Electrocardiogram abnormalities related to anti-malarials in systemic lupus erythematosus

T.K. McGhie[1], P. Harvey[2], J. Su[1], N. Anderson[1], G. Tomlinson[3], Z. Touma[1]

[1]University of Toronto Lupus Clinic, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, Ontario, Canada; [2]Women's College Research Institute, Women's College Hospital, Department of Medicine, University of Toronto, Ontario, Canada; [3]Department of Medicine, University Health Network and Mount Sinai Hospital, and Institute of Health Policy, Management and Evaluation, University of Toronto, Ontario, Canada.

Abstract

Objective

Cardiotoxicity with potential conduction/structural abnormalities on electrocardiogram (ECG) have been reported with anti-malarial (AM). We aimed to study whether cumulative AM is associated with ECG abnormalities.

Methods

A standard resting supine ECG was performed on consecutive patients attending the Lupus Clinic since 2012. ECG abnormalities were grouped into structural [left ventricular hypertrophy or atrial enlargement] and conduction abnormalities [prolonged corrected QT interval (QTc), short PR interval, left bundle branch block (LBBB), right bundle branch block (RBBB) and atrioventricular block (AVB), bradycardia, tachycardia, premature atrial complex, ectopic atrial rhythm, atrial fibrillation, premature ventricular complex and ventricular bigeminy]. Associations between cumulative AM and ECG abnormalities (structural or conduction) were assessed using logistic regression analysis (after adjusting for baseline patient characteristics) and in a nested case-control study (1:3).

Results

Of 453 patients treated with AM, the median cumulative AM was 1207 grams at ECG. Conduction abnormalities were more prevalent than structural abnormalities, 71 (15.7%) vs. 58 (12.8%). AM cumulative dose did not show a statistical significant association with ECG structural abnormalities, (OR 1.82, p=0.07) while it was protective for conduction ECG abnormalities (OR 0.42, p=0.006). The nested case-control analysis also found that AM cumulative dose is protective against conduction ECG abnormalities (OR 0.36, p=0.0007). SLE duration was a risk factor for both structural and conduction ECG abnormalities.

Conclusion

This study suggests an association between cumulative AM dose above the median (1207 g) and structural ECG abnormalities. More importantly, cumulative AM decreases the odds of ECG conduction abnormalities.

Key words

anti-malarial, hydroxychloroquine, systemic lupus erythematosus, electrocardiogram, cardiac arrhythmias, cardiotoxicity, structural abnormalities

Taneisha K. McGhie, BSc, MBBS, DM
Paula Harvey, BMBS, PhD, FRACP, Assoc. Prof.
Jiandong Su, MSc, BMSc, BSc
Nicole Anderson
George Tomlinson, MSc, PhD
Zahi Touma, MD, PhD, FACP, FACR, Assist. Prof.

Please address correspondence to:
Dr Zahi Touma,
University of Toronto Lupus Clinic
Centre for Prognosis Studies in the Rheumatic Diseases,
Toronto Western Hospital, EW, 1-412,
399 Bathurst Street,
M5T 2S8 Toronto (Ontario), Canada,
E-mail: zahi.touma@uhn.ca

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Introduction

Anti-malarials (AM), such as hydroxychloroquine (HCQ) and chloroquine (CQ), have long been used for the treatment of systemic lupus erythematosus (SLE). HCQ is preferred to CQ because of the lower incidence of adverse retinal effects (1, 2). The current treatment paradigm is to place all patients with SLE on HCQ unless contraindicated. This is based on a large body of evidence supporting a myriad of benefits including improvement of survival rates, prevention of lupus flares (3-5), prevention of renal damage (6) and prevention of central nervous system lupus (4, 5, 7). HCQ also reduces certain traditional cardiovascular risk factors including hyperlipidaemia and hyperglycaemia and has been found to be antithrombotic (1, 8).

HCQ, as the name implies, is identical to the CQ compound apart from the presence of a hydroxyl group at the end of the side chain. It is thought that hydroxychloroquine sulphate is less toxic and has at least the same efficacy as CQ. Thus, currently, HCQ is more often used. However, despite their general safety, both drugs have the potential to cause serious toxicity. These drugs have significant lysosomal affinity and induce the prominent development of autophagic vacuoles in several tissues (9). Anti-malarials are stored long-term in varying concentrations as intracellular deposits in the eye, skin, skeletal muscle, liver, kidneys, lungs, and cardiac tissue and have major inhibitory effects on lysosomal function (10). Though retinal toxicity (11-13) is the most recognised and discussed adverse effect, others include vacuolar neuromyopathy (14-16), and cardiomyopathy (17-23).

