Original article

Whole blood drug levels do not correlate with QTc intervals in hydroxychloroquine-treated systemic lupus erythematosus patients

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Abstract

Objectives. HCQ is recommended for all patients with SLE, but reports of cardiac toxicity in severe acute respiratory syndrome coronavirus 2 patients raised concerns. We aimed to study the relationship between HCQ blood levels and QTc intervals.

Methods. A retrospective review of 90 SLE patients (cohort 1) was conducted with data collected regarding demographics, QTc interval and chronic kidney disease (CKD). A prospective study of 84 SLE patients (cohort 2) was conducted with data collected regarding demographics, dose of HCQ, duration of HCQ treatment, presence of echocardiographic abnormalities and CKD simultaneous with whole blood HCQ levels measured by HPLC. Statistical analysis utilized one-way analysis of variance, Pearson's correlation coefficient and t tests.

Results. In cohort 1 there was no significant difference in mean QTc based on 75 HCQ-treated [437.91 msec (S.D. 20.02)] as compared with 15 untreated patients [434.6 msec (S.D. 27.49)]. In patients with CKD, the mean QTc in HCQ users [448 (S.D. 23.37)] as compared with non-users [444.5 msec (S.D. 24.61)] also had no significant difference. In cohort 2, HCQ levels did not correlate with QTc interval ($r = 0.017$) and this applied regardless of the dose prescribed ($r = 0.113$ for 400 mg and $r = 0.06$ for 200 mg), duration of exposure ($P = 0.36$ for 0–5, >5–10 or >10 years), CKD ($r = 0.482$) or underlying cardiac abnormalities ($r = 0.430$).

Conclusions. This is the first study relying on measured blood levels demonstrating the absence of a clinically consequential increase in QTc levels in HCQ-treated SLE patients.

Key words: SLE, HCQ, QTc interval, cardiac arrhythmia, torsades de pointes

BASIC SCIENCE

> **Rheumatology key messages**
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> - Hydroxychloroquine is the standard of care for SLE and is infrequently associated with major cardiovascular toxicities.
> - This is the first study to measure whole blood hydroxychloroquine and demonstrate the absence of an effect on the QTc interval.
> - Findings support avoiding delay or interruption of hydroxychloroquine treatment due to a concern for arrhythmia.

Introduction

HCQ is an antimalarial with immunomodulatory, anti-inflammatory and antithrombotic effects recommended as the standard of care for all patients with SLE. Prescribing HCQ as background medication regardless of SLE disease severity or activity is warranted based on several clinically meaningful benefits, including reduced disease flares, improved rates of renal response when combined with mycophenolate, lower risks of thrombotic events, reduced complications of pregnancy, improved glycemic and lipid management and reduced mortality [1–4]. Prior to 2020 and reports of cardiac toxicity, including prolonged QTc intervals, associated with HCQ use for severe acute respiratory syndrome coronavirus 2 infection, the rare reports of ventricular arrhythmias in SLE patients were not of concern to treating rheumatologists.

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The medical literature, including a December 2021 ACR white paper on antimalarial cardiac toxicity, has identified risk factors for conduction abnormalities with HCQ treatment, including the presence of chronic kidney disease (CKD), older patient age, underlying cardiomyopathy and the use of concomitant QTc prolonging agents [5–7]. However, the reports of the most serious ventricular arrhythmia, torsades de pointes (TdP), were limited to rare cases of intentional overdose or the use of high doses in the setting of renal failure [8–14]. The issue of increased risk of arrhythmias even when combined with other drugs known to prolong the QTc interval also had not been considered sufficiently impactful for lupus patients requiring providers to interrupt or discontinue HCQ treatment. In reality, however, there are limited data on the relationship between HCQ and QTc interval. Moreover, in prior studies, HCQ exposure was based exclusively on the dose as prescribed in medical or pharmacy records, which do not account for patient nonadherence and there are no studies in the literature relying on measured drug levels to reliably quantify HCQ in relationship to QTc interval. For example, Costadoat et al. [15] reported that in 85 patients with their medical chart indicating HCQ prescribed for a connective tissue disease, the QTc intervals were no different than control values. More recently, Lo et al. [16], relying on a retrospective analysis of a longitudinal health insurance database in Taiwan, found when comparing 3575 patients with SLE, SS or RA prescribed HCQ to 3575 propensity matched autoimmune rheumatic disease patients untreated with HCQ, that there was no increase in risk of ventricular arrhythmia, regardless of the duration of treatment or dose. Cardiovascular safety of HCQ was also reported in US veterans with RA, as the incidence of long QT syndrome and arrhythmia-related hospitalization was equally low in 4426 RA patients started on HCQ and in 4426 propensity matched RA patients treated with other nonbiologic conventional disease-modifying agents followed for up to 12 months after therapy initiation from December 2018 to December 2019 [17].

