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Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus

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Antimalarials have shown beneficial effects on systemic lupus erythematosus (SLE) activity. Our aim was to investigate whether antimalarials protect against thrombosis and influence survival in SLE patients. A prospective cohort including 232 patients with SLE were included in the study at the time of lupus diagnosis. End points were documented thrombosis and death due to any cause. A Cox regression-multiple-failure time survival analysis model was fitted to establish the effect of antimalarials on the development of thrombosis. Kaplan–Meier survival curves and propensity score adjusted-Cox regression analysis were performed to investigate the effect of antimalarials use on survival. Of our subjects, 204 patients (88%) were women. 230 patients (99%) were white. 150 patients (64%) had ever received antimalarials. Median time on antimalarials was 52 months (range three to 228 months). The Cox multiple-failure time survival analysis showed that taking antimalarials was protective against thrombosis (HR 0.28, 95%CI 0.08–0.90), while aPL-positivity (HR 3.16, 95%CI 1.45–6.88) and previous thrombosis (HR 3.85, 95%CI 1.50–9.91) increased the risk of thrombotic events. Twenty-three patients died, 19 of whom (83%) had never received antimalarials. No patient treated with antimalarials died of cardiovascular complications. Cumulative 15-year survival rates were 0.68 for never versus 0.95 for ever treated patients (P < 0.001). Age at diagnosis and propensity score-adjusted HR for antimalarials ever versus never users was 0.14 (95%CI 0.04–0.48). Our study shows a protective effect of antimalarials against thrombosis and an increased survival of SLE patients taking these drugs. These data support the routine use of antimalarials in all patients with SLE.


Key words: anticardiolipin antibodies; antiphospholipid antibodies; chloroquine; hydroxychloroquine; lupus anticoagulant; mortality; prognosis; stroke

Introduction

After decades of empirical use, a number of studies have shown the distinct beneficial effects of antimalarials in systemic lupus erythematosus (SLE). Randomized controlled trials have established that both hydroxychloroquine and chloroquine may help SLE patients keep their disease under remission.1,2 Moreover, the potential benefits of antimalarials go far beyond their effects on lupus activity. Specifically, cholesterol-lowering and antithrombotic properties of these compounds have been suggested in observational studies.3–5

These latter effects may be especially relevant to patients with SLE. Thromboses, either due to atherosclerotic disease or caused by antiphospholipid antibodies (aPL), are among the leading causes of death in lupus.6 We have shown in a previous study that antiphospholipid syndrome (APS) is a major adverse prognostic factor for survival.7

Thus, antimalarials could prevent thrombosis and affect the long-term course of SLE. However, the clinical implications of these potential influences have not been yet determined.

Methods

Study design

This is an observational prospective cohort study. All patients with SLE according to the American College
of Rheumatology (ACR) classification criteria, attending the Internal Medicine Department, Hospital de Cruces, University of The Basque Country, have joined an ongoing prospective, observational study aimed at identifying prognostic variables in lupus. The time of diagnosis of lupus, defined as the point when four ACR criteria were met, was the starting point for the follow-up (T₀ herein) in all patients.

Follow-up protocol

Patients are assessed every three months, unless requiring more (active patients) or less frequent visits (long-standing inactive patients). Clinical and immunological variables are recorded in a standardized protocol and incorporated into the database at T₀ and thereafter on every subsequent follow-up visit. Data recorded include demographic characteristics, clinical events during SLE course, autoantibody profiles, death, causes of death and treatments received. The Systemic Lupus International Collaborating Clinics (SLICC) damage index, or SDI, was used to quantify the degree of irreversible organ damage accrued within six months after T₀ (SDI₀ herein) and then at regular intervals. aPL positivity was defined according to Sapporo criteria, thus all patients coded as aPL-positive had lupus anticoagulant and/or anticardiolipin antibodies at medium-high titres on at least two occasions six weeks apart.

End points

The end-points of this study are thrombosis at any level and mortality due to any cause within the first 15 years after T₀. This period has been chosen due to the small population at risk beyond that point.

