Anti-malarials exert a protective effect while Mestizo patients are at increased risk of developing SLE renal disease: data from a Latin-American cohort

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Abstract

Objective. To examine the role of ethnicity and the use of anti-malarials (protective) on lupus renal disease.

Methods. A nested case-control study (1:2 proportion, n = 265 and 530) within GLADEL’s (Grupo Latino Americano De Estudio de Lupus) longitudinal inception cohort was carried out. The end-point was ACR renal criterion development after diagnosis. Cases and controls were matched for follow-up time (end-point or a comparable time, respectively). Renal disease predictors were examined by univariable and multivariable analyses. Additional analyses were done to determine if the protective effect of anti-malarials persisted after adjusting for intake-associated confounders.

Results. Of the cases, 233 (87.9%) were women; their mean (s.d.) age at diagnosis was 28.0 (11.9) years and their median (Q3/Q1 interquartile range) follow-up time for cases and controls was 8.3 months (Q3/Q1: 23.5); 56.6% of the cases and 74.3% of the controls were anti-malarial users. Mestizo ethnicity [odds ratio (OR) 1.72, 95% CI 1.19, 2.48] and hypertension (OR 2.26, 95% CI 1.38, 3.70) were independently associated with a higher risk of renal disease, whereas anti-malarial use (OR 0.39, 95% CI 0.26, 0.58), older age at disease onset (OR 0.98, 95% CI 0.96, 0.99) and female gender (OR 0.56, 95% CI 0.32, 0.99) were negatively associated with such occurrence. After adjusting for variables associated with their intake, the protective effect of anti-malarials on renal disease occurrence persisted (OR 0.38, 95% CI 0.25, 0.58).

Conclusion. Mestizo patients are at increased risk of developing renal disease, whereas anti-malarial use protects patients from such an occurrence.

Key words: LN, renal disease, SLE, anti-malarials, HCQ, chloroquine, ethnicity, race, mestizo, Latin America.
Introduction

Renal disease in SLE varies from silent to overt manifested by proteinuria, decreased renal function and even end-stage renal disease (ESRD); it is more frequent and severe in some ethnic/racial groups [1–4], but limited data have been reported in Latin-American lupus patients [5]. Over the last few years, significant insight has been gained in understanding the role of anti-malarials in lupus in general and on renal disease in particular, but these studies have not included Latin-American patients [6–10]. We have now conducted a nested case–control (renal disease yes/no) study within the GLADEL (Grupo Latino Americano De Estudio del Lupus, or Latin-American Group for the Study of Lupus) cohort to identify the role of ethnicity in renal disease and to determine if anti-malarials may have a protective effect regarding this occurrence.

Patients and methods

Patients

As previously described [5], GLADEL is a multi-ethnic, multi-national and multi-centre lupus inception cohort started in 1997 and constituted by 34 centres from nine Latin-American countries under institutional review boards’ regulations. Each centre enrolled 20–30 randomly selected SLE patients with up to 2 years of disease duration from diagnosis to achieve a balanced representation among centres.

The diagnosis of SLE was done based on the clinical and laboratory features present and the expertise of the investigator. ACR 1982 SLE criteria fulfilment at diagnosis was not mandatory; nevertheless, 1142 (79.5%) patients met ≥4 criteria at diagnosis and 1378 (95.9%) during the follow-up period.

Variables

Renal disease, the outcome of interest, was defined by the respective ACR criterion (persistent proteinuria or the presence of cellular casts). Independent variables included socio-demographic characteristics, clinical manifestations, ACR classification criteria, activity and damage scores and medications used. Hypertension (persistent abnormal systolic blood pressure over 140 mmHg and/or diastolic blood pressure 90 mmHg and/or antihypertensive use) and diabetes mellitus (abnormal plasma glucose values and/or insulin and/or hypoglycaemic use) were also included. These parameters were assessed on or before disease diagnosis, at entry into the cohort, and every 6 months thereafter (cumulative incidence). Disease activity was assessed with the SLEDAI at entry into the cohort and every 6 months thereafter [11], and damage with the SLICC/ACR Damage Index [12] yearly.

Exposure to anti-malarials (chloroquine and/or HCQ) was dichotomized according to their use/non-use prior to renal disease for the cases or to a comparable time for controls, independent of the length of time this medication was used. Other medications used were recorded in a similar manner.

