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Antimalarial Treatment May Have a Time-Dependent Effect on Lupus Survival

Data From a Multinational Latin American Inception Cohort

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Objective. **To evaluate the beneficial effect of antimalarial treatment on lupus survival in a large, multiethnic, international longitudinal inception cohort.**

Methods. **Socioeconomic and demographic characteristics, clinical manifestations, classification criteria, laboratory findings, and treatment variables were examined in patients with systemic lupus erythematosus (SLE) from the Grupo Latino Americano de Estudio del Lupus Eritematoso (GLADEL) cohort. The diagnosis of SLE, according to the American College of Rheumatology criteria, was assessed within 2 years of cohort entry. Cause of death was classified as active disease, infection, cardiovascular complications, thrombosis, malignancy, or other cause. Patients were subdivided by antimalarial use, grouped according to those who had received antimalarial drugs for at least 6 consecutive months (user) and those who had received antimalarial drugs for <6 consecutive months or who had never received antimalarial drugs (nonuser).**

Results. **Of the 1,480 patients included in the GLADEL cohort, 1,141 (77%) were considered antimalarial users, with a mean duration of drug exposure of 48.5 months (range 6–98 months). Death occurred in 89 patients (6.0%). A lower mortality rate was observed in antimalarial users compared with nonusers (4.4% versus 11.5%; $P < 0.001$). Seventy patients (6.1%) had received antimalarial drugs for 6–11 months, 146**

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(12.8%) for 1–2 years, and 925 (81.1%) for >2 years. Mortality rates among users by duration of antimalarial treatment (per 1,000 person-months of followup) were 3.85 (95% confidence interval [95% CI] 1.41–8.37), 2.7 (95% CI 1.41–4.76), and 0.54 (95% CI 0.37–0.77), respectively, while for nonusers, the mortality rate was 3.07 (95% CI 2.18–4.20) (*P* for trend < 0.001). After adjustment for potential confounders in a Cox regression model, antimalarial use was associated with a 38% reduction in the mortality rate (hazard ratio 0.62, 95% CI 0.39–0.99).

Conclusion. **Antimalarial drugs were shown to have a protective effect, possibly in a time-dependent manner, on SLE survival. These results suggest that the use of antimalarial treatment should be recommended for patients with lupus.**

Systemic lupus erythematosus (SLE) is a complex chronic autoimmune disorder that can be life-threatening. Although life expectancy in SLE has increased over the last few decades (1,2), mortality remains higher than that in the general population (3–5). Recent longitudinal studies have identified active disease, infection, atherosclerosis, and malignancies as important causes of death in SLE (5–9). Better survival in SLE, according to most investigators, has been attributed to 2 main factors: 1) diagnosis of milder cases, due to the wider availability of specific tests, and 2) better supportive treatment options (antibiotics, antihypertensive drugs, dialysis, and renal transplantation).

Use of antimalarial drugs could account for the improved survival of patients with lupus only since the 1990s, when the use of antimalarials became more generalized. In fact, the seminal studies from the Canadian Hydroxychloroquine Study Group demonstrated that patients with stable disease in whom this compound was discontinued were more likely to experience a flare compared with those who remained on treatment (10). It also has been demonstrated that treatment with hydroxychloroquine prevents damage overall, as well as damage in specific domains of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (11–13).

The beneficial effects of antimalarial drugs in lupus, however, go beyond control of disease activity and damage accrual. In fact, they seem to have a protective effect on survival, as noted in a study from Spain conducted in a homogeneous Caucasian population, in which a reduction in mortality was evident. Of interest, none of the patients treated with antimalarial drugs died of cardiovascular complications, the most frequent cause of death in untreated patients (14). Likewise, data from the LUpus in MInorities, NAture versus nurture (LUMINA) study, involving a multiethnic cohort from the US, reaffirmed the general protective effect of antimalarial drugs on survival (15). However, the minimal duration of drug exposure required to exert this effect could not be derived from those data.