We report on two cohorts exploring the relationship between HCQ and QTc interval. First, in a retrospective study of 90 SLE patients, we compared the QTc interval in 75 HCQ-treated patients vs 15 untreated patients and in relation to the presence or absence of CKD. In the second cohort of 84 patients, we prospectively investigated the association between whole blood HCQ levels and QTc intervals measured on simultaneous EKGs performed during a routine visit. In the second cohort, we also explored the effect of prescribed HCQ dose, duration of HCQ exposure, CKD, underlying cardiac disease and the use of concomitant QTc prolonging agents.

Methods

In cohort 1 we conducted a retrospective review using Epic electronic medical records (EMRs) of 90 SLE patients fulfilling 1997 ACR or 2012 SLICC criteria in a faculty practice at NYU Langone Health between 12 March 2020 and 1 May 2020. Data were collected on demographics, availability in EMRs of an EKG, QTc as the average of the first and, if more than one, last EKG with prolonged QTc, defined as >450 msec in males and >470 msec in females, and severe prolongation, defined as >500 msec irrespective of gender, creatinine and presence of CKD, defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2. The institutional review board (IRB) did not require specific consent as covered by general treatment permission at NYU Langone Health and all patients were deidentified. In cohort 2 we conducted a prospective study, approved by the NYU Langone Health IRB and all patients provided written informed consent. At the time of data lock, 84 patients fulfilled the 1997 ACR or 2012 SLICC criteria for SLE and were prescribed HCQ for at least 3 months at doses used for standard-of-care treatment. Data were collected on demographics; dose of prescribed HCQ; duration of HCQ use; presence of echocardiogram in EMRs with abnormalities defined as left ventricular hypertrophy, left ventricular ejection fraction <50%, pulmonary hypertension and valve abnormalities; creatinine and CKD defined as for cohort 1 and concomitant use of QTc prolonging agents including ciprofloxacin, levofloxacin, doxepin, albuterol, duloxetine, citalopram, quetiapine, hydroxyzine, metoclopramide and risperidone. HCQ whole blood levels were measured by HPLC and EKGs were simultaneously obtained during a routine outpatient faculty practice visit for patients consecutively seen between 5 February and 10 May 2021 by the senior author. Statistical analyses were performed using one-way analysis of variance, Pearson's correlation coefficient and t-tests.

Results

In the retrospective study, 90/194 patients had at least one EKG. Of these 90 patients, 91% were female, 32.2% were African American, 6.6% Asian, 38.8% Caucasian, 20% Hispanic and 2.2% other (Table 1). Seventy-five were treated with HCQ and 15 were not. There was no significant difference in mean QTc based on 75 HCQ-treated [437.91 msec (S.D. 20.02)] vs 15 untreated [434.6 msec (S.D. 27.49)] patients (Table 2). The QTc interval was prolonged in 8/75 patients (11%) on HCQ and 1/15 patients (7%) without HCQ, with no significant difference in mean QTc interval based on HCQ exposure (P = 0.586) (Table 2). In the 23 patients with CKD, QTc was prolonged in 4/19 (21%) on HCQ and 0/4 (0%) without CKD, and again there was no significant difference in mean QTc interval based on HCQ use (P = 0.784) (Table 2). Severe prolongation of the QTc interval was also not significantly different among the four groups (i.e. HCQ treated or untreated or with or without CKD). None of the patients had a documented tachyarrhythmia or TdP.