Statistical analyses

This was a nested case–control (1:2 proportion) study within the GLADEL cohort and was restricted to patients who developed renal disease (ACR criterion) after SLE diagnosis (n = 265) and two controls (n = 530). First, we study the role of ethnicity and anti-malarial use as predictors of renal disease occurrence. These two variables plus others from different domains were examined between cases and controls using univariable conditional logistic regression analysis, as appropriate; all independent variables were considered present prior to renal disease if it had already occurred, or to a comparable time for controls. Relevant variables and those significant at P < 0.10 in these analyses were then included in a conditional logistic regression model; a parsimonious multivariable model was constructed. Since we found anti-malarials to exert a protective effect, further analyses were done to adjust for possible confounding variables associated with their intake. All multivariable analyses are presented as odds ratios (ORs) with their corresponding 95% CIs. All statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Renal disease occurred in 265 patients (17.9%) after entering the GLADEL cohort (n = 1480 patients) (see supplementary figure available as supplementary data at Rheumatology Online). Eighty-eight patients (33.2%) developed persistent proteinuria and 44 (16.4%) cellular casts; 133 patients (50.2%) developed both. Two hundred and thirty-three of the cases (87.9%) were women; their mean (s.d.) age at diagnosis was 28.0 (11.9) years; their median follow-up time (Q3–Q1 interquartile range) was 8.3 months (Q3–Q1: 23.5); 139 (52.5%) of the cases were Mestizos (mixed Caucasian and Amerindian), 92 (34.7%) Caucasians and 34 (12.8%) were African-Latin Americans; 150 (56.6%) of the cases and 74.3% of the controls were defined as anti-malarial users.

Univariable analyses

Results are provided in a supplementary table available as supplementary data at Rheumatology Online. Male gender and abrupt disease onset were more common among cases than the controls and the proportion of Mestizos was higher among them; cases were also younger at diagnosis and from a lower socio-economic status than the controls. Within the clinical features, the presence of hypertension and ACR criteria oral ulcers, arthritis, serositis, haematological and immunological disorders were all more frequent in the cases than in the controls. Disease activity at diagnosis was also higher in the cases than in the controls. As for the treatment variables, antihypertensive drugs, AZA and CYC were found to be more common in the cases than in the controls. There was also a higher proportion of deceased patients among the cases than among the controls.
In addition to some of the ACR criteria (oral ulcers, arthritis, serositis, haematological disorder, immunological disorder and anti-nuclear antibodies), hypertension, older age at disease onset and female gender, Mestizo ethnicity (OR 1.72, 95% CI 1.19, 2.48) was independently associated with a higher risk of renal disease, whereas anti-malarial use (OR 0.39, 95% CI 0.26, 0.58) was negatively associated with such occurrence (Table 1). In an alternative model, the possible interaction of anti-malarial use and ethnicity was evaluated but it could not be demonstrated (data not shown).

Additional analyses to adjust for confounding by indication related to anti-malarial use

Of the 795 GLADEL cohort patients included in this study, 544 (68.4%) had taken anti-malarials (241 HCQ, 261 chloroquine and 42 either HCQ or chloroquine) prior to the development of renal disease or to last study visit, whereas 251 (31.6%) had never taken anti-malarials. The total duration of anti-malarial intake was comparable in both groups, whereas the median daily dose was higher (but non-significant) for those who did not develop renal disease (400 versus 300 mg). None of the socio-economic /demographic characteristics differed between takers and non-takers. Anti-malarial takers were more likely to exhibit malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, immunological disorder and anti-nuclear antibodies than the non-takers, whereas takers were more frequent users of AZA and oral low or medium doses of glucocorticoids. In the corresponding multivariable analyses (Table 2), the OR for the development of renal disease as a function of anti-malarial use was 0.38 (95% CI 0.25, 0.58).

Discussion

In this study we have shown that Mestizo patients are at increased risk of developing renal disease and that anti-malarials exert a protective effect on renal disease occurrence, and this was the case after adjusting for those variables that differed between anti-malarial users and non-users or confounding by indication; this is even
more notable since exposure to anti-malarials was considered present regardless of its duration. These findings, when viewed in light of the other known beneficial effects of these compounds (retarding damage in general and in the renal system in particular, preventing flares and prolonging survival), have practical implications for the management of lupus patients beyond the Latin-American countries due to current world immigration patterns.

The possible protective effect of anti-malarials in the kidney may result from the down-regulation of the immune response by interfering with antigen presentation, the formation of autoantibodies and the production of TNF-α and by reducing the production of IFN, one of the key molecules involved in the pathogenesis of SLE [13-15]. It may also result from their anticoagulant and lipid-lowering properties and their ability to reduce vascular stiffness and resistance with increased elasticity [16].

Of the other variables found to be significant in our analyses, ethnicity deserves special comment, having shown, after adjusting for socio-economic and clinical variables, that being Mestizo is a risk factor for the development of renal disease. In the LUMINA cohort, African American and Hispanic (originally of Mexican ancestry) ethnicities have also been found to be significant predictors of renal involvement; in that study, socio-economic status explained 14.5% of the ethnicity variance, whereas admixture (primarily African, but also Amerindian) accounted for another 36.8%, and a combination of the two that could not be separated further contributed 12.2%. These findings, taken together, highlight the role that genetic factors play in the ethnicity-dependent susceptibility to renal involvement [17].

