where indicated otherwise, values are the mean ± SD. SLE = systemic lupus erythematosus; HCQ = hydroxychloroquine; NS = not significant; CNS = central nervous system; ACR = American College of Rheumatology; SLAM = Systemic Lupus Activity Measure; SDI = Systemic Lupus International Collaborating Clinics damage index; anti-dsDNA = anti–double-stranded DNA; ER = emergency room; IBQ = Illness Behavior Questionnaire (75).

SSB, anti–-small nuclear RNP by immunodiffusion, IgG and IgM antiphospholipid antibodies by enzyme-linked immunosorbent assay, and lupus anticoagulant by the Statclot test). Medications used to treat lupus, including corticosteroids, HCQ, methotrexate, azathioprine, mycophenolate mofetil, leflunomide, cyclophosphamide, and cyclosporine, were recorded. Disease activity during the month preceding the study visit was measured using the Systemic Lupus Activity Measure (SLAM) (36), a validated instrument for assessing disease activity.

In the LUMINA cohort, disease-related damage is measured using the Systemic Lupus International Collaborating Clinics damage index (SDI) (37,38) and is assessed at each visit. This validated instrument measures the extent of irreversible organ damage caused either by the disease or by the treatments used for it from the time of diagnosis. A manifestation is recorded in the SDI if it has been present for at least 6 months and is (or is expected to be) irreversible. Manifestations from 9 organ systems (ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin), as well as premature gonadal failure, diabetes, and malignancy (if the latter 3 developed after the onset of SLE), constitute the domains of the SDI. The outcome of interest for the present study was the development of new damage, both overall and within specific domains, during the followup period. Patients who developed any new damage were, for the purpose of this study, considered to have the outcome of interest. The primary independent variable of interest in this study was HCQ use. Patients were divided into 2 categories: those who were taking HCQ at time 0 and those who were not.

Statistical analysis. Socioeconomic, demographic, clinical, immunologic, and treatment characteristics were compared between patients who were HCQ users at the time of enrollment and those who were not, using *t*-tests and chi-square tests for continuous and categorical variables, respectively. To adjust for the inherent bias in grouping of patients based on use or nonuse of HCQ, propensity analysis was performed. Using a multivariable logistic regression model that includes the baseline demographic, clinical, immu-