The first case of chronic cardiac toxicity due to an antimalarial agent was reported in 1971 and since then several cases of concentric hypertrophy (biatrial enlargement and biventricular hypertrophy) with restrictive features and conduction abnormalities with or without congestive heart failure or atrioventricular block (AVB) have been attributed to this class of drugs (24, 25). Also such structural abnormalities have been demonstrated in the absence of conduction abnormalities (26). Heart conduction disorders, including bundle-branch block, incomplete or complete AVB, QT-prolongation and consequent torsades de pointes have been observed among patients treated with HCQ and CQ (27-30). Antimalarial cardiotoxicity may be of particular importance in patients with SLE, given their already increased cardiac risk because of primary heart disease and accelerated atherosclerosis (31). Additionally, inflammation and immunity have been increasingly recognised as novel factors crucially involved in modulating ventricular repolarisation (32). For instance, data obtained from large SLE cohorts found a 7–15% incidence of QTc prolongation with a significant association between QTc and overall inflammatory burden (32). Resting electrocardiography (ECG) is universally available and its direct harms seem to be trivial (33). ECG has the potential to detect important SLE-associated cardiovascular involvement, as well as abnormalities potentially related to drug toxicity. Our objective was to study whether treatment with anti-malarials is associated with ECG abnormalities in patients with SLE.

Materials and methods

Study population

Patients were identified from the prospective longitudinal University of Toronto Lupus cohort followed from 1970. Patients with adult SLE (≥18 years with 4 ACR criteria or 3 ACR criteria plus a typical histological lesion of SLE on renal or skin biopsy) have been followed prospectively at the Lupus Clinic since 1970 (34, 35). Patients attend the clinic at 2–6 month intervals, regardless of the state of activity of their lupus, and the standard protocol includes complete history, physical, and laboratory evaluation. Collection, storage, and use of clinical and laboratory data on patients followed at the clinic are conducted in accordance with the Declaration of Helsinki and are approved by the Research Ethics Board of the University Health Network, Toronto, Canada. Signed informed consent was obtained from all patients.

Study variables

• *Resting ECG*

A standard digitally recorded 12-lead

resting supine ECG was performed on consecutive patients attending the Lupus Clinic since 2012. ECGs were analysed and tracings were coded by a single cardiologist blinded to identifying data and previous AM exposure on the basis of the Minnesota criteria. ECG findings were further pooled into 2 categories: *structural abnormalities* [left ventricular hypertrophy (LVH) or atrial enlargement] or *conduction abnormalities* [prolonged corrected QT interval (QTc), short PR interval, left bundle branch block (LBBB), right bundle branch block (RBBB) and atrioventricular block (AVB) as well as arrhythmias (bradycardia, tachycardia, premature atrial complex, ectopic atrial rhythm, atrial fibrillation, premature ventricular complex and ventricular bigeminy)].

• *Clinical and laboratory data*

Clinical and laboratory variables from the baseline (corresponds to the ECG visit) were studied as potential factors associated with ECG abnormalities, and included age, sex, disease duration, Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) within 2 years prior to ECG, arterial hypertension (systolic >140 or diastolic >90 mmHg for ≥3 months or hypertensive treatment) ever before ECG test, diabetes mellitus type I and II, eGFR, ever smoked before ECG, alcohol consumption, history of CAD (including myocardial infarction, percutaneous coronary intervention (PCI), and coronary bypass surgery), pulmonary hypertension, myocarditis, pericarditis, endocarditis, mitral valve prolapse, other valvular heart disease, and cardiomyopathy. Cumulative anti-malarial dose was calculated after equating 3.0 mg of CQ with 6.5 mg of HCQ (2). Relevant medication use that could impact cardio-vascular status other than anti-malarials included nonsteroidal anti-inflammatory drugs (NSAIDs), antihypertensive agents (diuretics, alpha-adrenergic inhibitors, beta-blockers, central alpha agonists, calcium-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers), statins, glucocorticosteroids, thyroid replacement, mood stabilisers, anti-psychotics and immunosuppressive drugs. The following laboratory tests [anti–double-stranded DNA; anti-extractable nuclear antigen (anti-ENA) profile (anti-Ro/SSA subspecificities [52 kd and 60 kd], anti-La/SSB, anti-Sm, anti-RNP) and antiphospholipid antibodies (anticardiolipin IgG/IgM and lupus anticoagulant)] were studied.

Table I. Baseline characteristics of the 453 patients.

