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Hydroxychloroquine Use is Associated with Lower Odds of Persistently Positive Antiphospholipid Antibodies and/or Lupus Anticoagulant in SLE

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Abstract

Objective—Antiphospholipid antibodies (aPL Abs) play an active role in the pathogenesis of the antiphospholipid syndrome (APLS). Primary prevention in APLS may be aimed at decreasing existing elevated aPL Ab levels, or preventing high aPL titers and/or lupus anticoagulant (LAC) from developing in the first place. Hydroxychloroquine (HCQ) has been shown to decrease aPL titers in laboratory studies, and to decrease thrombosis risk in systemic lupus erythematosus (SLE) patients in retrospective studies. We investigated an association between HCQ use and persistent aPL Abs and/or LAC in SLE.

Methods—We identified all patients over 21 years old with SLE, from an urban tertiary care center, who had aPL Abs and LAC measured on at least 2 occasions, at least 12 weeks apart. We defined the presence of persistent LAC+ and/or at least one aPL Ab ≥ 40 units (IgA, IgG or IgM) as the main outcome variable.

Results—Among 90 patients included in the study, 17 (19%) had persistent LAC+ and/or at least one aPL Ab ≥ 40 units. HCQ use was associated with significantly lower odds of having persistent LAC+ and/or aPL Abs ≥ 40 U, OR 0.21 (95% CI 0.05, 0.79) $p=0.02$, adjusted for age, ethnicity, and gender.

Conclusion—This is the first study to show that HCQ use is associated with lower odds of having persistently positive LAC and/or aPL Abs. Data from this study provides a basis for the design of future prospective studies investigating the role of HCQ in primary and secondary prevention of APLS.

Key Indexing Terms

Lupus Erythematosus, Systemic; Antiphospholipid Antibodies; Lupus Anticoagulant; Hydroxychloroquine

Introduction

According to the two-hit hypothesis, the presence of antiphospholipid antibodies (aPL Abs) is necessary to create a prothrombotic state (1st hit). However, aPL Abs alone are not sufficient, and may persist for a long time before the 2nd hit results in the actual thrombotic

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event (1, 2). Therefore, primary thrombosis prevention may be aimed at decreasing existing elevated aPL Abs, or preventing high aPL titers and/or lupus anticoagulant (LAC) from developing (3).

Hydroxychloroquine (HCQ) has been shown to decrease aPL titers in laboratory studies (4, 5). However, only one published study to date evaluated the association between HCQ and aPL Abs in a secondary analysis with a negative result (6). We investigated whether SLE patients treated with HCQ were less likely to develop or to maintain persistently positive aPL Abs and/or LAC.

Materials and methods

We included all adult patients with SLE by ACR criteria (7) who had LAC, anticardiolipin (aCL), anti-beta2 glycoprotein I (anti-b2GPI), and antiphosphatidylserine (aPS) antibodies measured at least twice, at least 12 weeks apart, between January 2006 and May 2012 at Montefiore Medical Center (MMC), a large urban tertiary care center in Bronx, NY.

Patients were considered to be on a medication (immunosuppressives, aspirin, HCQ, prednisone, or anticoagulation) if they were ever on this medication, similar to previous retrospective studies (6, 8). Race and ethnicity were analyzed as African-American/non-African-American and Hispanic/non-Hispanic, respectively, based on self report. Over 90% of non-Hispanics were African-American, reflecting the overall racial/ethnic distribution in our center.

aPL Abs were tested using EIA kits (BIO-RAD Laboratories, Hercules, CA). Moderate to high aPL Ab positivity (aPL+) was defined as at least one aPL Ab (IgG, IgM or IgA) ≥ 40 units ("moderate/high") (10). LAC was reported as positive or negative (LAC+/LAC-) by the MMC laboratory in accordance with the guidelines of the International Society on Thrombosis and Hemostasis (9).

