Published in final edited form as:
Arthritis Rheum. 2009 June 15; 61(6): 830–839. doi:10.1002/art.24538.

Protective Effect of Hydroxychloroquine on Renal Damage in Patients with Lupus Nephritis: Data from LUMINA, a Multiethnic U.S. Cohort

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Abstract

Objective—To assess if hydroxychloroquine can delay renal damage development in lupus nephritis patients.

Methods—Lupus nephritis patients (n=256) from LUMINA (n=635), a multiethnic cohort of African Americans, Hispanics and Caucasians, age ≥16 years, disease duration ≤5 years at baseline (T0) were studied. Renal damage was defined per the SLICC Damage Index (≥1 of the following lasting at least six months: estimated/measured glomerular filtration rate <50%, 24-hour proteinuria ≥3.5 g and/or end-stage renal disease, regardless of dialysis or transplantation). Patients with renal damage before T0 were excluded (n=53). The association between hydroxychloroquine use and renal damage (as defined, or omitting proteinuria) was estimated using Cox proportional regression analyses adjusting for potentially confounders. Kaplan-Meier survival curves based on hydroxychloroquine intake or World Health Organization (WHO) Class glomerulonephritis were also derived.

Results—Sixty-three (31.0%) of 203 patients developed renal damage over a mean (standard deviation) disease duration of 5.2 (3.5) years. The most frequent renal damage domain item was proteinuria. Hydroxychloroquine-takers (79.3%) exhibited a lower frequency of WHO Class IV glomerulonephritis, lower disease activity and received lower glucocorticoid doses than non-takers. After adjusting for confounders, hydroxychloroquine was protective of renal damage occurrence in full (HR=0.12; 95% CI 0.02-0.97; *p*=0.0464) and reduced (HR=0.29; 95%CI 0.13-0.68; *p*=0.0043) models. Omitting proteinuria provided comparable results. The cumulative probability of renal damage occurrence was higher in hydroxychloroquine non-takers and in WHO Class IV glomerulonephritis (p<0.0001).

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Conclusions—After adjusting for possible confounding factors the protective effect of hydroxychloroquine in retarding renal damage occurrence in SLE is still evident.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder that can affect multiple organs with varying degrees of severity. Renal involvement in SLE can range from silent disease to severe renal insufficiency occurring in 50-70% of lupus patients depending on the population studied (1-3). Despite advances in therapy, the morbidity and mortality in patients with lupus nephritis remain high. Lupus nephritis leads to the development of end-stage renal disease in 17-25% of patients (4-6), decreased survival (7,8), and higher health care costs (9). However, to date none of the available therapies have been proven conclusively to protect against the development of renal damage.

Hydroxychloroquine is an antimalarial agent which traditionally has been used to treat mucocutaneous, musculoskeletal, serosal and constitutional manifestations of SLE. Previous studies from our group and others have shown that hydroxychloroquine usage is associated with a reduced risk of damage accrual (10), improved survival (11-12), a decreased frequency of lupus flares (13-14), an increased probability of remission in patients with membranous nephritis treated with mycophenolate mofetil (15), and even a decreased probability of renal failure if used prior to the onset of lupus nephritis (16). Given these beneficial effects, hydroxychloroquine is gaining ground as an essential therapy in SLE.

The aim of the present study was to investigate whether hydroxychloroquine use delays the development of overall renal damage [as measured by the Systemic Lupus Collaborating Clinics Damage Index (SDI) renal domain (17)] by studying patients from LUMINA, a U.S. multi-ethnic cohort, who had renal involvement. Our working hypothesis is that indeed the use of hydroxychloroquine will be associated with delaying such occurrence in these patients.

PATIENTS AND METHODS

Patients

LUMINA is a longitudinal observational cohort that was established in 1994 as a multicenter collaborative effort between the University of Alabama at Birmingham (UAB), the University of Texas Health Science Center at Houston (UTH) and the University of Puerto Rico Medical Sciences Campus (UPR) with the goal of understanding the clinical and genetic differences observed in SLE patients from various ethnic groups. The Institutional Review Board of all participating institutions approved the study according to the declaration of Helsinki for research in humans.