TABLE 1 Demographics of cohort 1 and 2 patients, including mean HCQ levels

Demographics	Cohort 1 patients (N = 90), n (%)	Demographics	Cohort 2 patients (N = 84), n (%)	HCQ, ng/ml, mean (S.E.M.)	P-value
Gender		Gender			
Female	82 (91)	Female	78 (93)	1006.5 (74.9)	0.93
Male	8 (9)	Male	6 (7)	980.7 (200.6)	
Race		Race			
African ancestry	38 (42)	African ancestry	29 (35)	1212.5 (142.1)	0.08
Asian ancestry	6 (7)	Asian ancestry	15 (18)	1011.1 (134.7)	
European ancestry	44 (49)	European ancestry	40 (47)	864.8 (89.4)	
Other	2 (2)				
Ethnicity		Ethnicity			
Non-Hispanic	72 (80)	Non-Hispanic	63 (75)	963.7 (121.9)	0.11
Hispanic	18 (20)	Hispanic	21 (25)	727.5 (126.8)	

There were no significant differences between any of the groups.

TABLE 2 QTc level by HCQ exposed and unexposed

Total (n = 90)	HCQ (n = 75)	No HCQ (n = 15)	P-value
Prolonged QTc, n (%)	8 (10.6)	1 (6.6)	
Severely prolonged QTc, n (%)	3 (4)	1 (6.6)	
QTc, msec, mean (S.D.)	437.91 (20.02)	434.6 (27.49)	0.5859
CKD (n = 23)	HCQ (n = 19)	No HCQ (n = 4)	P-value
Prolonged QTc, n (%)	4 (21)	0 (0)	
Severely prolonged QTc, n (%)	3 (15.8)	1 (25)	
QTc, msec, mean (S.D.)	448.11 (23.37)	444.5 (24.61)	0.7844

Prolonged and severely prolonged QTc interval not significantly greater in HCQ-treated (n = 75) compared with untreated (n = 15) patients regardless of the presence of CKD.

The prospective study included 84 patients: 93% female, 47% European, 35% African American, 15% Asian and 25% Hispanic (Table 1). For all studied HCQ samples (i.e. total of 86, as 2 of the 84 patients were studied twice) there was no correlation between the whole blood level and the QTc interval ($r = 0.017$, $P = 0.87$) (Fig. 1). SLE patients with high HCQ levels >2000 ng/ml (as shown on the x-axis in Fig. 1) had QTc intervals similar to patients with low HCQ levels <500 ng/ml. The absence of correlation between whole blood HCQ level and QTc interval applied whether the patient was prescribed HCQ at a dose of 200 mg ($n = 22$; $r = 0.113$, $P = 0.61$) or 400 mg ($n = 51$; $r = -0.06$, $P = 0.65$) (Fig. 2). There were no significant differences in mean QTc interval between patients treated for periods of <5 years, >5–10 years or >10 years ($P = 0.3$) (Table 3). There was no correlation between blood HCQ levels and QTc intervals in patients who had CKD (defined as eGFR <60 ml/min/1.73 m^2; $r = -0.482$, $P = 0.09$) or those with underlying cardiac abnormalities noted on transthoracic echocardiogram ($r = -0.430$, $P = 0.16$) (Fig. 3). However, there was a positive correlation between blood HCQ levels and QTc intervals in patients who were on concomitant QTc prolonging agents ($r = 0.795$, $P = 0.005$), but none in excess of 456 msec (Fig. 3).

Discussion

HCQ has both beneficial and deleterious cardiovascular effects. Antimalarial drugs have antiatherogenic and thromboprotective benefits that can reduce major adverse cardiovascular events such as myocardial infarction, cardiovascular death and ischemic stroke in SLE and RA patients [18]. On the other hand, these medications interfere with cardiac ion channels and may have a paradoxical effect on the risk for atrial as opposed to ventricular arrhythmia, including TdP. For example, in a recent study, authors reported on 1647 SLE patients—917 HCQ users and 730 nonusers—and found an 88% decrease in the risk of incident atrial fibrillation with antimalarial exposure [19].

The mechanism by which HCQ prolongs the QTc interval is not fully established. In an animal model, HCQ had inhibitory effects on cardiac ion channels, resulting in delayed depolarization and repolarization of guinea pig cardiocytes [20]. Although these effects on myocytes