Thrombosis was defined as the presence of compatible clinical signs and symptoms and eventually confirmed by complementary tests. Deep vein thrombosis was documented by ultrasonography and/or venography; pulmonary embolism by lung scan or helical computed tomographic (CT) scanning; peripheral and visceral arterial thrombosis by arteriography or surgery; myocardial infarction was defined as typical chest pain with characteristic electrocardiographic features and elevated levels of creatine kinase (MB fraction) and/or T troponine; stroke by CT scanning or magnetic resonance imaging; cerebral transient ischemic attacks (TIAs) were diagnosed in the setting of acute focal neurologic symptoms/signs lasting less than 24 hours. Small vessel thrombosis needed pathologic confirmation. Any asymptomatic radiological findings at any level were not recorded.

All causes of death have been recorded and grouped under the following categories: active lupus, cardiovascular (including thrombosis at any site, heart failure of any cause, sudden cardiac death and pulmonary hypertension), infection, malignancy, and others.

Statistical analysis

The statistical packages StatView, version 5.0.1 for Apple Macintosh (SAS Institute Inc., Cary, NC) and STATA Release 8.2 for Windows (StataCorp, 2005, College Station, TX) were used for all analyses.

Patients were divided in two groups: ever and never treated with antimalarials. Univariate comparisons between both groups were performed using chi-square test (with Yates’ correction) or Student’s t-test, as appropriate.

For the analysis of thrombotic events, the entire follow-up period of each patient was divided into time intervals according to the exposure status to antimalarials. Each period started with either T₀, a change of treatment (starting or withdrawing antimalarials) or after a thrombotic event and ended with either a change of treatment, a thrombotic event, death or the end of follow-up. Periods on anticoagulant therapy were excluded from this analysis. A Cox regression-multiplesurvival analysis model, which accounted for the time-varying nature of some potential predictors of thrombosis, was fitted. Robust standard errors were estimated to account for the lack of independence in the occurrence of repeated events.

Thromboses at T₀ were not considered as events, but its presence was used as a potential predictor in the model. Therefore, variables included in the analysis were:

- thrombosis at T₀ (yes/no, fixed variable);
- presence of aPL (yes/no, fixed variable);
- use of antimalarials (yes/no, time-varying predictor);
- use of aspirin (yes/no, time-varying predictor).

For the univariate survival analysis, Kaplan–Meier 15-year survival curves were obtained and compared by means of the log-rank test. Patients not suffering the end-point event (ie, death) were censored at the time of the last visit to clinic. In order to overcome the potential bias of confounding by indication, the propensity score, a statistical adjustment tool that balances the covariates between treated and untreated/control groups, has been used.

A binary logistic regression model showed the influence of a number of variables in the indication of antimalarials. The propensity score was calculated using all independent variables shown in Table 1, irrespective of their level of statistical significance. Then, strata based on quintiles of propensity score were obtained and the balance within strata was assessed using standard statistical techniques (Student’s t and chi-square
Eighty-four patients (57%) started antimalarials hydroxychloroquine only, 46 chloroquine only and 42 malarials at any time during the course of SLE (62%).

