EXTENDED REPORT

Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L)

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Objective: In patients with systemic lupus erythematosus (SLE), hydroxychloroquine prevents disease flares and damage accrual and facilitates the response to mycophenolate mofetil in those with renal involvement. A study was undertaken to determine whether hydroxychloroquine also exerts a protective effect on survival.
Methods: Patients with SLE from the multiethnic LUMINA (LUpus in MInorities: NAture vs nurture) cohort were studied. A case-control study was performed within the context of this cohort in which deceased patients (cases) were matched for disease duration (within 6 months) with alive patients (controls) in a proportion of 3:1. Survival was the outcome of interest. Propensity scores were derived by logistic regression to adjust for confounding by indication as patients with SLE with milder disease manifestations are more likely to be prescribed hydroxychloroquine. A conditional logistic regression model was used to estimate the risk of death and hydroxychloroquine use with and without the propensity score as the adjustment variable.
Results: There were 608 patients, of whom 61 had died (cases). Hydroxychloroquine had a protective effect on survival (OR 0.128 (95% CI 0.054 to 0.301 for hydroxychloroquine alone and OR 0.319 (95% CI 0.118 to 0.864) after adding the propensity score). As expected, the propensity score itself was also protective.
Conclusions: Hydroxychloroquine, which overall is well tolerated by patients with SLE, has a protective effect on survival which is evident even after taking into consideration the factors associated with treatment decisions. This information is of importance to all clinicians involved in the care of patients with SLE.

Hydroxychloroquine, considered decades ago to be a relatively minor component in the overall treatment of patients with systemic lupus erythematosus (SLE), is now considered an essential therapeutic element in this disease; in fact, hydroxychloroquine has been shown to decrease the probability of flares, the accrual of damage, to possibly protect patients with SLE from the occurrence of vascular and thrombotic events and to facilitate the response to other agents in patients with renal involvement.[1–7] More recently, chloroquine and hydroxychloroquine have been shown to exert a protective effect on survival in a cohort of 232 patients with SLE. In this study, patients treated with either of these compounds experienced a better survival rate than those not treated with either agent, even after adjusting for patient characteristics,[8] as patients treated with hydroxychloroquine or chloroquine generally tend to have milder disease than untreated patients.[2 6 8] However, this study was conducted in an almost entirely Caucasian population from Spain. We have now investigated if such a protective effect also occurs in patients with SLE from non-Caucasian ethnic groups, which generally are known to have more severe disease.[9–13] A case (deceased)-control (alive) study was conducted in a well characterised multiethnic cohort of patients with SLE known as LUMINA (LUpus in MInorities: NAture vs nurture).

METHODS

Patients

The LUMINA study is being performed under the guidelines of the Declaration of Helsinki for the participation of human subjects in research and was approved at the three participating institutions; all patients gave written informed consent. The constitution of this cohort, the participating institutions (The University of Alabama at Birmingham (UAB), The University of Texas Health Science Center at Houston and the University of Puerto Rico Medical Science Campus), ethnic composition (Hispanics from Texas primarily of Mexican and Central American ancestry and from the Island of Puerto Rico, African Americans and Caucasians), entry criteria (revised and updated American College of Rheumatology (ACR) classification criteria for SLE,[14 15] ⩾16 years of age, up to 5 years of disease duration) and visit frequency (baseline visit (T0) and visits every 6 months for the first year and yearly thereafter) have been described in detail elsewhere.[16–18] Time of diagnosis was the time at which a patient met four revised and updated ACR classification criteria. Although ''loss to follow-up'' in our cohort approached 36% at 5 years,[19] efforts have been made to ascertain if patients lost to follow-up are alive or not by searching the vital statistic records of the Health Departments of Alabama and Texas and of the Commonwealth of Puerto Rico.

Variables

Socioeconomic-demographic, clinical, immunological, genetic, behavioural and psychological features were obtained at each study visit using validated instruments, questionnaires and procedures. The variables from these different domains included in the analyses were age, sex, ethnicity, education, marital status, health insurance, health behaviours (smoking, drinking, not exercising, coping with illness), number of ACR criteria, specific clinical manifestations (attributable to SLE), disease activity, disease damage, selected *HLA-DRB1* alleles, medication utilisation (including hydroxychloroquine), health-care utilisation (hospital admissions and emergency room

Abbreviations: SLE, systemic lupus erythematosus

visits) and survival/mortality.[20] Causes of death were those recorded in the patients' death certificates.