Fig. 1 QTc correlation with HCQ whole blood level
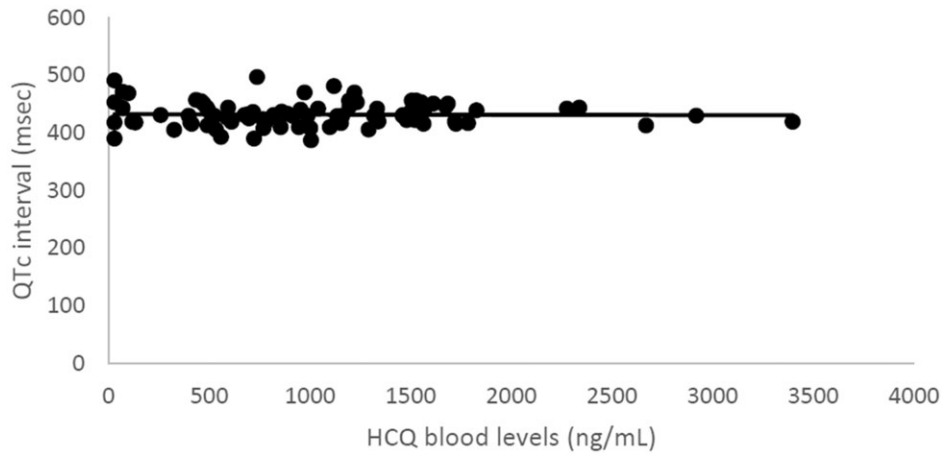
No correlation ($r = 0.017$, $P = 0.87$) between whole blood HCQ and QTc interval ($n = 86$ HCQ samples with 2/84 patients studied twice).

**Fig. 2** QTc correlation between HCQ 200 and 400 mg dosing
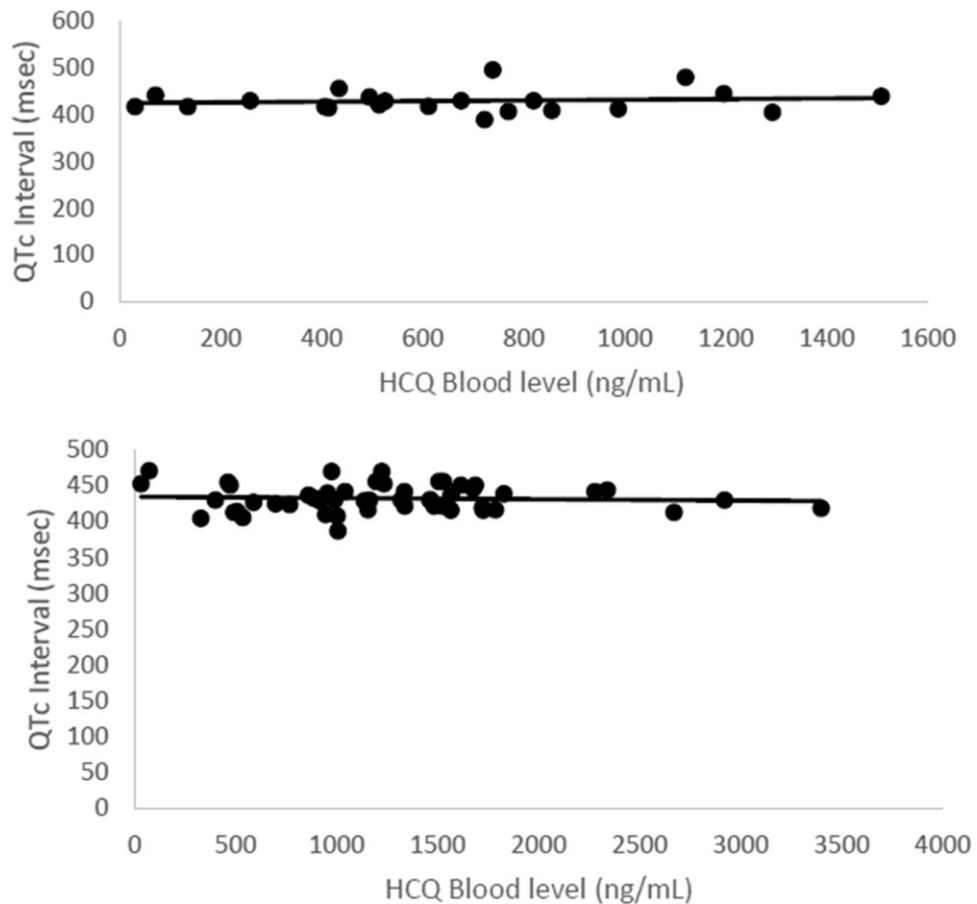
(Upper panel) No correlation ($r = 0.113$, $P = 0.61$) between blood HCQ level and QTc interval in patients on HCQ 200 mg ($n = 22$). (Lower panel) No correlation ($r = 0.06$, $P = 0.65$) between blood HCQ level and QTc interval in patients on HCQ 400 mg ($n = 51$)