Any use of tobacco & 61/150 & 23/82 & 1.99 (0.89–4.45) \\
Use of cyclophosphamide & 37/150 & 26/82 & 0.5 (0.17–1.46) \\
Use of azathioprine & 49/150 & 22/82 & 2.8 (1.13–6.93) \\
Anti-DNA antibodies & 107/150 & 55/82 & 0.99 (0.41–2.36) \\
Anti-Ro antibodies & 63/150 & 17/81 & 5.7 (1.64–19.78) \\
Anti-La antibodies & 29/150 & 11/81 & 0.52 (0.12–2.21) \\
Anti-RNP antibodies & 39/150 & 9/81 & 0.57 (0.17–1.89) \\
Anti-Sm antibodies & 32/150 & 1/81 & 16.64 (1.67–165.59) \\
Antiphospholipid antibodies & 70/149 & 35/81 & 1.44 (0.64–3.24) \\
Use of prednisone & 135/150 & 72/82 & 1.41 (0.42–4.68) \\
Use of azathioprine & 49/150 & 22/82 & 2.8 (1.13–6.93) \\
Use of cyclophosphamide & 37/150 & 26/82 & 0.5 (0.17–1.46) \\
Any use of tobacco & 61/150 & 23/82 & 1.99 (0.89–4.45) \\
Hypertension & 35/150 & 38/82 & 0.39 (0.17–0.87) \\
SDI<sub>0</sub> = 0 & 120/150 & 52/82 & Reference \\
SDI<sub>0</sub> = 1 & 25/150 & 17/82 & 0.69 (0.28–1.71) \\
SDI<sub>0</sub> ≥ 2 & 5/150 & 13/82 & 0.24 (0.01–1.08) \\
Cohort 1975–1985 & 21/150 & 13/82 & Reference \\
Cohort 1986–1995 & 55/150 & 48/82 & 1.29 (0.47–3.54) \\
Cohort 1996–2004 & 74/150 & 21/82 & 3.69 (1.09–12.5) \\

CNS: central nervous system; SDI<sub>0</sub>: Systemic Lupus International Collaborating Clinics damage index at six months after the diagnosis of lupus; OR: odds ratio; CI: confidence interval.

Results

Data on 232 patients were available in our database for this study. Thirty-four patients entered the cohort between 1975–1985, 103 between 1986–1995 and 95 between 1996–2004.

Two-hundred and four patients were women (88%) and 230 were white (99%). Mean age at T<sub>0</sub> was 36.2 (16) years. Average (standard deviation, SD) follow-up since T<sub>0</sub> was 10.6 (7) years.

One-hundred and fifty patients (64%) received antimalarials at any time during the course of SLE (62 hydroxychloroquine only, 46 chloroquine only and 42 both). Eighty-four patients (57%) started antimalarials at T<sub>0</sub>. Median time on antimalarials was 52 months (range 3–228). One-hundred and thirty-three patients (89% of patients ever receiving antimalarials) were treated for a period of at least 12 months.

Patients ever treated with antimalarials were younger at T<sub>0</sub> than never treated patients (mean age 34 versus 40 years, P = 0.003). Time of follow up was similar in both groups (mean 10.3 versus 11.3 years, P = 0.3).

Nineteen patients (8% of the cohort, 10 patients in the antimalarials group and nine patients in the non-antimalarials group) were lost, due to change of residence in all cases, after a mean (SD) follow-up of nine (6) years since T<sub>0</sub>. All patients were known to be alive at the time of leaving the cohort.

Clinical comparison of patients ever and never treated with antimalarials are shown in Table 1. Generally, patients in both groups were quite homogeneous. However, patients treated with antimalarials were more likely to suffer rash, had a higher incidence of anti-Ro and anti-Sm antibodies and received azathioprine more frequently. Hypertension was more prevalent in the untreated group. The proportion of patients in both groups with a SDI<sub>0</sub> of 0 or 1 was similar; less patients in the antimalarials group had a SDI<sub>0</sub> of 2 or higher, however the absolute number of patients with severe damage at six months was only 18. No differences were seen regarding other indicators of SLE severity, such as the presence of nephritis, neurological or pulmonary involvement, anti-DNA or aPL antibodies. Patients joining the cohort after 1995 were treated with antimalarials in a higher proportion.

Thrombosis

Eleven patients suffered a thrombotic event at T<sub>0</sub>. Thirty-seven patients suffered thrombosis after T<sub>0</sub> during the study time at risk: 32 patients had one episode of thrombosis whereas five suffered two episodes. Twenty-two events were arterial and 20 were venous.

Seven events (17%) happened while the patient was taking antimalarials. An additional seven thrombotic episodes (17%) took place after the patient had stopped antimalarials. The remaining 28 events (66%) occurred in 24 patients who had never received antimalarials.