Given the observational nature of our cohort, hydroxychloroquine and all other medications were prescribed by the patients' treating physicians (usually rheumatologists) but not by study physicians. The differences in prescribing patterns observed among the various ethnic groups were not due to a centre effect, as we have previously shown.[21] Exposure to hydroxychloroquine was defined as use of the drug during the matched time independent of dose and duration; however, as per the LUMINA protocol, exposure was recorded as present if documented at the time of the study visit or during the interval between visits and if it occurred for at least 20% of the duration of the interval. None of the patients received >400 mg hydroxychloroquine/day (median 400 mg/day, range 200–400 mg/day for both cases and controls). Likewise, none received the antimalarial chloroquine.

Study design and statistical analyses

This is a nested case-control study within the LUMINA cohort. Deceased patients were cases and were disease duration-matched (from time of diagnosis and within 6 months), but alive patients were randomly chosen as controls. Three controls were selected for each deceased patient (case). The baseline socioeconomic-demographic and clinical features of these two patient groups were then compared using standard descriptive statistics. Based on previously published information and our own clinical experience,[2 6 18] we expected that patients treated with hydroxychloroquine would have milder disease and experienced better outcomes than those not treated with it; thus ''confounding by indication'' needed to be taken into consideration. One analytical approach to account for this is to enter all clinical and socioeconomic-demographic variables that differ between treated and untreated patients into a multivariable analysis. The other is to determine the probability that a patient will be treated with hydroxychloroquine based on these differing variables or to develop a propensity score. It is expected that patients with milder disease will have a higher probability of being treated with hydroxychloroquine than those with more severe disease, but for each quintile of the score there will be treated and untreated patients, achieving a de facto pseudorandomisation.[22 23] We thus derived propensity scores using the baseline variables listed in table 1.

Finally, to assess the contribution of hydroxychloroquine use to survival independent of socioeconomic-demographic and clinical characteristics (the propensity score), a conditional logistic regression model was examined. All analyses were performed using SAS Version 9.1, SAS, Cary, North Carolina, USA).

Table 1 Baseline disease characteristics as a function of survival in patients in the LUMINA cohort

Feature	Alive (n = 183)	Deceased (n = 61)	p Value*
Median (range) age at T0 (years)	35.4 (16.4–62.4)	34.6 (15.7–77.8)	
Sex (% women)	85.3	90.2	
Ethnicity (%)			
Hispanic Texas (n = 55)	20.8	27.9	
Hispanic Puerto Rico (n = 25)	13.1	1.6	0.0014
African American (n = 93)	33.0	50.8	
Caucasian (n = 71)	32.2	19.7	
Health insurance (%)	82.2	61.8	0.0016
Median (range) education (years)	12.0 (5.0–20.0)	12.0 (3.0–17.0)	0.0002
Below poverty line (%)	26.1	56.0	<0.0001
Smoking (%)	14.8	17.9	
Median (range) disease duration at T0 (months)	11.4 (0.3–75.4)	7.0 (0.2–59.1)	0.0525
Median (range) disease duration at TL (months)	53.1 (0.7–146.2)	48.9 (0.4–141.4)	
Median (range) follow-up time (T0–TL) (months)	41.8 (0.4–145.9)	41.9 (0.2–144.2)	
Median (range) number of ACR criteria at diagnosis	5.0 (4.0–10.0)	6.0 (4.0–9.0)	0.0323
Clinical manifestations (%)			
Integument	88.0	78.7	0.0736
Arthritis	78.5	68.3	
Pleuritis or pericarditis	38.9	71.7	<0.0001
Pulmonary disease	8.3	18.6	0.0265
Renal disease	33.3	63.3	<0.0001
Immune-mediated cytopenias	77.2	89.1	0.0551
CNS involvement	29.1	53.3	0.0007
Myositis	7.3	23.3	0.0007
Median (range) SLAM-R at T0	8.0 (0–30.0)	14.0 (2.0–31.0)	<0.0001
Median (range) SDI at T0	0 (0–5.0)	1.0 (0–5.0)	<0.0001
Anti-ds DNA antibodies (%)	27.0	42.4	0.0322
Antiphospholipid antibodies (%)	25.1	26.2	
*HLA-DRB1*08* (%)	11.4	10.2	
Hospitalisations due to SLE (%)	24.8	56.6	<0.0001
ER visits due to SLE (%)	22.5	52.8	<0.0001
Glucocorticoid use (%)	89.6	88.5	
Azathioprine use (%)	9.8	14.8	
Cyclophosphamide use (%)	14.2	26.2	0.0316
Low dose aspirin and/or anticoagulant use† (%)	27.3	21.3	
Median (range) IBQ total score at T0	20.0 (3.0–35.0)	19.5 (5.0–31.0)	

T0, baseline visit; TL, last visit (cases and controls were matched for disease duration from diagnosis to TL within 6 months); ACR, American College of Rheumatology; CNS, central nervous system; SLAM-R, Systemic Lupus Activity Measure-Revised; SDI, SLICC (Systemic Lupus International Collaborating Clinics) damage index; SLE, systemic lupus erythematosus; ER, emergency room; IBQ, Illness Behavior Questionnaire.
*χ^2 test for proportions and Wilcoxon rank test for continuous variables; only p values $\leqslant 0.10$ are shown.
†Warfarin and/or low molecular weight heparin.