We therefore evaluated the possible beneficial effect of at least 6 months of antimalarial drug exposure on the survival of SLE patients. In addition, we examined the causes of mortality in a large, multiethnic, international inception cohort from the Grupo Latino Americano de Estudio del Lupus Eritematoso (GLADEL) study (see Appendix A for study group members).

PATIENTS AND METHODS

Study design. The present study was designed as an observational inception cohort study. The general characteristics and composition of the GLADEL cohort have been described in detail elsewhere (16). Briefly, the GLADEL study was started in 1997 by the establishment of a common protocol, consensus definitions, and outcome measures in 34 centers distributed among 9 Latin American countries. The local ethics committee of each center approved the protocol, and informed consent was obtained from all patients.

To achieve a balanced representation among the participating centers, and despite the large numbers of SLE patients being followed up at some of these institutions, each center enrolled 20–30 randomly selected SLE patients with up to 2 years of disease duration from the time of diagnosis. After incorporating the initial 30 patients, each center continued to incorporate 1 new patient per month into the ARTHROS database (version 2.0 or, subsequently, the improved ARTHROS version 6.0) over the next 2 years. Prior to each patient's inclusion into the cohort, all previously available medical records were reviewed by the site investigator; these data were validated during an interview in order to properly capture the time at which each of the ACR criteria for the classification of SLE had initially occurred. A physical examination and laboratory tests were performed at entry and at all subsequent visits, which took place every 6 months thereafter; however, data gathered during nonscheduled visits were also recorded in the database.

ARTHROS version 6.0 is a user-friendly database developed by Argentinean rheumatologists using a Windows platform, Visual Basic language, and Microsoft Access (Microsoft, Redmond, WA). All data are submitted via the Internet to the coordinating center, where data are reviewed to ensure their quality. The diagnosis of SLE was done on the basis of clinical and laboratory data and confirmed according to the expertise of the investigator (a rheumatologist or qualified internist with experience in diagnosing SLE). Fulfillment of 4 of the ACR 1982 classification criteria for SLE (17) at the time of diagnosis was not mandatory. In addition, disease diagnosis could be made subsequent to a patient accruing at least 4 of the ACR criteria. The time at which each of the ACR criteria was fulfilled as well as the time at which SLE was diagnosed (by a rheumatologist) were identified.

Studies were performed in the clinical laboratory of each participating center. Each center defined the cause of death as attributable to active disease, infection, cardiovascular complications, thrombosis, malignancy, or other cause, either alone or in combination, or designated as unknown. Patients were subdivided according to use or nonuse of an antimalarial agent (chloroquine and/or hydroxychloroquine) based on each patient's entire followup period during the study. Patients were classified as an antimalarial "user" if they had received an antimalarial agent for at least 6 consecutive months, whereas "nonusers" comprised patients who had received antimalarial drugs for <6 consecutive months or who had never received them. This approach was taken to ensure a minimal period of exposure to antimalarial drugs, given the known latency period for their effects to occur.

Statistical analysis. Categorical variables were summarized as frequencies and percentages, while continuous variables were presented as the mean and SD or median and interquartile range. Antimalarial users and nonusers were compared using chi-square tests, *t*-tests, and Wilcoxon's tests, as appropriate (18). Mortality rates, grouped according to duration of exposure to antimalarial drugs, were compared using a generalized linear model, assuming Poisson distribution for number of deaths within each category of exposure duration.

The effect of antimalarial use on survival was examined using a Cox regression model, with time from diagnosis to death or to last followup visit expressed in number of months (19). Antimalarial use was considered a time-dependent predictor, i.e., at any given time during the followup, patients receiving antimalarial drugs for ≥6 months were considered users, while patients receiving them for <6 months or not receiving them at all were considered nonusers. Thus, each patient could potentially be classified in both categories, user and nonuser, during her or his followup period in the cohort. Variables considered for adjustment were selected from the socioeconomic and demographic characteristics and clinical manifestations present at or before diagnosis that were significantly different in the univariable analysis between those patients who ultimately died and those who remained alive at the time that these analyses were performed. In an alternative model, variables that differed between antimalarial users and nonusers were included in the regression model.