There were 419 time intervals analysed (range per patient 1–8). The Cox multiple-failure time survival analysis showed that antimalarials were protective against thrombosis (HR 0.28, 95% CI 0.08–0.90), while aPL-positivity (HR 3.16, 95% CI 1.45–6.88) and thrombosis at T<sub>0</sub> (HR 3.85, 95% CI 1.50–9.91) increased the risk of subsequent thrombotic events. Aspirin had no effect (HR 1.14, 95% CI 0.59–2.22). Cox regression-estimated free-of-thrombosis survival

Table 1 Adjusted probability of receiving antimalarials according to variables included in the development of the propensity score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ever</th>
<th>Never</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>117/150</td>
<td>37/82</td>
<td>5.4 (2.38–12.24)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>86/150</td>
<td>49/82</td>
<td>0.92 (0.43–2)</td>
</tr>
<tr>
<td>Non-thrombotic CNS disease</td>
<td>19/150</td>
<td>9/82</td>
<td>2.75 (0.78–9.73)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>49/150</td>
<td>34/82</td>
<td>0.89 (0.33–2.46)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>16/150</td>
<td>9/82</td>
<td>0.78 (0.25–2.44)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27/150</td>
<td>24/82</td>
<td>0.64 (0.26–1.57)</td>
</tr>
<tr>
<td>Previous thrombosis</td>
<td>6/150</td>
<td>5/82</td>
<td>0.45 (0.16–1.24)</td>
</tr>
<tr>
<td>Anti-DNA antibodies</td>
<td>107/150</td>
<td>55/82</td>
<td>0.99 (0.41–2.36)</td>
</tr>
<tr>
<td>Anti-Ro antibodies</td>
<td>63/150</td>
<td>17/81</td>
<td>5.7 (1.64–19.78)</td>
</tr>
<tr>
<td>Anti-La antibodies</td>
<td>29/150</td>
<td>11/81</td>
<td>0.52 (0.12–2.21)</td>
</tr>
<tr>
<td>Anti-RNP antibodies</td>
<td>39/150</td>
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</tr>
<tr>
<td>Anti-Sm antibodies</td>
<td>32/150</td>
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<td>16.64 (1.67–165.59)</td>
</tr>
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<td>Use of prednisone</td>
<td>135/150</td>
<td>72/82</td>
<td>1.41 (0.42–4.68)</td>
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<tr>
<td>Use of azathioprine</td>
<td>49/150</td>
<td>22/82</td>
<td>2.8 (1.13–6.93)</td>
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<td>Use of cyclophosphamide</td>
<td>37/150</td>
<td>26/82</td>
<td>0.5 (0.17–1.46)</td>
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<td>Any use of tobacco</td>
<td>61/150</td>
<td>23/82</td>
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<tr>
<td>Hypertension</td>
<td>35/150</td>
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<td>0.39 (0.17–0.87)</td>
</tr>
<tr>
<td>SDI&lt;sub&gt;0&lt;/sub&gt; = 0</td>
<td>120/150</td>
<td>52/82</td>
<td>Reference</td>
</tr>
<tr>
<td>SDI&lt;sub&gt;0&lt;/sub&gt; = 1</td>
<td>25/150</td>
<td>17/82</td>
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</tr>
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<td>SDI&lt;sub&gt;0&lt;/sub&gt; ≥ 2</td>
<td>5/150</td>
<td>13/82</td>
<td>0.24 (0.01–1.08)</td>
</tr>
<tr>
<td>Cohort 1975–1985</td>
<td>21/150</td>
<td>13/82</td>
<td>Reference</td>
</tr>
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<td>74/150</td>
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<td>3.69 (1.09–12.5)</td>
</tr>
</tbody>
</table>
Mortality rates and causes of death

Twenty-three patients (9.9%) died during the study period. Cumulative 15-year survival of the entire cohort was 84%. Mean (SD) age at the time of death was 57.6 (20.4) years. Average (SD) follow-up time to death was 7.5 (4.2) years. Six patients (26%) died within the first five years of SLE course, nine patients (39%) between six and 10 years and eight (35%) between 11 and 15 years.