Because of the retrospective nature of this study, we did not obtain informed consent from the patients, as no identifying information was stored or used in the data analysis. This project was approved by the Institutional Review Board at the Albert Einstein College of Medicine/MMC.

Statistical analysis was performed using the STATA 12.0 software package (StataCorp, College Station, Tx). No adjustments were made for multiple comparisons in this exploratory study.

Results

The frequencies of aPL and/or LAC among 90 patients included in the study are shown in Table 1. The number of patients who converted from aPL and/or LAC positive to negative, or from negative to positive, was small.

The results of the bivariate comparisons between patients with persistently positive LAC and/or any aPL ≥ 40 U (n=17), and patients with either transiently positive or persistently negative LAC and aPL (n=73) are summarized in Table 2. The two groups were similar with respect to age, gender, co-morbidity scores, HCQ duration, and disease duration. HCQ use was lower in the persistent aPL/LAC positive group than in the comparison group, 11 (65%) and 65 (89%), respectively, $p=0.02$. The median (IQR) duration of HCQ use was 49 (31, 61) months in the aPL/LAC positive group, and 36 (19, 56) months in the comparison group, $p=0.6$. The minimum duration on HCQ was over 1 month.

The results of the logistic regression adjusted for age, ethnicity, and gender are shown in Table 3. HCQ use was associated with significantly lower odds of having persistent LAC+ and/or aPL Abs 40 U (IgA, IgG or IgM), OR 0.21 (95% CI 0.05, 0.79) $p=0.02$. We did not observe an association between use of other immunosuppressives or prednisone and persistent LAC+ and/or aPL Abs 40U. Adding these variables to the above model did not change the association between HCQ and LAC/aPL Abs. Age and gender were not independently associated with persistent LAC/aPL Abs.

Similarly, persistently positive LAC and/or moderate/high Sapporo criteria aPL Abs (aCL IgG or IGM, or anti-b2GPI IgG or IgM) (10) were associated with HCQ use, OR 0.24 (0.06, 0.94), $p=0.04$, and Hispanic ethnicity, OR 4.2 (1.0, 16.7), $p=0.04$ (Table 3).

We performed additional analyses to explore a possibility of “by indication” bias with respect to HCQ use in our study, i.e. if HCQ is prescribed for milder SLE, the differences observed in our study may be confounded by SLE severity and multiple co-morbidities. When we compared patients on HCQ (HCQ+) with patients not on HCQ (HCQ-), no differences were observed with respect to demographics, disease duration, Charlson Co-morbidity Score (11), or medications. When we limited our analysis to a subgroup of SLE patients who were not on immunosuppressives, presuming less severe SLE ($n=49$), HCQ was associated with the OR (95%CI) of 0.17 (0.03, 0.88), $p = 0.03$ of LAC+ and/or Sapporo criteria aPL Abs 40 units, suggesting that HCQ was independently associated with LAC/aPL positivity.

Discussion

HCQ treatment is currently recommended for SLE patients with persistent moderate-high aPL Ab or LAC+ for primary prevention (grade 1B to 2B recommendation) based on the other beneficial effects of HCQ in SLE (12, 13) and thrombosis (14). However, this is the first study to show that HCQ use may be associated with lower odds of having persistently positive LAC and/or aPL Abs in SLE, and, therefore, may be beneficial in primary prevention.

We also showed that Hispanic ethnicity was associated with higher odds of persistent Sapporo criteria aPL Abs and/or LAC compared with non-Hispanics (predominantly African-Americans). While it was previously reported that LAC was more prevalent in Caucasians (15), the association between Hispanic ethnicity and the higher odds of positive aPL and/or LAC has not been previously reported. It is likely that aPL Abs are affected by multiple demographic and SLE-specific factors. Therefore, further studies are needed to investigate the cumulative effect of protective factors and risk factors on developing and maintaining LAC+ and/or elevated aPL Abs.