Previously, the cohort has been described in relation to the study visits and variables that constitute this database (18-19). Briefly, at the time this study was performed the LUMINA cohort was comprised of 635 patients of Hispanic (from Texas, n=118 and Puerto Rico, n=102), African American (n=234) and Caucasian (n=181) ethnicities who met at least four of the updated and revised American College of Rheumatology (ACR) criteria for SLE (20-21). In general, African Americans and Texan Hispanics tended to have renal involvement more frequently than the Puerto Rican Hispanics and Caucasians. They also tended to accrue damage more rapidly than the other two groups. These patients were also, overall, of lower socioeconomic status (22-23).

Patients were ≥16 years of age and had disease duration of ≤5 years. Each patient had a baseline or enrollment visit (T0) followed by a six month visit (T0.5) and subsequent yearly

visits. Time of diagnosis (TD) was defined as the time when each patient met four ACR criteria. Each visit included interview, physical examination, and laboratory tests. Additional clinical information covering the period between scheduled visits as well as data for missed study visits were obtained by review of all available medical records.

For the purpose of these analyses, disease duration was defined as the period covering the interval between T0 and the last visit (TL). TL was truncated at the time renal damage first occurred for those patients who had developed it; for those patients who had not developed renal damage, TL was the time of their last visit, as already noted. Patients who had developed renal damage on or before T0 were not included in these analyses.

Cumulative hydroxychloroquine intake was recorded up to the time of renal damage occurrence or to TL if renal damage had not occurred.

Variables

Lupus nephritis was defined as (1) a renal biopsy demonstrating World Health Organization (WHO) Class II-V histopathology; and/or (2) proteinuria ≥0.5 g per 24 hours or 3+ proteinuria attributable to SLE; and/or (3) one of the following features also attributable to SLE and present on two or more visits performed at least 6 months apart:proteinuria ≥2+, serum creatinine ≥1.4 mg/dl, creatinine clearance ≤79 ml/min, ≥10 RBCs or WBCs per high power field (hpf), or ≥3 granular or cellular casts per hpf (2). Creatinine was measured at the laboratories of the participating institutions by the modified method of Jaffe in which creatinine combines with picrate in an alkaline solution to form a creatinine-picrate complex (22-24).

Renal damage, the outcome of interest, was defined as per the SDI as one or more of the following manifestations lasting for at least six months: estimated or measured glomerular filtration rate <50%, 24-hour proteinuria ≥3.5 g and end-stage renal disease (regardless of dialysis or transplantation). Of note, as per the SDI scoring instructions all variables are clinically ascertained and the maximum number of possible points for renal damage is 3. Thus, for those patients that presented with end-stage renal disease, without previous points on the renal domain the maximum score of 3 was given. The independent variable for this study was the cumulative use of hydroxychloroquine prior to renal damage if it had occurred, or before TL for those who had not developed renal damage (takers); if otherwise, patients were categorized as non-takers.

Variables from the different domains were selected based on those known to differ between hydroxychloroquine-takers and non-takers using as a reference our previously published experience and that of others (10,25-26). These variables are now described; variables included from the socioeconomic-demographic domain, all obtained at T0, were age, gender, ethnicity, education, poverty (as defined by the US Federal Government adjusted for the number of subjects in the household) (27) health insurance and smoking.

Variables selected from the clinical domain are noted. Clinical manifestations, as per the ACR criteria, including arthritis, photosensitivity, malar rash, serositis, renal, hematologic and neurologic disorders (20-21); the number of visits to the emergency room and hospitalizations; and whether the patients were alive or dead. Disease activity was assessed using the Systemic Lupus Activity Measure-Revised (SLAM-R) (28-29) while damage was ascertained with the SDI (renal domain excluded), as already noted. Other variables such as hypertension (≥2 separate abnormal readings ≥140 and/or 90 mmHg for systolic and diastolic, respectively and/or the use of antihypertensive medications), diabetes (use of insulin and/or hypoglycemic agents) and abnormal creatinine values (per categories of the

SLAM-R) were also included because of their potential relationship with the outcome of interest. All variables included in these analyses were measured at T0.

Medication variables studied included the cumulative exposure to cyclophosphamide, azathioprine, mycophenolate mofetil, glucocorticoids (as prednisone equivalent), angiotensin converting enzyme (ACE) inhibitors and blockers and statins.