P values less than or equal to 0.05 were considered significant in all cases. All statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

At the time that these analyses were performed (June 2005), 1,480 patients were included in the GLADEL cohort. The patients in this cohort had a mean ± SD age at disease onset of 29.5 ± 12.3 years, the median time from entry to SLE diagnosis was 5.0 months (range 1–584 months), and the median duration of followup in the entire cohort was 55 months (range 1–102 months). Of the 1,480 patients, 1,141 (77%) were considered antimalarial users, whereas 339 (23%) were nonusers. The nonuser group included 267 patients who had never received antimalarial drugs and 72 who had received antimalarial drugs for <6 months. The mean antimalarial exposure time for the users was 48.5 months (range 6–98 months). Seventy patients (6.1%) had received antimalarial drugs for 6–11 months, 146 (12.8%) had received them for 1–2 years, and 925 had received them (81.1%) for >2 years. The mortality rates among the users by treatment duration (per 1,000 person-months of followup) were 3.85 (95% confidence interval [95% CI] 1.41–8.37), 2.70 (95% CI 1.41–4.76), and 0.54 (95% CI 0.37–0.77), respectively, while the mortality rate for the nonuser group was 3.07 (95% CI 2.18–4.20) (*P* for trend < 0.001). These data are shown in Table 1.

Table 1. Mortality rates as a function of duration of exposure to antimalarial drugs in the Grupo Latino Americano de Estudio del Lupus Eritematoso cohort

Group, exposure time	No. of patients	Mortality rate (95% CI)*
Nonuser	339	3.07 (2.18–4.20)
Never	267	
<6 months	72	
User	1,141	
6–11 months	70	3.85 (1.41–8.37)
12–23 months	146	2.70 (1.41–4.76)
≥24 months	925	0.54 (0.37–0.77)

* The mortality rate (95% confidence interval [95% CI]) is the rate per 1,000 person-months of followup. *P* for trend < 0.0001.

In the entire cohort, antimalarial use was associated with a lower mortality rate when compared with nonuse (4.4% versus 11.5%; $P < 0.001$). The corresponding Kaplan-Meier survival curve as a function of antimalarial use for the entire cohort is shown in Figure 1.

The socioeconomic and demographic characteristics of the antimalarial users and nonusers are shown in

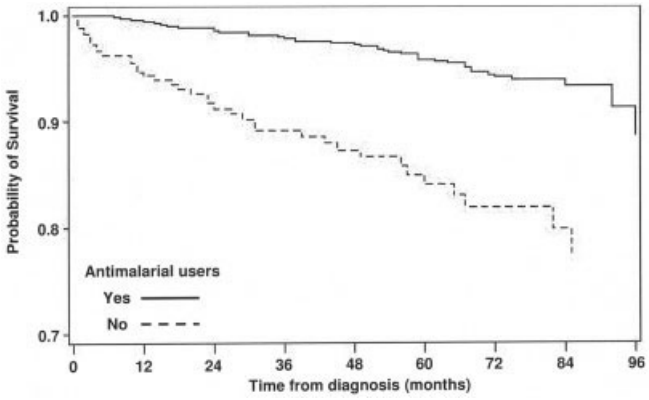

Figure 1. Kaplan-Meier survival curves showing time-dependent survival rates according to duration of antimalarial use in the entire cohort of patients with systemic lupus erythematosus.

Table 2. Socioeconomic and demographic characteristics of the patients with systemic lupus erythematosus as a function of antimalarial use*