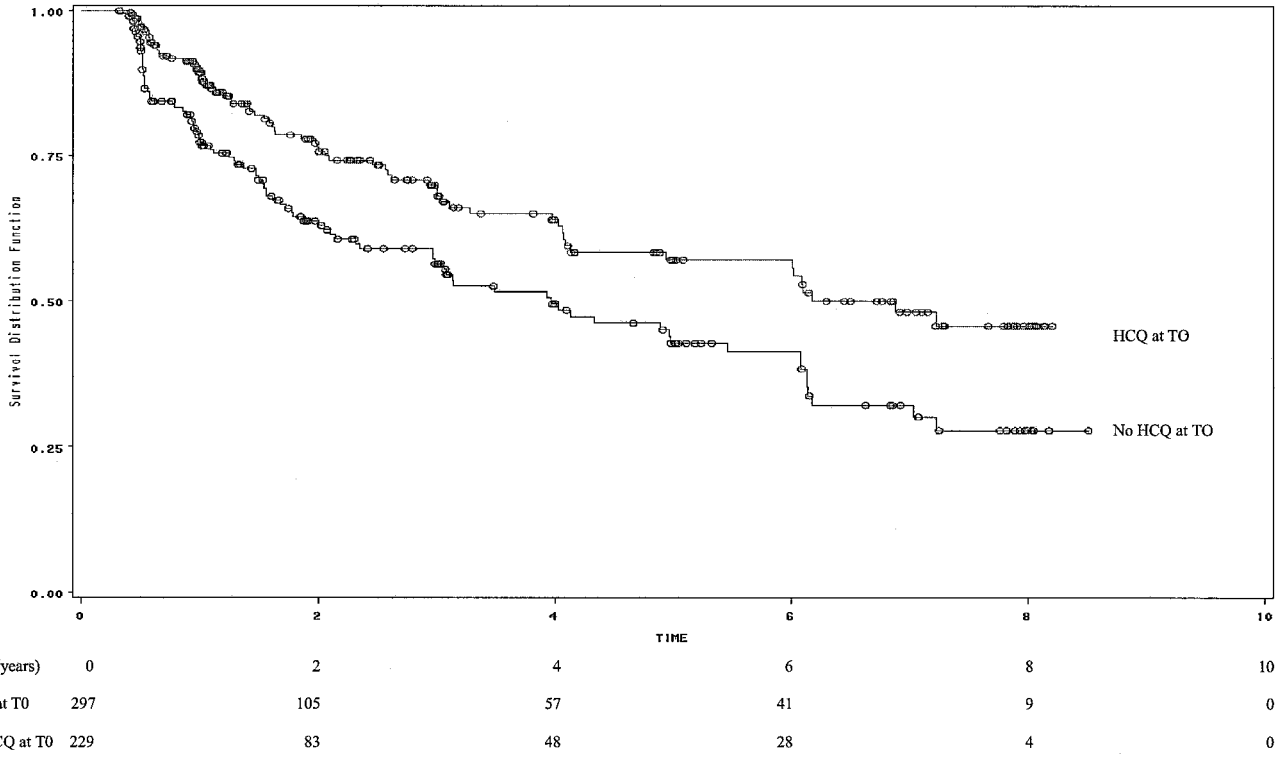

Figure 1. Time to accrual of new damage (unadjusted for propensity score) in systemic lupus erythematosus patients who were and those who were not treated with hydroxychloroquine (HCQ) at time 0 (T0).

nologic, and treatment characteristics as the independent variables, the probability of HCQ use was determined. The specific variables included in the propensity score model are shown in Table 1. The study population was divided into quintiles according to the propensity score, and the probability of HCQ use was computed in each group. To adjust for heterogeneity between the 2 groups, the propensity score was then entered as a continuous variable in a Cox proportional hazards model along with the primary independent variable. A hazard ratio (HR) and its associated 95% confidence interval (95% CI), comparing the time to new damage among users and nonusers of HCQ, were computed. This was done for the occurrence of any new damage as well as for damage in specific domains.

RESULTS

Five hundred eighteen patients in the LUMINA study (178 Hispanic [105 from Texas and 73 from Puerto Rico], 190 African American, 150 Caucasian) were included in these analyses. The majority of the patients were women (89%). The mean ± SD age of the patients at time 0 was 36.5 ± 12.5 years. Detailed descriptions of the demographic, socioeconomic, clinical, and immunogenetic characteristics of the LUMINA cohort have been published previously (39,40). Patients included in these analyses were comparable in their features with those included in previously reported studies from the LUMINA group (5,10,13,40).

Baseline characteristics. Of the 518 patients included in these analyses, 291 (56%) were taking HCQ at time 0; 67% of the patients were treated with HCQ at some point during the study followup period, and 33% were never treated with HCQ. Table 1 summarizes the differences in baseline characteristics by HCQ status. Patients who were not treated with HCQ were significantly more likely to have a higher SLAM score and SDI score at time 0. Nonusers were more likely to have serositis, renal disease, cytopenias, central nervous system involvement, and myositis than users of HCQ. Emergency room visits and hospitalizations due to lupus were more common in nonusers. The length of followup among users of HCQ versus nonusers was comparable (mean ± SD 2.47 ± 2.74 years and 2.42 ± 2.79 years, respectively).

The HR for new damage among all users of HCQ (prior to adjustment for the propensity score) was 0.68 (95% CI 0.53–0.93) (P = 0.014). Among patients who had no damage at time 0 and were being treated with

Table 2. Relationship between propensity score quintile and treatment with hydroxychloroquine

Propensity score quintile	No. of patients in quintile	No. of patients treated	Observed probability of treatment
1	30	3	10
2	84	23	27
3	135	81	59
4	233	160	68
5	36	30	79

HCQ, the HR was 0.57 (95% CI 0.37–0.88) (P = 0.0019). In contrast, patients who had damage at time 0 and were being treated with HCQ had a hazard ratio of 0.85 (95% CI 0.54–1.33) (P = 0.47). Figure 1 demonstrates the time to damage accrual in patients who were taking HCQ at time 0 compared with those who were not. The results suggest that patients who do not have damage early in their disease course are the ones who benefit the most from the protective effects of HCQ.

Propensity analysis. A logistic regression model was used to generate a propensity score for the study population. The study population was divided into quintiles according to the propensity score, and the probability of HCQ use was computed for each group (Table 2). The propensity score and data on HCQ use were entered into a Cox proportional hazards model. As seen in Table 3, HCQ use was associated with a reduced risk of damage accrual. Analysis of the individual domains on the SDI was performed; however, due to the low number of events, no statistically significant decrease in damage accrual was demonstrated in the HCQ users (data not shown). After adjustment for the propensity score, the HR among patients without damage at time 0 was 0.55 (95% CI 0.34–0.87) (P = 0.0111), as compared with 1.106 (95% CI 0.70–1.74) (P = 0.6630) among patients with damage at time 0.