Autoantibodies obtained at T0 including anti-double-stranded DNA [anti-dsDNA, by immunofluorescence against *Crithidia luciliae* (normal <1:10)] (30) and antiphospholipid antibodies [(aPL, abnormal >13 IgG phospholipid (GPL) units/ml and/or >13 IgM phospholipid (MPL) units/ml, by enzyme-linked immunoabsorbents assay (ELISA) technique or a positive lupus anticoagulant test (LAC, Staclot Test Diagnostica Stage 92600, Asniére-Sur-Seine, France)] (31) were also examined. Patients were considered to be aPL positive if they exhibited abnormal levels of IgM and/or IgG aPL antibodies (> 13 units/ml GPL and/or > 13 IgM units/ml MPL, respectively) or LAC positivity. Total cholesterol, and low-density lipoprotein (LDL) cholesterol calculated using the Friedewal formula in sera obtained at T0 were also included.

From the behavioral and psychological domain abnormal illness-related behaviors as assessed by the Illness Behavior Questionnaire (IBQ)] (32) was included.

Genetic polymorphisms previously found to be associated with hydroxychloroquine intake (*HLA-DRB1*08*) (10) or with some items of the renal domain damage (worsening proteinuria) (*HLA-DRB1*1503*) (33), were also examined.

Statistical Analyses

This is a prospective study (from the attribute or hydroxychloroquine intake to the event or renal damage) in the context of a longitudinal observational cohort study. As noted before, patients who developed renal damage on or before T0 were not included in these analyses (n=53). The study is limited to those patients with lupus nephritis at the baseline to T0 visit (n=203). First, all variables listed above were compared between hydroxychloroquine-takers and non-takers using either Students' t tests or *Chi* square tests; those variables significant at $p \leq 0.10$ (except death) or clinically relevant (*HLA-DRB1*1503,* ACE inhibitors and blockers use) were included into a Cox proportional hazards regression model with renal damage, as defined, being the end-point. In an alternative model proteinuria was excluded from the end-point. Disease duration from TD to T0 was adjusted for in these models. In both cases, the variables included in the reduced models were selected using a stepwise procedure. Each variable was systematically entered (or omitted) from the model contingent upon it being associated with the dependent variable with an $p \leq 0.10$ until a final, parsimonious model was obtained. Results are presented as hazard ratios (HRs) with their corresponding 95% confidence intervals (95% CIs). HRs >1 indicate a shorter time-to-the event (renal damage) while values <1 indicate a longer time. Kaplan-Meier survival curves as a function of hydroxychloroquine intake and WHO Class IV glomerulonephritis were also examined with renal-damage being the end-point.

Results

As depicted in Figure 1, 256 of the 635 LUMINA patients had renal involvement at T0 but 53 were excluded because they had already accrued renal damage. Thus, 203 patients were included in these analyses; of them sixty-three (31.0%) had developed one or more renal damage domain items over a mean (standard deviation, SD) disease duration of 5.2 (3.5) years, the cumulative incidence being 20.2 % and 30.0% at 5 and 10 years, respectively. As expected, patients were predominantly women (92.1%) of middle age, mean (SD) 36.9 (12.6) years. All ethnic groups were represented; there were 54 (26.6%) Texan-Hispanics,

26 (12.8%) Puerto Rican-Hispanics, 100 (49.3%) African Americans and 23 (11.3%) Caucasians. The ethnic distribution among those patients who developed renal damage was 39.7% for the Texan-Hispanics, 3.2% for the Puerto Rican-Hispanics, 47.6% for the African Americans and 9.5% for the Caucasians (p=0.0051). The mean age (SD) for patients who developed renal damage was 30.4 (9.2) years while disease duration at TL was 4.0 (2.6) years. Regarding the renal domain items of the SDI, 24 hour proteinuria ≥3.5 g was recorded in 60.3%, while an estimated or measured glomerular filtration rate <50% occurred in 12.7%, and end-stage renal disease in 6.4%. In the remaining 20.6% of the patients two (14.2%) or three (6.4%) damage items were recorded concomitantly.

Hydroxychloroquine Use—Of the 203 patients, 79.3% had taken hydroxychloroquine prior to the event or to TL for those who had not experienced renal damage while 20.7% had never taken it. For those patients taking hydroxychloroquine, the average daily dose was comparable regardless of renal damage occurrence (200 mg); the highest daily average dose was, however, somewhat higher for those who did not develop renal damage vs those who did (384.0 mg vs 331.1 mg; p=0.0008). The total duration of hydroxychloroquine intake was comparable in both groups. Table 1 shows the different characteristics of the patients by hydroxychloroquine category. Hydroxychloroquine-takers were more likely to have higher frequencies of arthritis, malar rash and photosensitivity and less severe disease overall. On the other hand, hydroxychloroquine non-takers were more likely to be smokers and had more severe disease with higher frequencies of serositis, WHO Class IV glomerulonephritis and higher SLAM-R scores. They also had higher levels of LDL-cholesterol, and had received higher doses of glucocorticoids but had been exposed less frequently to azathioprine. There was a higher number of deaths among them. There were no differences between hydroxychloroquine takers and non-takers in terms of the frequency of diabetes, hypertension and abnormal serum creatinine values and on the use of mycophenolate mofetil, cyclophosphamide, statins and ACE inhibitors and blockers.