Characteristic	Antimalarial use		
	User (n = 1,141)	Nonuser (n = 339)	*P*
Age at diagnosis, mean (range) years	27 (7–86)	28 (6–77)	0.10
Delay in diagnosis, median (range) months	5 (<1–490)	6 (<1–301)	0.35
Duration of followup, median (range) months	60 (6–102)	31 (1–99)	<0.001
Female sex	1,032 (90.5)	298 (87.9)	0.18
Ethnic group			0.53
White	464 (40.7)	142 (41.9)	
Mestizo	494 (43.3)	151 (44.5)	
African Latin American	146 (12.8)	40 (11.8)	
Other	37 (3.2)	6 (1.8)	
Socioeconomic status			0.28
Low	684 (60.2)	215 (63.6)	
Medium/high	453 (39.8)	123 (36.4)	
Education			0.08
≤7 years	325 (29.5)	106 (34.0)	
8–12 years	502 (45.6)	146 (46.8)	
≥13 years	274 (24.9)	60 (19.2)	
Medical coverage			<0.001
No coverage	168 (14.8)	82 (24.6)	
Partial coverage	256 (22.6)	69 (20.7)	
Full coverage/private	708 (62.5)	182 (54.7)	

* Except where indicated otherwise, values are the numer (%) of patients. Antimalarial users were defined as those receiving either chloroquine or hydroxychloroquine for ≥6 consecutive months.

Table 2. The duration of followup was significantly longer in users compared with nonusers ($P < 0.001$), in spite of the fact that patients in each group had a comparable mean age at diagnosis ($P = 0.10$); likewise, the delay in diagnosis was of comparable duration between users and nonusers ($P = 0.35$). No differences between users and nonusers were observed in terms of sex distribution, ethnic group, socioeconomic status, and education ($P > 0.05$). However, there were more patients with full coverage/private medical insurance among the antimalarial users than among the nonusers ($P < 0.001$).

The clinical features and type of therapy at or before the time of diagnosis in the antimalarial users and nonusers are shown in Table 3. Antimalarial users had more cutaneous manifestations compared with nonusers (85.5% versus 79.1%; $P = 0.007$) and had more articular involvement compared with nonusers (76.8% versus 65.8%; $P < 0.001$). In contrast, renal disease was less frequent among antimalarial users (28.4% versus 42.8%; $P < 0.001$). However, the frequency of anti–double-stranded DNA antibodies was comparable between the user and nonuser groups (38.6% versus 42.5%; $P = 0.21$). Regarding type of antimalarial treatments, users were less likely to have received azathioprine than were nonusers (3.6% versus 7.1%; $P = 0.01$).

To assess the effect of the use of antimalarial drugs on mortality, a Cox regression model was per-

Table 3. Cumulative clinical manifestations and therapy use at or before diagnosis as a function of antimalarial use in patients with systemic lupus erythematosus*

	Antimalarial use		
	User (n = 1,141)	Nonuser (n = 339)	*P*
Manifestation			
Cutaneous	975 (85.5)	268 (79.1)	0.007
Articular	876 (76.8)	223 (65.8)	<0.001
Serositis (pleuritis/pericarditis)	223 (19.5)	77 (22.7)	0.22
Pulmonary	30 (2.6)	10 (3.0)	0.71
Renal	324 (28.4)	145 (42.8)	<0.001
Hematologic	599 (52.5)	200 (59.0)	0.04
Neurologic	151 (13.2)	56 (16.5)	0.13
Myositis	149 (13.1)	44 (13.0)	1.00
Any infection	94 (8.2)	29 (8.6)	0.85
Anti-dsDNA antibodies	440 (38.6)	144 (42.5)	0.21
Treatment			
Glucocorticoid	760 (66.6)	211 (62.2)	0.15
Azathioprine	41 (3.6)	24 (7.1)	0.01
Cyclophosphamide	53 (4.7)	22 (6.5)	0.20

* Values are the number (%) of patients. The features were present at diagnosis and study entry for the prevalent cases, and at diagnosis or study entry for the incident cases. Antimalarial users were defined as those receiving either chloroquine or hydroxychloroquine for ≥6 consecutive months. Anti-dsDNA = anti–double-stranded DNA.