TABLE 3 QTc interval by duration of HCQ exposure

Duration of exposure (years)	N	QTc interval, msec, mean (S.D.)	HCQ level, ng/ml, mean (S.D.)
0–5	21	428 (14)	1385 (692)
>5–10	22	428 (19)	1099 (733)
>10	43	435 (25)	769 (493)

Mean QTc interval and whole blood level not significantly different based on 0–5, >5–10 or >10 years of exposure ($P = 0.3$).

FIG. 3 QTc correlation with CKD, cardiac disease or concurrent QTc prolonging agents
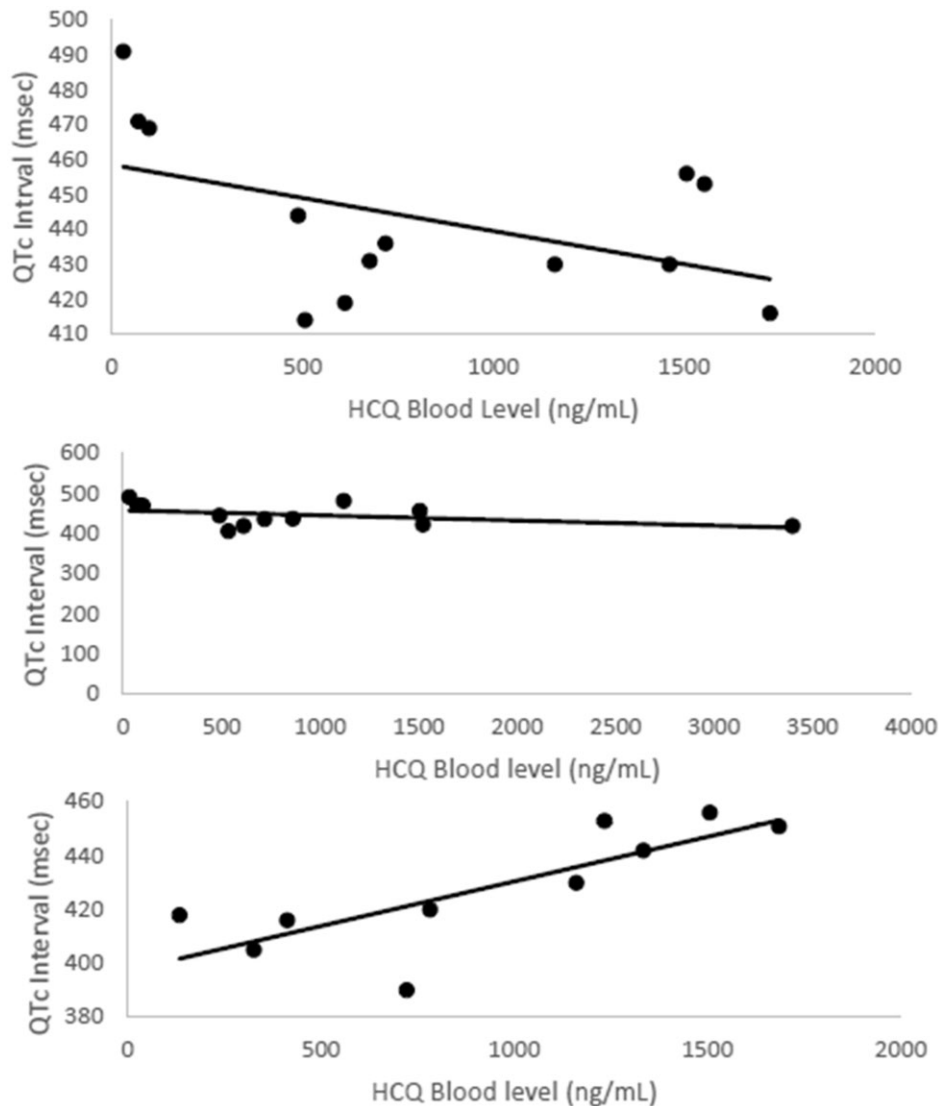
Whole blood HCQ level and QTc interval. (Upper panel) No correlation ($r = 0.482$, $P = 0.09$) in patients with CKD ($n = 13$). (Middle panel) No correlation ($r = 0.430$, $P = 0.16$) in patients with abnormal transthoracic echocardiograms ($n = 12$). (Lower panel) Positive correlation ($r = 0.430$, $P = 0.16$) in patients ($n = 10$) receiving QTc prolonging agents (i.e. one each ciprofloxacin, levofloxacin, doxepin, albuterol, risperidone, duloxetine, escitalopram, quetiapine, hydroxyzine and metoclopramide) but none severely prolonged in excess of 500 msec.