Multivariable Analyses—Hydroxychloroquine was associated with a longer time-to-the occurrence of renal damage either in a full (HR=0.12; 95% CI 0.02-0.97) or a reduced (HR=0.29; 95% CI 0.13-0.68) model, after adjusting for confounders as per Table 1. Other variables significant in the final model include Texan-Hispanic ethnicity (HR=2.86; 95% CI 1.51-5.40), SLAM-R (HR=1.09; 95% CI 1.04-1.14) and LDL-cholesterol (HR=1.00; 95% CI 1.00-1.01). These data are noted in Table 2. In the alternative model in which proteinuria was omitted from the end-point hydroxychloroquine was also associated with a longer time to the occurrence of the event reaching significance in the reduced model (HR=0.38; 95% CI 0.16 – 0.86). These data are shown in Table 3.

Survival Analysis—As noted in Figure 2a, the cumulative probabilities of developing renal damage at five and 10 years for those patients who were on hydroxychloroquine were 20% and 38% compared to 47% and 70% for those who were not (p ≤0.0001). As noted in Figure 2b, the corresponding figures for those patients with WHO Class IV glomerulonephritis were 65% and 85% compared to 30% and 43% for those without it (p<0.0001).

Discussion

In this study we have shown that hydroxychloroquine retards the development of renal damage in lupus nephritis patients after adjusting for confounding variables associated with its intake whether proteinuria is omitted from the end-point or not. These data are relevant to the care of patients with SLE given that renal damage is one of the most important causes of morbidity and mortality in these patients (34-35), it imposes a burden on the patient and society and it is responsible for a significant portion of SLE-related health care costs (9).

While the occurrence of clinically evident renal involvement in SLE can be as high as 75% over the course of the disease (36), renal damage has been reported in up to 20% of the patients in some studies (37-39). Although we realize that renal involvement and damage represent a continuum and that some of the histopathological changes observed in lupus nephritis indeed indicate “tissue damage”, these changes are not recorded in the damage index. Furthermore, these histopathological changes are reversible with treatment, albeit that does not occur in all patients. Thus, for the purpose of this study and according with the definitions used, these two constructs, renal involvement and renal damage, can be distinguished. By definition, renal damage as per the SDI is a composite end-point; nevertheless, excluding proteinuria which can be argued may reverse even after six months; the protective effect of hydroxychloroquine was still evident. Several investigators have attempted to determine possible predictors of renal damage (33;40-41) and significant work is taking place to develop better treatment strategies than the ones currently available. There is, however, limited information about medications that may either retard the occurrence of lupus nephritis (42) or delay the onset of renal failure (16). Our results reinforce those from Kasitanon et al indicating that when hydroxychloroquine is added to patients with membranous lupus nephritis being treated with mycophenolate mofetil, remission is more likely to occur (15), and the recent data from Sisó et al suggesting that exposure to antimalarials prior to the onset of lupus nephritis may prevent the occurrence of renal failure (16). Although propensity score analyses were not performed to adjust for confounding by indication, all the variables which differed between hydroxychloroquine takers and non-takers were included in the analyses; as noted by several investigators regression models provide comparable results to those obtained by propensity score analyses, and thus inferences derived using such methods should be regarded as being entirely adequate (43-44).