Table 4. Effect of antimalarial drugs on mortality in patients with systemic lupus erythematosus, determined by Cox multivariable regression analysis*

Parameter	Comparison	Hazard ratio	95% CI
Antimalarial use	User vs. nonuser	0.62	0.39–0.99
Age at diagnosis			
<40 years	One-year increase in age	0.95	0.92–0.98
≥40 years	One-year increase in age	1.07	1.04–1.11
Medical coverage			
None	None vs. full/private	2.19	1.32–3.63
Partial	Partial vs. full/private	1.48	0.89–2.47
Full/private	Referent	–	–
Neurologic disorder (at diagnosis)	Yes vs. no	1.73	1.03–2.91

* Antimalarial users were defined as those receiving either chloroquine or hydroxychloroquine for ≥6 consecutive months. 95% CI = 95% confidence interval.

formed, in which all potential confounders (features that differed between deceased and living patients at last followup) were included (Table 4). However, renal disease was not incorporated into the final model, because it had no impact on the hazard ratio (HR) and it would have made the estimates for the other variables in the model less precise. After adjustment for all of these variables, the use of antimalarial drugs for ≥6 months was associated with a 38% reduction in the mortality rate (HR 0.62, 95% CI 0.39–0.99). In the alternative model, in which only those clinical manifestations and treatment types that differed between users and nonusers were included (i.e., cutaneous involvement, arthritis, renal manifestations, azathioprine use, and the SLICC/ACR Damage Index), a quite comparable HR (0.72) for the effect of antimalarial treatment on survival was observed, but statistically significant differences between the 2 groups were not reached. The nonsignificant interaction that was observed between ethnic group and antimalarial use suggests that the antimalarial effect is the same for all ethnic groups; however, our sample size precluded a detailed examination of this.

Table 5. Causes of death as a function of antimalarial use in patients with systemic lupus erythematosus (SLE)*

Cause of death	Total (n = 89)	Antimalarial use	
		User (n = 50)	Nonuser (n = 39)
SLE activity plus infection	37 (41.5)	23 (46.0)	14 (35.9)
SLE activity	18 (20.2)	5 (10.0)	13 (33.3)
Infection	15 (16.8)	9 (18.0)	6 (15.4)
Cardiovascular complications	7 (7.9)	4 (8.0)	3 (7.7)
Thrombosis	2 (2.3)	2 (4.0)	0
Malignancy	2 (2.3)	2 (4.0)	0
Other	3 (3.4)	1 (2.0)	2 (5.1)
Unknown	5 (5.6)	4 (8.0)	1 (2.6)

* Values are the number (%) of patients. $P = 0.11$ for the overall comparison of distribution of causes of death, by Fisher's exact test. Antimalarial users were defined as those receiving either chloroquine or hydroxychloroquine for ≥6 consecutive months.

As noted in Table 5, causes of death were similarly distributed between users and nonusers. Specifically, no apparent protective effect of antimalarial drugs was observed in terms of the frequency of deaths attributed to either cardiovascular complications or thrombotic events (each $P = 0.11$ for users versus nonusers, by Fisher's exact test).

DISCUSSION

In this study of patients from the GLADEL cohort, we were able to demonstrate that antimalarial use offers protection in terms of prolonged survival. This finding corroborates the data from the Spanish study by Ruiz-Irastorza et al (14) and the findings from the LUMINA cohort (15). Furthermore, our analyses suggest that there is a time-dependent effect of antimalarial use, since patients in whom antimalarial use was longer exhibited lower mortality than those who were treated for shorter times with these compounds. It should be noted, however, that the comparison of the mortality rates according to the different exposure times did not take into consideration any other variables that may act as confounders. Furthermore, in the Cox regression, we examined any use versus no use (as defined in Patients and Methods), and therefore, this time-dependent effect needs to be interpreted with some caution.

There is substantial evidence to indicate a survival benefit conferred by antimalarial drugs by 2 years of treatment, and our test indicating a positive trend would suggest that perhaps there is a time effect before this interval that cannot be precisely identified in this study. Nevertheless, our observations, coupled with the other beneficial effects of antimalarial drugs that have

been reported in patients with lupus, as well as the observations of flares recurring upon discontinuation of the treatment and the retarding of damage accrual overall and in specific domains of the SLICC/ACR Damage Index (10–12,20–23), indicate that antimalarial drugs should unquestionably be used as an anchor treatment for patients with lupus, regardless of the clinical manifestations present, degree of disease activity and damage, disease duration, and other treatments being administered.