Nineteen of these 23 deaths (83%) occurred in the group of patients who had never received antimalarials, versus four (17%) in those ever treated with antimalarials ($P < 0.001$). Mean (SD) age at the time of death was not significantly different in both groups: 52.5 (18) versus 58.6 (21) years ($P = 0.59$). Likewise, mean (SD) follow-up to the time of death was similar in never and ever treated patients: 7.7 (4.1) versus 6.5 (5.1) years ($P = 0.60$). Causes of death are shown in Table 2. Overall, cardiovascular events were the most frequent causes of death, followed by cancer and infection. Miscellaneous included suicide in two patients. No patient died as a direct result of SLE activity. Remarkably, none of the patients treated with antimalarials died of cardiovascular complications.

Survival analysis

Kaplan–Meier survival curves are shown in Figure 2. Cumulative 15-year survival rate in the antimalarial group was 0.95, versus 0.68 in the non-antimalarial group ($P < 0.001$). Covariate balance was achieved within each quintile created across the range of propensity score. Stratification in quintiles was well balanced (data not shown). The HR for antimalarials users versus non-users was 0.13 (95% CI 0.04–0.39). After adjustment for age at $T_0$ and the propensity score it was virtually unchanged (0.14, 95% CI 0.04–0.48). Of note, the upper limit of the 95% CI indicates a mortality reduction of at least 50% among patients treated with antimalarials.

Discussion

This study supports the protective effect of antimalarials against thromboses in lupus patients. One of the main consequences of this protection could be the increased survival seen among patients treated with antimalarials, none of whom died of cardiovascular events, the leading cause of death in untreated patients.

Cardiovascular events are increasingly recognized as major prognostic markers in SLE. Recent studies have shown a higher frequency of both carotid plaque\textsuperscript{13} and coronary artery calcifications\textsuperscript{14} in lupus patients as compared with matched controls, a difference even more striking among patients younger than 40 years of age.\textsuperscript{13} Epidemiological studies have shown a marked increase of cardiovascular risk among young premenopausal women with SLE as compared with

Table 2 Causes of death by treatment group

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Antimalarials Ever ($n = 4$)</th>
<th>Antimalarials Never ($n = 19$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>0</td>
<td>7*</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

*Included arterial thrombosis ($n = 2$), heart failure ($n = 2$), sudden cardiac death ($n = 1$), valve disease ($n = 1$) and pulmonary hypertension ($n = 1$).
matched controls. Thus, it is not surprising that arterial thrombotic events are among the leading causes of death in most lupus cohorts.

The pathogenetic mechanisms underlying the increased cardiovascular morbidity are not completely elucidated. Traditional risk factors do certainly play an important role, yet a growing body of evidence points to the contribution of additional players. Among these, chronic inflammation is an important issue. The influence in the development of atherosclerosis of factors such as aPL, mannose-binding lectin polymorphisms and homocysteine levels is still debated. The effect of corticosteroids in atherosclerotic disease is difficult to establish. The balance between the intrinsic unfavourable properties of steroids and their beneficial effect as inhibitors of inflammation may explain the contradictory findings of different studies. APS is strongly linked to thrombosis in patients with SLE, and is consequently a major adverse prognostic factor.

In this setting, and beyond their complex immunomodulatory properties involving different phases of the immune response — such as the recently described inhibition of toll-like receptors pathways — the potential beneficial effects of antimalarials include protection against thrombosis and improvement of lipid profiles. In the 1970s and 1980s, antimalarials were used to prevent postoperative deep vein thrombosis. Hydroxychloroquine has shown to reduce the size and the time of persistence of aCL-induced clots in a mouse model and reverse in vitro platelet activation induced by aPL in a dose-dependent fashion. Antimalarials have also shown to ameliorate lipid profiles, decreasing total and LDL cholesterol, increasing HDL levels and, interestingly, being able to reverse the negative effect of corticosteroids on serum lipid levels.