Our findings can be explained by the variety of effects antimalarials possess. First, antimalarials have immunoregulatory properties; they inhibit intracellular toll-like receptors (TLRs), and the traffic of nuclear material into the cells, preventing the formation of auto-antibodies and the activation of plasmocytoid dendritic cells with the subsequent diminished production of interferon α, a hallmark of active lupus (45-48). Second, antimalarials exert mild anticoagulant properties inhibiting platelet aggregation and adhesion, and reducing blood viscosity and thrombus size (26;49-50). Third, antimalarial agents have a favorably effect on serum lipid profile and glucose concentrations (51-52). Thus, by preventing the formation of autoantibodies and immune-complexes, diminishing inflammation, and favorably acting at the vascular endothelial level, antimalarials may contribute to an adequate therapeutic response in patients with lupus nephritis retarding the onset of renal damage. We were, however, unable to examine the precise dose of hydroxychloroquine or the length of time needed for it to exert this beneficial effect since these data are not captured in our study visits. Of note, however, although the average daily dose of hydroxychloroquine was comparable for those who had not developed renal damage than for those who had developed it, the maximum average dose was higher in the first than in the second group, again supporting its protective role.

Some limitations of our study are worth noting. First, we could not include the prevalent cases of renal damage in our analyses since the exact temporal relationship between renal damage and hydroxychloroquine use could not be inferred from the data collected. Second, hydroxychloroquine exposure was recorded in a non-blinded manner at the time of study visits; however, the hypothesis tested in this study occurred subsequently and thus a systematic bias is unlikely to have occurred. Third, all auto-antibodies were examined only once; this may significantly impact the possible relationship between renal damage and aPL antibodies which tend to significantly fluctuate over time. Finally, although ethnicity was entered into the multivariable analyses and the data presented are likely to apply to lupus

patients of similar characteristics than our LUMINA patients, we cannot absolutely conclude that they apply to patients of each ethnic group individually since we could not perform ethnic-specific analyses (sample size).

In summary, using multivariable analyses to adjust for confounding by indication, we have shown that hydroxychloroquine retards the onset of renal damage in patients with lupus nephritis. Although, it is possible that not all confounders have been eliminated, based on our current knowledge and our previously published data, we strongly believe, however, that residual confounding has been kept to a minimum. Although the best possible way to reduce confounding to a minimum is to conduct a randomized clinical trial, given the many proven beneficial effects of hydroxychloroquine in patients with lupus, such a study is unlikely to be conducted; in fact, it may even be considered unethical. The data presented, taken in conjunction with those previously reported by others (15-16), suggest that renal damage can be prevented with the administration of hydroxychloroquine.

Acknowledgments

The authors would like to acknowledge all LUMINA patients without whom this study would have not been possible, our supporting staff (Jigna M. Liu, M.P.H. and Ellen Sowell, A.A. at UAB, Carmine Pinilla-Díaz, M.T. at UPR and Robert Sandoval B.A. at UTH) for their efforts in securing our patients' follow-up and performing other LUMINA-related tasks and Ms. Maria Tyson, A.A. for her most expert assistance in the preparation of this manuscript. We also gratefully acknowledge Drs. William J. Koopman and Vineeta Kumar for their most helpful comments to an earlier version of this manuscript.

Supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases P01 AR49084, General Clinical Research Centers M01-RR02558 (UTH) and M01-RR00032 (UAB) and from the National Center for Research Resources (NCRR/NIH) RCMI Clinical Research Infrastructure Initiative (RCRII) 1P20RR11126 (UPR) and by the STELLAR (Supporting Training Efforts in Lupus for Latin American Rheumatologists)

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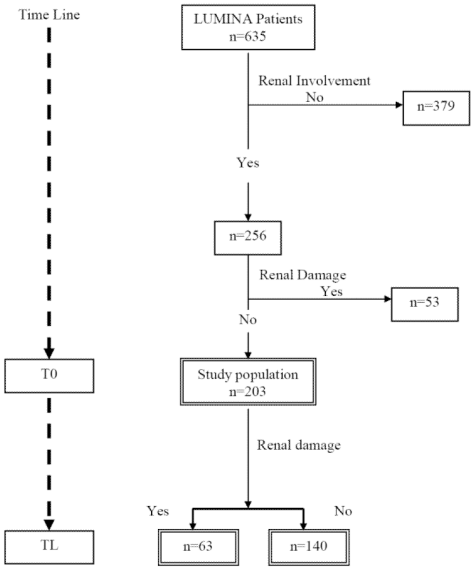

Figure 1.

Graphic representation of LUMINA patients included in this study and all others. LUMINA-Lupus in Minorities: Nature vs. Nurture; T0:Baseline or recruitment visit; TL: last visit or development of renal damage.