Variable	Total n=453
Female (%)	407 (89.8%)
Ethnicity	
Asian	47 (10.4%)
Black	70 (15.4%)
Caucasian	280 (61.8%)
Others	56 (12.4%)
Age at ECG (years)	49.2 ± 13.7
SLE duration at ECG (years)	19.7 ± 10.4
First visit to ECG (years)	14.2 ± 10.7
Alcohol consumption	99 (21.9%)
Cardiovascular Risk Factors ever before ECG	
Hypertension	296 (65.3%)
Diabetes Type I/II	26 (5.7%)
Smoking at ECG	43 (9.5%)
Ever smoking before ECG	149 (32.9%)
Adjusted mean SLEDAI-2K 2 years prior to ECG	3.47 ± 3.82
Known cardiovascular disease ever before ECG	
Mitral valve prolapse	22 (4.9%)
Other valvular lesions	56 (12.4%)
Pericarditis	0
Myocarditis	1 (0.2%)
Endocarditis	0
Congestive heart failure	0
Pulmonary hypertension	22 (4.9%)
Coronary heart disease ever before ECG	
Myocardial infarction	2 (0.4%)
Angina	3 (0.7%)
PCI	1 (0.2%)
Coronary bypass surgery	7 (1.5%)
Labs at ECG	
CPK elevation	71 (15.7%)
CPK absolute value	104.2 ± 81.0
Anti-ds DNA antibodies	180 (39.7%)
Antiphospholipid antibodies within 1 year of ECG	68 (15.0%)
Drug therapy at ECG	
Statin	117 (25.8%)
Anti-depressant	71 (15.7)
Anti-epileptic	39 (8.6%)
Sedative/hypnotics/anxiolytic/anti-psychotics	26 (5.7%)
Cumulative prednisone dose 3 years before ECG (grams) mean	424.3 ± 708.6
Average prednisone dose within 3 years before ECG (mg/day)	10.7 ± 13.3
Patients treated with CQ or HCQ before ECG	409 (90.3%)
Years on AM before ECG	10.5 ± 8.7
Calculated AM dose, CQ was converted to the equivalent HCQ dose	1525.8 ± 1393.6
Patients treated with immunosuppressives within 3 years before ECG	260 (57.4%)

Values are percentages unless indicated otherwise. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity index-2000. ENA antibodies (anti-Ro/SSA, anti-La/SSB, anti-Sm, and anti-RNP antibodies) were studied but the results are not presented in this table.

Cohort development

Of the 582 patients who had ECG tests up until August 2016, 129 patients were excluded: 96 patients had SLE duration <5 years since diagnosis, 10 patients had permanent pacemaker, and 23 patients had anti-arrhythmic drug treatment (*e.g.* amiodarone, flecainide or sotalol)

Nested case-control study

For each case (abnormal ECG: structural or conductive), 3 controls were selected from the study participants matching for sex, SLE duration at ECG within 5 years, ECG testing year within 5 years and hypertension status. Age at ECG moderately correlated (r=0.60) with SLE duration at ECG test so the latter variable was used in matching. Hypertension before ECG was significantly correlated with cardiovascular disease (Chi-square test p=0.001) so the former was used in matching.

Statistical analysis

Descriptive statistics for demographics and laboratory tests (including anti-ENA profile), and treatments at ECG test were presented as mean ± SD and frequency (%). Characteristics were compared between ECG groups by t-test and Chi-square tests. Univariate and multivariable logistic regression analyses were used to estimate the associations of the dosage of AM treatment with the development of the two categories of ECG abnormalities (structural and conduction abnormalities), controlling for patients' demographics, disease activity, and treatment. Variable selection was preceded in the following manner: p-value <0.35 in univariate regression, then step-down selection method using Akaike Information Criterion as the goodness of fit. Conditional logistic regression was used for the nested case-control analysis. The statistical software SAS (v. 9.3; SAS Institute, Cary, NC) was used for all statistical analyses and the significance level was set at 5%.

Results

Patients' characteristics

A total of 453 patients had their ECGs analysed in this study. The majority were women (407, 89.6%) with Caucasian predominance (280, 61.8%). Mean age at ECG was 49.2±13.8 years and SLE duration was 19.8±10.4 years. CQ or HCQ had been used by 409 (90.3%) before the ECG; 107 (23.6%) were treated with CQ prior to ECG and 381 (84.1%) were HCQ treated. Baseline characteristics of the patients are shown in Table I.

The proportions of patients with various ECG abnormalities are shown in Table II. Conduction abnormalities (71, 15.7%) were more prevalent than structural abnormalities (58, 12.8%). RBBB (15, 3.3%) was the most prevalent conduction abnormality followed by bradycardia (12, 2.6%) and 1st degree AVB (11, 2.4%). Of the structural ECG abnormalities, LVH (43, 9.5%) was more prevalent than atrial enlargement (18, 4.0%).