Table 2 Probability of being treated with hydroxychloroquine as a function of the quintiles of the propensity score* in LUMINA cases and controls

Propensity score quintile		Treated with hydroxychloroquine: Yes n (%)	Treated with hydroxychloroquine: No n (%)
1	(0.00–0.20)	19 (39.6)	29 (60.4)
2	(0.21–0.40)	43 (87.8)	6 (12.2)
3	(0.41–0.60)	46 (95.8)	2 (4.2)
4	(0.61–0.80)	43 (86.0)	7 (14.0)
5	(0.81–1.00)	49 (100.0)	0 (0)
Total		200	44

*Highest quintile, milder disease; lowest quintile, more severe disease.

RESULTS

At the time these analyses were performed there were 608 patients in the LUMINA cohort (117 Hispanics from Texas, 101 Hispanics from Puerto Rico, 220 African Americans and 170 Caucasians). After a median follow up time of 39 months there had been 61 deaths, 17 in patients who were taking hydroxychloroquine at T0 (n = 349, 5%) and 44 in those not taking it (n = 259, 17%; $p<0.0001$). One hundred and eighty-three patients matched for disease duration were randomly chosen as controls for the 61 deceased patients in a proportion of 3:1.

Table 1 shows the distribution of the T0 variables in cases (deceased) and controls (alive). As expected, deceased patients had more severe disease—as indicated by more organ system involvement, active disease, damage accrued and hospital admissions, among other features—but they also had a lower socioeconomic status—as reflected in fewer years of education and a higher proportion of patients below the poverty line or lacking health insurance. Table 2 shows the quintiles of the propensity score and the percentage of patients being treated with hydroxychloroquine for all 244 SLE patients (61 cases and 183 controls). Patients in the highest quintile of the propensity score (milder disease and/or better socioeconomic status) had the highest probability of hydroxychloroquine use (100%) while those in the lowest quintile (more severe disease and/or less favourable socioeconomic status) had the lowest (39.6%). In the conditional logistic regression, hydroxychloroquine alone had an odds ratio (OR) of 0.128 (95% confidence interval (CI) 0.054 to 0.301), indicating that it exerts a protective effect on survival. When the propensity score was added to the model, the protective effect of hydroxychloroquine on survival remained significant, although the 95% CI was wider (OR 0.319, 95% CI 0.118 to 0.864). These data are shown in table 3.

Deaths due to vascular events were somewhat higher in the hydroxychloroquine-treated group (11.1%) than in the treated group (8.0%), but the difference was not statistically significant. Other causes of death are given in table 4.

DISCUSSION

Patients treated with hydroxychloroquine tend to have less severe disease than those not treated with this medication. This applies to patients with SLE in general,[2] but is also the case for patients in the LUMINA cohort as noted before and confirmed here.[6] In our cohort, patients treated with hydroxychloroquine also tended to have better socioeconomic status than those not treated with it.[6] Given the beneficial effects of hydroxychloroquine in preventing disease flares,[1] the accrual of damage,[6] facilitating a response to other agents in patients with renal involvement,[7] its favourable impact on survival[8] and its overall high degree of usefulness in patients with SLE,[2] it is highly unlikely (and even unethical) that a double-blind placebo-controlled trial could be done to determine what other possible beneficial effects it may have, including survival. An alternative to a placebo-controlled trial is to determine the probability of a patient with SLE being treated with hydroxychloroquine based on clinical and socioeconomic-demographic characteristics, or to derive a propensity score as described by Landewé.[22] Once the propensity score is determined, there will be patients with different degrees of probability of being treated with hydroxychloroquine according to the severity of their disease (and their socioeconomic status), but there will be patients with the same probability who have not been treated with hydroxychloroquine, as shown in table 2. Thus, pseudorandomisation occurs de facto, and this score can then be used as a single variable to adjust for patients' characteristics in multivariable analyses of outcome.[22] This statistical method is now being used with increasing frequency.[6 24 25]

Table 3 Conditional logistic regression analyses of mortality as a function of the use of hydroxychloroquine and the propensity score in LUMINA cases and controls*

Model†	Variable	OR (95% CI)	p Value
1	Hydroxychloroquine	0.128 (0.054 to 0.301)	<0.0001
2	Hydroxychloroquine	0.319 (0.118 to 0.864)	0.0246
	Propensity score	0.035 (0.005 to 0.228)	0.0004

*Matched for disease duration from diagnosis to last visit within 6 months.
†Model 1 does not include the propensity score, model 2 does.