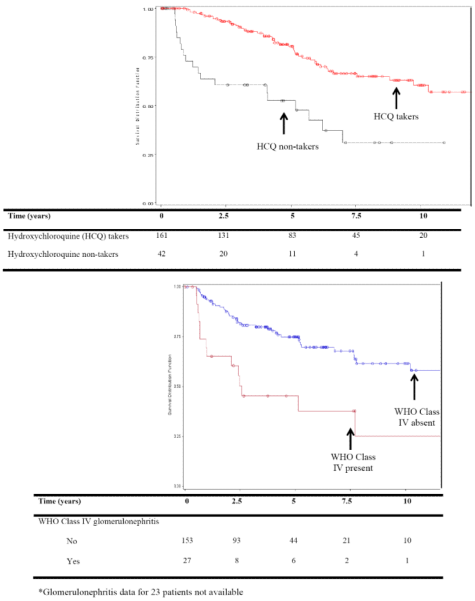

Figure 2.

Cumulative probability of developing renal-damage in LUMINA patients with lupus nephritis by Kaplan-Meier survival analyses. Tables below show the number of patients at risk at each time point

2a. As a function of hydroxychloroquine intake

2b. As a function of the presence of WHO Class IV glomerulonephritis

Table 1

Baseline Socioeconomic-demographic, Clinical, Serologic, Genetic and Treatment Characteristics in LUMINA Patients with Renal Involvement as a Function of the Cumulative Hydroxychloroquine Intake*

Variable	Hydroxychloroquine use		p value
	Yes (n=161)	No (n=42)	
Age, years*	32.9 (10.7)	32.4 (12.5)	0.7934
Female, %	90.5	91.3	0.8665
Ethnicity, %			
Texan Hispanic (n=54)	35.7	24.2	
Puerto Rican Hispanic (n=26)	7.1	14.3	0.2805
African American (n=100)	42.9	50.9	
Caucasian (n=23)	14.3	10.6	
Education level, years*	12.5 (3.1)	11.8 (3.0)	0.1941
Have medical insurance, %	72.8	66.7	0.4350
Below the poverty line†, %	39.9	47.7	0.3996
Smoking, %	10.0	21.4	0.0453
Systemic lupus erythematosus (SLE) clinical manifestations, %			
Arthritis	87.6	64.3	0.0004
Photosensitivity	60.9	38.1	0.0081
Malar rash	62.7	38.1	0.0040
Serositis	65.2	78.6	0.0985
WHO Class IV glomerulonephritis	9.9	33.3	0.0003
Hematological disease	88.2	88.1	0.9852
Neurological disease	14.9	16.7	0.7777
Non-SLE clinical manifestations			
Diabetes	6.8	7.1	0.9423
Hypertension	34.8	28.6	0.4474
SLAM-R*‡	9.0 (5.8)	10.8 (6.8)	0.0839
SDI*§	0.50 (0.90)	0.68 (1.31)	0.3219
Anti-dsDNA antibodies, %	83.2	76.2	0.2926
aPL antibodies ¶, %	39.8	40.5	0.9319
Serum creatinine, % abnormal	20.5	16.7	0.5784
*HLA-DRB1*08, %*	20.9	31.7	0.1430
*HLA-DRB1*1503*, %	21.5	9.8	0.0877
LDL-Cholesterol	110.4 (48.0)	138.8 (95.8)	0.0155
IBQ ††	19.4 (6.7)	18.5 (6.5)	0.4729
Hospitalizations due to SLE, %	64.7	62.2	0.7792
Emergency Room visits due to SLE, %	55.6	54.1	0.8638
Medications			
ACE inhibitors and blockers, %	20.5	12.5	0.4577

Variable	Hydroxychloroquine use		p value
	Yes (n=161)	No (n=42)	
Statins, %	7.3	12.5	0.4698
Azathioprine, use %	34.2	19.1	0.0594
Glucocorticoids, dose *‡‡	11.3 (12.0)	16.8 (20.5)	0.0247
Cyclophosphamide use, %	34.8	28.6	0.4475
Mycophenolate mofetil	8.5	7.7	0.9275
Death during follow-up, %	13.0	42.9	<0.0001

*Values are the mean (SD). LUpus in MInorities: NAture vs Nurture;

†as per US Federal government guidelines, adjusted for the number of persons in the household;

‡Systemic Lupus Activity Measure-Revised;

§SLICC (Systemic Lupus International Collaborating Clinics) Damage Index;

¶IgG and/or IgM antiphospholipid antibodies and/or the Lupus anticoagulant;

††ascertained with the Illness Behavior Questionnaire;

‡‡as prednisone dose (per mg).