This exploratory study has several limitations related to its retrospective design and the sample size, including differential selection, differential and non-differential misclassification, disease activity, and medication dosage, duration and compliance. However, we included only patients who satisfied ACR criteria for SLE, and performed several sensitivity analyses with consistent results. Most importantly, the causal relationship between HCQ use and aPL/LAC positivity could not be established in this cross-sectional study. However, while our study was not designed or powered to evaluate whether HCQ decreased aPL Ab levels, the information learned from this study may be used to design prospective studies to evaluate this important question.

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Table 1

The frequencies of aPL/LAC positivity in the entire cohort (n=90)

	At the time of the first measurement n (%)	At the time of the last measurement n (%)	At the time of both first and last measurements n (%)
LAC+ and/or at least one aPL Ab 40 U	25 (28)	20 (22)	17 (19)
LAC+ and APL 40 U	7 (8)	4 (4)	4 (4)
LAC- and APL 40 U	6 (7)	2 (2)	1 (1)
LAC+ and APL < 40 U	1 (1)	3 (3)	1 (1)
LAC unknown and APL 40 U	11 (12)	11 (12)	7 (8)
LAC unknown and aPL < 40 U	37 (41)	28 (31)	24 (27)
At least one aPL Ab 40 U	24 (27)	17 (19)	16 (18)
At least 2 aPL Abs 40 U	18 (20)	11 (12)	10 (11)
Triple positive (LAC+, and b2GPI IgG or IgM 40 U, and aCL IgG or IgM 40 U)	7 (8)	3 (3)	3 (3)
Sapporo criteria using moderate/high titers: LAC+, and/or aCL IgG or IgM 40 U, and/ or b2GPI IgG or IgM 40 U	24 (27)	17 (19)	14 (16)

Table 2

Baseline Characteristics of the Study Patients *

	Persistent LAC and/or aPL Ab 40 U n = 17	LAC and aPL transiently positive or negative n = 73	p-value
Age at last aPL/LAC, mean (SD)	41 (16)	39 (13)	0.80
n (%) female	14 (83)	69 (95)	0.12
Race, n (%) African-American **	3 (27)	41 (64)	0.02
Ethnicity, n (%) Hispanic	12 (75)	32 (46)	0.03
Hydroxychloroquine, n (%)	11 (65)	65 (89)	0.02
Aspirin, n (%)	6 (35)	14 (19)	0.29
Prednisone, n (%)	11 (65)	60 (83)	0.10
Immunosuppressives, n (%)	5 (29)	35 (49)	0.18
Anticoagulation ever for arterial or venous thrombosis or for pregnancy complication, n (%)	7 (41)	13 (18)	0.02
Duration on HCQ, months, median (IQR)	49 (31, 61)	36 (19, 56)	0.38
Time between first and last aPL/LAC measurement, months, median (IQR)	18 (9, 42)	25 (13, 38)	0.60
Charlson co-morbidity, median (IQR)	4.0 (2.0, 7.0)	5.0 (2.0, 7.0)	0.81

* P values in bold typeface indicate statistical significance.

** Race information not available for 15 patients.

Table 3

Logistic regression for persistent LAC+ and/or aPL 40 (IgA, IgG, or IgM) and for persistent positive LAC and/or Sapporo criteria aPL (aCL or b2GPI IgG or IgM) 40 U *

LAC+ and/or aPL 40 (IgA, IgG, or IgM) *			
	OR	95% CI	p-value
Hydroxychloroquine use	0.21	0.05, 0.79	0.02
Age at last follow-up	1.0	0.96, 1.0	0.94
Male Gender	2.3	0.34, 14.4	0.40
Hispanic ethnicity	3.1	0.84, 11.4	0.09
LAC+ and/or Sapporo criteria aPL (aCL or b2GPI IgG or IgM) 40 U			
Hydroxychloroquine use	0.24	0.06, 0.94	0.04
Hispanic ethnicity	4.2	1.0, 16.7	0.04

* P values in bold typeface indicate statistical significance.