The mechanisms underlying the beneficial effects of antimalarial drugs are being sorted out. It has been demonstrated, for example, that antimalarials interfere with the formation of immune complexes and thus inhibit the production of interferon by preventing the incorporation of RNA and DNA fragments into Toll-like receptors 7 and 9, respectively (24,25). In addition, we and other investigators have demonstrated the lipid-lowering effects of these compounds in lupus patients, both in terms of glucocorticoid-enhanced lipoprotein synthesis and triglyceride catabolism by interfering with lipoprotein lipase activity (21,26,27). Benefits in terms of glucose metabolism have also been demonstrated (23,28).

Finally, the antithrombotic and vascular protective properties of antimalarial drugs have been demonstrated in laboratory animals (29); the antithrombotic effects have also been shown in patients with lupus from both the Spanish cohort alluded to before (14) and in a recent study from the US (30). Thus, by diminishing the active inflammatory process, having favorable effects on lipid and glucose metabolism, and preventing thrombosis via favorable effects on the vascular endothelium, antimalarials may contribute to diminished disease activity, decreased damage accrual, and possibly fewer vascular thrombotic events, and thus they may positively affect patients' survival. It should be noted, however, that the antithrombotic effect as a possible mediator of improved survival was observed by Ruiz-Irastorza et al (14), and the diminishment of damage accrual was observed in the LUMINA cohort (11,12). We could not demonstrate the antithrombotic effect and had not assessed damage accrual in our cohort.

The possibility that our observations regarding the protective effect of antimalarial drugs in the survival of lupus patients could be due to confounding by indication has been addressed in the previously published studies from Spain and the US (14,15). When variables that could differentiate antimalarial users from nonusers were added to the model, the HR remained essentially unchanged, albeit statistical significance was not reached. Thus, it does not appear likely that the effect observed in patients from the GLADEL cohort is merely due to the fact that patients with milder disease were treated with antimalarials and those with more severe disease were not.

The clear strengths of our study include its large sample size (more than 1,000 patients), the multiethnic and multinational composition of the cohort (Latin Americans of European, Amerindian, African, and mixed ancestry), and the fact that we were able to examine the relationship between treatment duration and the desired effect. Furthermore, >80% of the patients who had been treated with antimalarial drugs had received them for more than 2 years. The limitations of our study are mainly related to our inability to perform ethnic-specific regression analyses, due to the small number of deaths by ethnic group; nevertheless, the nonsignificant interaction between ethnic group and antimalarial use suggests that the beneficial effect of these compounds is the same for all ethnic groups in our cohort. Likewise, our study was not powered to perform subset analyses for the different categories of medical insurance coverage.

Of note, relatively few deaths occurred in several of the categories examined, and thus a clear protective effect of antimalarial drugs on the risk of cardiovascular complications, thrombotic events, and malignancies was not observed. However, such events require longer observation times before they might occur, and therefore differences may, in fact, be observed as follow up of the cohort continues. Thus, the data presented herein, considered in conjunction with the data from the published literature, suggest that antimalarial treatment should be used in all lupus patients, regardless of the disease manifestations or duration of disease.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Pons-Estel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDIX A. MEMBERS OF THE GLADEL STUDY GROUP

In addition to the authors, the following individuals are members of the GLADEL Study Group and have incorporated at least 20 patients into the database: from Argentina, Luis J. Catoggio, Enrique R. Soriano, Maria Flavia Ceballos Recalde, and Edson Velozo (Medical Clinic Service, Hospital Italiano and Fundación Dr. Pedro M. Catoggio para el Progreso de la Reumatología, Buenos Aires), Jorge A. Manni, Sebastián Grimaudo, and Judith Sarano (Instituto de Investigaciones Médicas "Alfredo Lanari," Buenos Aires), José A. Maldonado-Cocco, Maria S. Arriola, and Graciela Gómez (Instituto de Rehabilitación Psicofísica, Buenos Aires), Mercedes A. García, Ana Inés Marcos, and Juan Carlos Marcos (Hospital

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