We have studied the possible protective effect of hydroxychloroquine using a case (deceased)-control (alive) approach. Propensity scores were used to adjust for the many differences in socioeconomic-demographic and clinical characteristics between hydroxychloroquine users and non-users; the distribution of the propensity score quintiles were comparable to that derived when the cohort had only about 500 patients,[6] although not so perfect given that all patients in the highest quintile (milder disease) were taking hydroxychloroquine. We thought the case-control study design was the best approach to overcome the relative lack of precise exposure data to hydroxychloroquine in all patients. Our analyses show that hydroxychloroquine exerts a clear protective effect in terms of survival, regardless of whether or not clinical and socioeconomic-demographic characteristics (propensity score) are taken into consideration. There may, of course, be other features that affect confounding by indication which may not be clearly evident and thus might not have been included in the generation of the propensity score, so some degree of residual confounding may still persist when propensity scores are calculated.[22 23 26] Based on current knowledge, however, we believe that residual confounding has been relatively minor in our derivation of these scores. Furthermore, given the magnitude of the protective effect detected, some degree of

Table 4 Causes of death in LUMINA patients as a function of hydroxychloroquine use*

Causes	Hydroxychloroquine use: Yes n (%)	Hydroxychloroquine use: No n (%)	Total n (%)
SLE	11 (44.0)	18 (50.0)	29 (47.5)
Vascular events	2 (8.0)	4 (11.1)	6 (9.8)
Infectious processes	6 (24.0)	10 (27.8)	16 (26.2)
Other†	6 (24.0)	4 (11.1)	10 (16.4)
Total	25 (100.0)	36 (100.0)	61 (100.0)

SLE, systemic lupus erythematosus.
*Differences not significant by Fisher's exact text.
†Malignant processes (n = 2), accidents (n = 1), unknown (n = 7).

residual confounding may have diminished this protective effect somewhat but it is unlikely that it will have been completely abrogated. Our data corroborate the recently published data from Spain using a very similar method (propensity score analyses).[8] Furthermore, a similar protective effect was recently reported by Pons-Estel on behalf of GLADEL (Grupo Latino Americano de Estudio de Lupus or Latino American Group for the Study of Lupus) at the most recent PANLAR meeting (www.panlarperu.org). This protective effect of hydroxychloroquine is probably mediated by its ability to prevent the occurrence of flares and damage, both of which can be regarded as mediators of a later outcome such as death.[1 27–29] Our results and those from the Spanish cohort (and GLADEL) are therefore not unexpected.

The underlying basis for the observed protective effect of hydroxychloroquine includes many factors. In general, antimalarial drugs have anti-inflammatory, antithrombotic, antihyperlipidaemic, antihyperglycaemic and immunomodulatory properties.[3 30] Their antithrombotic, antihyperlipidaemic and antihyperglycaemic effects may independently contribute to the decreased occurrence of vascular thrombotic events, as was shown in the Spanish cohort.[8] The ultimate result is an improvement in survival. Despite these considerations, however, a clear cut difference in the causes of death in patients treated and not treated with hydroxychloroquine was not observed in our cohort, but it was observed in the Spanish study in which the duration of follow-up was much longer.[8] Deaths due to vascular events were, however, higher in our non-hydroxychloroquine treated patients.

Over the last decade clinicians have emphasised the role of hydroxychloroquine in SLE in terms of disease activity and damage accrual, but the possibility that this compound—which had been thought to be a relatively minor component in the overall treatment of SLE—could also improve survival had not been anticipated even by those most enthusiastically supporting its use.[2 3 5] Our data, taken together with the findings from the Spanish study and those presented by GLADEL, are of importance to practising clinicians (rheumatologists and non-rheumatologists) managing patients with SLE. We suggest that hydroxychloroquine should be considered as a therapeutic option in all patients with SLE and should be administered using established guidelines so that the proper dose is prescribed (not exceeding 6.5 mg/kg of (ideal) body weight) and adequate ophthalmological monitoring is performed.[31 32] Hydroxychloroquine is generally well tolerated so, unless side effects occur, it can be administered for the duration of the disease.

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The first two authors contributed equally to the investigation.

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