Such potential beneficial effects has been translated into the clinical arena. Observational studies have suggested a reduction of thrombotic events in lupus patients treated with antimalarials. A recent cross-sectional study in patients with aPL has shown that patients treated with hydroxychloroquine were significantly less likely to suffer thrombotic events. However, other studies have not found such a clear association. All these observations could be biased by the potential influence of confounding variables as well as the fact that the time-varying nature of hydroxychloroquine exposure has not been taken into account.

In addition, the study by Roman et al. found a borderline inverse association between hydroxychloroquine use and the presence of carotid plaque. Results from two prospective lupus cohorts from Israel and USA have found that hydroxychloroquine users had a decreased damage accrual, which is a strong predictive factor for mortality in SLE. Thus, data suggest that antimalarials prevent lupus activity, thrombosis, atherosclerosis and damage accrual; it is therefore conceivable that they could also improve the survival of lupus patients.

Our data reinforce this hypothesis. A clear and independent reduction in mortality has been shown among those patients treated with antimalarials. A recent study performed in the LUMINA cohort has obtained remarkably similar results. In fact, no other drug has demonstrated such a long-term effect in SLE. Only trials focused on lupus nephritis have addressed short-term mortality, usually in the context of combined end-points.

Some limitations of this work must be taken into account. This is an observational cohort study, therefore treatment allocation was only based on the clinical judgement of the treating physician. As a result, any observed effect attributed to antimalarials can be biased by a number of confounders that influenced treatment indication. However, in the current state of knowledge, a placebo-controlled randomized trial would be unethical. Furthermore, the important contributions of observational cohorts studies with ‘real world’ patients with SLE have been recently emphasized by Urowitz and Gladman. In this setting, propensity score analysis, which allows adjustment for a number of observed variables that can influence the decision of treating a given patient, offers the best evidence possible.

It is obvious that propensity score analyses cannot account for those variables not included in the model and thus non-identified confounders may have still biased our results. One of these unidentified variables is the average SLE activity, estimated by tools such as the adjusted mean SLEDAI. which could not be calculated with the data contained in our database. Instead, we included in the calculation of the propensity score a set of variables related to disease severity and with known prognostic significance (Table 1), for which both groups were very homogeneous. Although it is conceivable that the differences we found are not entirely attributable to antimalarials, we believe they are too large to be fully explained by unidentified confounders.

A second potential drawback of this study is the variability in the exposure time to antimalarials (three to 228 months), which means that a substantial number of patients included in the antimalarials group only spent a fraction of their follow-up time being actually treated with these drugs. Bias in this case, though, would have tended to dilute drug effects rather than falsely increase differences between groups. In addition, as many as 9% of treated patients received antimalarials for more than 12 months, with a median time of antimalarial treatment of 52 months.
Another limitation is the homogeneity of our study population in terms of ethnicity, universal access to health facilities and relatively mild to moderate disease, a fact that may establish important differences with other groups. Yet, the similar results obtained in the LUMINA cohort, a US multiethnic population with more aggressive SLE than ours, support our conclusions.

Finally, the analysis of thrombotic events did not take into account several important variables (such as smoking, hypertension and hypercholesterolemia) for which time-dependent data were not available. As a group, patients receiving antimalarials were less likely to suffer from hypertension, however, smoking was more frequent among these patients (Table 1). Arterial and venous thrombosis could not be analysed separately due to sample size limitations.

It is noteworthy that, despite the efficacy data already available and the excellent safety profile of antimalarials, more than half lupus patients do not receive these drugs, maybe because they are prescribed for mild-moderate disease only. A good example is the last update of the Eurolupus cohort, which has shown that whilst 40.2% of patients were treated with antimalarials during 1990–1995, only 34.8% has shown that whilst 40.2% of patients were treated with antimalarials during 1990–1995, only 34.8% received chloroquine or hydroxychloroquine between 1995–2000.

As a conclusion, we believe that our results support the continued use of hydroxychloroquine in all lupus patients without known contraindications.

References