could increase the QTc interval and risk for ventricular arrhythmia such as TdP, as mentioned, they may also have a protective effect on atrial arrhythmia.

In both the retrospective cohort of 90 and prospective cohort of 84 SLE patients, HCQ was not associated with clinically meaningful effects on the QTc interval. In the retrospective cohort, at least one EKG was available in 90/196 (46%) records reviewed and there was no significant difference in mean QTc between the 75 HCQ-treated and 15 untreated patients. Although patients in the retrospective cohort with CKD were more likely to have prolonged QTc when compared with those without CKD, there was no significant difference in the mean QTc based on HCQ use as well in this subset. Severe prolongation of QTc was rare in all groups and no episodes of serious tachyarrhythmia or TdP were observed. The prospective cohort is the first published study relying on measured blood levels of HCQ to quantify cardiac ion channel exposure to the drug. The absence of correlation between the measured blood level of HCQ and QTc interval was the case regardless of the dose prescribed, duration of exposure, CKD or underlying cardiac abnormalities. The lower mean HCQ level in patients treated for >10 years is best explained by provider's awareness that HCQ toxicities (i.e. maculopathy, neuromyopathy and cardiac) increase with the duration of HCQ exposure and the practice after 7 years of not prescribing doses >5 mg/kg/day, which is typically 200–300 mg/day, whereas early in the course of lupus treatment the default dosing, regardless of body weight, is 400 mg. There was a positive correlation between blood HCQ levels and QTc intervals in patients on concomitant QTc prolonging agents, but none were severely prolonged (e.g. >500 msec). This is the first study relying on measured blood levels demonstrating the absence of a consequential increase in QTc levels in HCQ-treated SLE patients.

Limitations of the study include the modest sample size in both cohorts, absence of information regarding the use of QTc prolonging medications in the retrospective cohort and the small numbers of patients with concurrent QTc prolonging agents in the prospective cohort. The retrospective cohort has the potential for selection bias, but here the availability of an EKG in the 46% of records studied favors more likely, than less likely, a clinical concern for heart disease and cardiac toxicity as compared with lupus patients in whom no EKG was performed. Additionally, determining the presence of underlying cardiovascular disease in the prospective cohort was limited to echocardiograms and was available for only 12 patients. Details regarding SLE disease severity or activity and concurrent DMARD use were unavailable for both cohorts.

Several studies have demonstrated the benefits of measuring HCQ levels with a goal of improving adherence and achieving therapeutic targets that can improve outcomes [21, 22]. Our findings provide the most direct confirmation of HCQ safety with regards to arrhythmia by relying on measurement of the drug in the patient's blood, eliminating concerns such as adherence with prescribed doses. Furthermore, these findings support the current standard of care that does not require baseline or serial EKG determination of QTc intervals during routine use of HCQ for lupus patients. Future studies can focus on the potential role of disease activity as well as cohorts of elderly patients with underlying cardiac disease and concurrent use of QTc prolonging medications to determine whether there are subgroups of greater concern that would benefit from EKG monitoring of the QTc interval. Additionally, this work relates to the issue of HCQ-related acquired cardiac ion channel disruption and the risk for acute ventricular arrhythmia but does not address the issue of drug-induced cardiomyopathy and heart failure that is the result of HCQ interference with lysosomal autophagic function resulting in cardiocyte accumulation of metabolites that interfere with normal cellular function [23]. Moreover, the relationship between the acute effect of HCQ on cardiac ion channels and cardiomyopathy is uncertain and requires more studies. In conclusion, this study adds to the data that are reassuring regarding the absence of clinically consequential risk for malignant ventricular arrhythmias such as TdP in HCQ-treated SLE patients.

Data availability statement

Data are available upon request to the corresponding author.

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