Our study has several limitations, first being that this an observational study, anti-malarials were prescribed at the discretion of the treating physicians at the time of study visits; their use under these circumstances can be biased by a number of confounders influencing treatment decisions. However, the hypothesis tested occurred subsequently to their prescription, making unlikely the occurrence of a systematic bias; although some may have favoured propensity score analyses, statisticians believe that regression models provide comparable results [18] and are adequate. Secondly, since the study was designed using the combined variable (anti-malarials), it was not felt appropriate to parcel the data out post facto, thus specific analyses for each of these compounds were not performed. Therefore, we cannot conclude whether our observations relate to a class effect or are driven primarily by one of these two compounds. Thirdly, we were unable to include histopathological information in our analyses, as only 97 (36.8%) of the cases had renal biopsies and sample size would have been reduced considerably. Lacking a uniform protocol for obtaining them among all 34 GLADEL centres may account for this relatively low rate of biopsies performed. Fourth, we were unable to conduct ethnic-specific analyses because of sample size that would have limited our ability to draw firm conclusions; however, we examined interaction terms for anti-malarials and each ethnic group which, by

### Table 2

<table>
<thead>
<tr>
<th>Features</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female</td>
<td>0.52 (0.29, 0.94)</td>
<td>0.0304</td>
</tr>
<tr>
<td>Ethnic group</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.63 (1.12, 2.36)</td>
<td>0.0104</td>
</tr>
<tr>
<td>Mestizo</td>
<td>1.07 (0.62, 1.83)</td>
<td>0.8213</td>
</tr>
<tr>
<td>African-Latin American</td>
<td>0.98 (0.97, 0.99)</td>
<td>0.0087</td>
</tr>
<tr>
<td>Older age at disease onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malar rash</td>
<td>1.43 (0.94, 2.17)</td>
<td>0.0920</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>0.62 (0.35, 1.09)</td>
<td>0.0950</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>0.71 (0.48, 1.06)</td>
<td>0.0949</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>1.53 (1.09, 2.17)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.98 (1.21, 3.23)</td>
<td>0.0064</td>
</tr>
<tr>
<td>Serositis</td>
<td>2.27 (1.51, 3.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Haematological disorder</td>
<td>1.68 (1.12, 2.50)</td>
<td>0.0114</td>
</tr>
<tr>
<td>Immunological disorder</td>
<td>1.52 (1.04, 2.24)</td>
<td>0.0326</td>
</tr>
<tr>
<td>ANAs</td>
<td>0.58 (0.32, 1.09)</td>
<td>0.0823</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.08 (1.25, 3.44)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.34 (0.17, 10.43)</td>
<td>0.7771</td>
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<tr>
<td>Medications</td>
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<tr>
<td>Anti-malarials</td>
<td>0.38 (0.25, 0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucocorticoid, dose (oral)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (≤20 mg)</td>
<td>0.78 (0.45, 1.36)</td>
<td>0.3812</td>
</tr>
<tr>
<td>Medium (&gt;20 to &lt;60 mg)</td>
<td>1.07 (0.63, 1.81)</td>
<td>0.8150</td>
</tr>
<tr>
<td>High (≥60 mg)</td>
<td>0.74 (0.41, 1.33)</td>
<td>0.3121</td>
</tr>
<tr>
<td>AZA use</td>
<td>1.39 (0.82, 2.33)</td>
<td>0.2273</td>
</tr>
</tbody>
</table>

See Table 1 for additional definitions.
and large, validate our findings. Fifth, ethnicity was defined operationally, the same as that of parents and all grandparents, which may be imprecise; however, the final assignment of ethnicity was the prerogative of the clinician, who also considered the patients’ anthropomorphic characteristics. Sixth, prevalent cases of renal disease could not be included, which could have biased the results in either direction; however, given the magnitude of the OR, it is unlikely that the OR would have flipped altogether. Finally, some clinical and laboratory data (i.e. smoking history, genetic polymorphisms and anticardiolipin antibody) were not uniformly obtained and for the purpose of this study were excluded.

In conclusion, we have demonstrated for the first time the increased risk of renal disease among Mestizo patients from the largest Latin-American cohort of SLE patients and that anti-malarials exert a protective effect on such occurrence after adjusting for important confounders. Our data reinforce the published literature [6–10], suggesting that the use of anti-malarials should be the cornerstone of the management of patients with SLE; preventing renal disease in patients with lupus has positive effects in terms of morbidity (no renal damage will ensue), survival (increasing it) and health care cost (associated with the management of both renal disease and renal damage) [19].

Rheumatology key messages

- Mestizo SLE patients living in Latin America are at increased risk of developing renal disease.
- Anti-malarial use exerts a protective effect against renal disease in Latin-American SLE patients.
- Rheumatologists should be aware of the course and outcome of SLE in Latin-American immigrant populations.

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Supplementary data

Supplementary data are available at Rheumatology Online.

References


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