Table 2

Protective Effect of Hydroxychloroquine in Renal Damage* Development among SLE Patients with SLE and Renal Involvement from the LUMINA Cohort by Multivariable Cox Regression Analyses

	Full Model			Reduced Model		
Variable	**Hazard Ratio**	**95% Confidence interval**	***p* value**	**Hazard Ratio**	**95% Confidence interval**	***p* value**
Age	0.92	0.82 – 1.02	0.1060	0.97	0.95 – 1.00	0.0547
Gender (female)	1.18	0.12 – 11.29	0.8839			
Ethnicity						
Texan Hispanic	0.60	0.05 – 7.28	0.6883	2.86	1.51 – 5.40	0.0012
Puerto Rican Hispanic	0.06	0.00 – 1.12	0.0598			
African American	0.18	0.01 – 2.40	0.1954			
Caucasian		Reference Group				
Time (TD - T0)†	0.90	0.52 – 1.56	0.7116			
Smoking	1.40	0.05 – 37.72	0.8405			
Malar rash	0.55	0.10 – 2.91	0.4781	0.59	0.31 – 1.11	0.0989
Photosensitivity	0.65	0.11 – 3.70	0.6225			
Arthritis	1.02	0.10 – 10.17	0.9851			
Serositis	0.88	0.15 – 5.13	0.8878			
WHO Class IV glomerulonephritis‡	2.00	0.28 – 14.62	0.4913			
SLAM-R¶	1.03	0.92 – 1.15	0.6537	1.09	1.04 – 1.14	0.0001
LDL-Cholesterol	1.03	1.00 – 1.05	0.0137	1.00	1.00 – 1.01	0.0005
HLA-DRB1*1503	8.78	0.69 – 112.06	0.0949	2.00	0.98 – 4.-06	0.0567
ACE§ inhibitors and blockers	1.27	0.15 – 11.02	0.8288			
Hydroxychloroquine	0.12	0.02 – 0.97	0.0464	0.29	0.13 – 0.68	0.0043
Azathioprine	0.58	0.07 – 4.78	0.6139			

*As determined by the SLICC Damage Index (estimated or measured <50% glomerular filtration rate, proteinuria ≥3.5 g or end-stage renal disease).

†Diagnosis-recruitment or baseline visit;

‡World Health Organization;

¶Systemic Lupus Activity Measure-Revised (without renal manifestations);

§Angiotensin converting enzyme.

Table 3

Protective Effect of Hydroxychloroquine in Diminished Glomerular Filtration Rate and/or End-Stage Renal Disease* among SLE Patients with Renal Involvement from the LUMINA Cohort by Multivariable Cox Regression Analyses

	Full Model			Reduced Model		
Variable	**Hazard Ratio**	**95% Confidence interval**	***p* value**	**Hazard Ratio**	**95% Confidence interval**	***p* value**
Age	0.97	0.94 – 1.01	0.1159			
Gender (female)	1.25	0.26 – 6.04	0.7826			
Ethnicity						
Texan Hispanic	2.68	0.49 – 14.52	0.2533	2.99	1.44 – 1.22	<0.0001
Puerto Rican Hispanic	0.97	0.07 – 13.02	0.9827			
African American	0.76	0.13 – 4.40	0.0954			
Caucasian		Reference Group				
Malar rash	0.28	0.11 – 0.75	0.0111	0.46	0.23 – 0.96	0.0371
Photosensitivity	0.75	0.31 – 1.86	0.5373	0.47	0.23 – 0.97	0.0398
Arthritis	2.81	0.58 – 13.74	0.2019			
Serositis	1.64	0.65 – 4.14	0.2932			
WHO Class IV glomerulonephritis	1.22	0.49 – 3.04	0.6746			
SLAM-R	1.14	1.08 – 1.21	<0.0001			
LDL-Cholesterol	1.00	1.00 – 1.00	0.4520			
*HLA-DRB1*1503*	3.03	1.19 – 7.72	0.0201	2.13	0.96 – 4.70	0.0615
Hydroxychloroquine	0.38	0.13 – 1.06	0.0647	0.38	0.16 – 0.86	0.0206
Azathioprine	0.69	0.28 – 1.62	0.3788			

*As determined by the SLICC Damage Index (estimated or measured <50% glomerular filtration rate or end-stage renal disease);

†World Health Organization;

‡Systemic Lupus Activity Measure-Revised (without renal manifestations).