DISCUSSION

HCQ has been used to treat SLE for many years. It is generally well tolerated and has a favorable risk-to-benefit ratio (25,41). Utilization rates of HCQ in different cohorts of lupus patients range from 35% to 65% (18,42–44). Over the last 15 years, evidence has accumulated to suggest that HCQ use may result in a myriad of health benefits in addition to treating those symptoms for which it is prescribed. The current study provides evidence that HCQ is associated with reduced risk of damage accrual. In particular, it appears that patients who do not have damage early in their disease course are the ones who benefit the most from HCQ. To adjust for the bias associated with nonrandom treatment assignments, propensity score analysis was performed. This technique allowed us to control for known factors that influence disease activity and/or damage accrual.

Table 3. Probability of developing new damage*

	HR	95% CI	P
Hydroxychloroquine use	0.73	0.52–1.00	0.05
Propensity score	0.22	0.09–0.52	0.0006

* HR = hazard ratio; 95% CI = 95% confidence interval.

Although our analysis represents a unique approach to addressing the potential protective effect of HCQ in a well-characterized, diverse cohort, there are potential limitations to this study. Despite our use of propensity scores, there may still be residual confounding by unidentified factors. However, confounding by indication tends to deflate contrast in treatment efficacy, leading to a Type II error (33,45) and thus making the positive findings observed in this study even stronger. We were unable to examine the dosage or duration of treatment with HCQ that is necessary to produce an impact on damage accrual, because these data were not collected as part of the routine study visits. In addition, our study did not have the statistical power to determine whether treatment with HCQ had a greater impact on certain domains of the SDI and whether it is useful in combination with other more potent immunosuppressive agents, such as cyclophosphamide.

What properties do antimalarial agents possess that would support their role in protecting against the development of damage in patients with SLE? In general, antimalarial medications exhibit a wide array of antiinflammatory, antithrombotic, and immunomodulatory properties. These agents inhibit antigen processing and presentation by macrophages and lymphoid dendritic cells (46,47), phospholipase A_2 activation (48), DNA and RNA synthesis (49), and secretion of several cytokines (interleukin-1, interleukin-6 [50–53], and tumor necrosis factor α [48,53]). In addition, they induce apoptosis in lymphocytes (54) and endothelial cells (55) and disrupt T cell receptor crosslinking–dependent calcium signaling (56). It may be postulated that interference with one or more of these mechanisms blunts the perpetuation of the immunologic response in lupus. Indeed, it has been shown that HCQ has a protective effect against major flares of disease (30,57,58). By decreasing the frequency of disease flares, the overall long-term risk of damage would also be decreased, since

damage in lupus has been consistently found to be associated with higher degrees of disease activity in the LUMINA cohort (5) as well as in other studies (12,59,60). In addition to its direct biologic effects, HCQ may indirectly influence damage accrual by virtue of its corticosteroid-sparing properties.

Antimalarial medications inhibit lysosomal hydrolysis, decrease synthesis of cholesterol (61), inhibit secretion of very low-density lipoprotein (62), and increase hydroxymethylglutaryl-coenzyme A reductase activity (63). Indeed, HCQ usage has been associated with reduced serum cholesterol levels (18,20,27,28,64,65), and this effect is enhanced in patients who are being treated with corticosteroids (29). HCQ has also been shown in some studies to affect platelet aggregation and adhesion (66). It has been used to reduce the risk of pulmonary embolism in patients who undergo hip replacement (67,68). In patients with SLE and antiphospholipid antibody syndrome, treatment with HCQ decreases the risk of thrombotic events (69,70).

HCQ has been shown to have antihyperglycemic properties in patients with type 2 diabetes mellitus (71,72). It has been demonstrated that chloroquine stabilizes intracellular lysosomes, thereby retarding the breakdown of the internalized insulin receptor complex (73). Among SLE patients, mean glucose levels in those who are taking HCQ have been shown to be lower than in those not receiving this treatment (18). HCQ is protective against abnormal glucose tolerance and is associated with lower fasting insulin levels (74).

In summary, the results of this study, using propensity score analysis of data accumulated in a longitudinal study of SLE patients, indicate that HCQ usage is associated with a reduced risk of damage accrual. The precise mechanisms by which HCQ influences damage accrual are unknown, but most likely involve its effects on inflammation, lipid and serum glucose levels, and platelet aggregation, as outlined above. A randomized controlled trial would be needed in order to prove that HCQ is truly protective against damage accrual in patients with SLE. Unfortunately, it is unlikely that such a trial will ever be conducted. The numbers of patients and the length of followup necessary to demonstrate differences in damage accrual, especially in specific domains on the SDI, would be prohibitively expensive. In addition, based on the available clinical data, it would be unethical to perform a placebo-controlled trial of HCQ. In the absence of such a randomized controlled trial addressing the critical question of whether HCQ is protective against damage, and the unlikeliness that such a trial would be performed due to these practical barriers, our present findings can be used to lend further support for the routine use of HCQ in the treatment of SLE.

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