The overall prevalence of hypertension (HTN) in the cohort studied was 65.3%. Of 58 patients with structural ECG abnormalities, 18 patients had LVH. Of the 18 patients, 13 had HTN. Of the 395 patients without structural abnormalities, the prevalence of HTN was 62.3%. There was no statistical difference between the patients with and without structural abnormalities (p=0.38 from Chi-square test).

Out of 453 patients in the cohort, 252 (55.6%) had cumulative AM above the median of 1207 gram before ECG test and 201 (44.4%) are at or below the median. The prevalence of HTN in these two groups was 174/252 (69.0%) and 122/201 (60.7%), respectively. There was no statistical difference between the groups (p=0.06 from Chi-square test).

The multivariable analysis

• *Structural ECG abnormalities*

There was a non-statistically significant increase in the odds of ECG structural abnormalities in those having cumulative AM dose above the median; OR 1.82 (95% CI: 0.95–3.47, p=0.07). The following were statistically significantly associated with structural ECG abnormalities: SLE duration at ECG (OR 1.03; 95% CI: 1.004–1.06, p=0.025) [every 1 year increase in age increases the odds of structural abnormalities by 3%] and eGFR at ECG (OR 0.83; 95% CI: 0.76–0.92, p=0.0002) [every 1 unit increase in eGFR decreases the odds of structural abnormalities by 17%] (Table III).

• *Conduction ECG abnormalities*

Cumulative AM was associated with reduced frequency of conduction abnormalities (OR 0.42; 95% CI: 0.22–0.77, p=0.006) while SLE duration (OR 1.03, 95% CI: 1.01–1.06, p=0.008) and cumulative prednisone 3 years before ECG (OR 1.05; 95% CI: 1.01–1.09, p=0.015) were associated with higher likelihood of ECG conduction abnormalities. Non-dihydropyridines and beta blockers were associated with conduction abnormalities (OR 2.75; 95% CI: 1.42–5.33; p=0.003) (Table III).

There was no association between anti-ENA antibodies and ECG conduction and structural abnormalities. The compared prevalence of anti-phospholipid antibodies in patients with and without structural ECG abnormalities was 12.1% and 15.0%, respectively, and was not statistically significant. The prevalence of anti-phospholipid antibodies in patients with and without conduction ECG abnormalities was 16.9% and 14.7%, respectively, and did not reach significance. For the regression, antiphospholipid antibodies did not meet the criteria of p<0.35 to enter the multivariable analysis.

• *Nested case-control analysis*

For structural ECG abnormalities, there were 58 cases and 159 controls and for conduction abnormalities 71 cases and 191 controls.

As in the multivariable logistic regression, conditional logistic regression (in matched case-control sets) also found decreased odds of conduction abnormalities when cumulative AM dose was higher than the median (OR 0.36; 95% CI: 0.17–0.75; p=0.007), suggesting that AM may be protective against

Table II. Electrocardiographic abnormalities.

ECG Abnormalities	n=453
Structural abnormalities*	58 (12.8%)
Left ventricular hypertrophy	43 (9.5%)
Atrial enlargement	18 (4.0%)
Conduction abnormalities	71 (15.7%)
Prolonged corrected QT interval (QTc)	3 (0.7%)
Short PR interval	2 (0.4%)
Left bundle branch block	2 (0.4%)
Right bundle branch block	15 (3.3%)
First degree AVB	11 (2.4%)
Tachycardia	7 (1.5%)
Bradycardia	12 (2.6%)
Atrial fibrillation	1 (0.2%)
Ectopic atrial rhythm	7 (1.5%)
Premature atrial complex	5 (1.1%)
Premature ventricular complex	4 (0.9%)
Ventricular bigeminy	2 (0.4%)

*3 patients overlapping with structural and conduction abnormalities.

Table III. Multivariable logistic regression analysis for structural or conduction abnormalities.

ECG Abnormality	Variables	OR 95% CI	*p*-value
ECG structural abnormality	SLE duration at ECG test (years)	1.03 (1.004, 1.06)	0.0248
	Hypertension *vs*. normotension	2.21 (0.98, 4.99)	0.0567
	eGFR at ECG (each 10 mL/min/173 m^2)	0.83 (0.76, 0.92)	0.0002
	Cumulative AM dose prior to ECG higher than median dose (1207 grams)	1.82 (0.95, 3.47)	0.0707
ECG conduction abnormality	SLE duration at ECG test	1.03 (1.01, 1.06)	0.0080
	Hypertension	1.66 (0.85, 3.25)	0.1357
	Pulmonary hypertension	2.37 (0.82, 6.80)	0.1090
	Treatment with N-CBB* or beta-blockers	2.75 (1.42, 5.33)	0.0026
	Cumulative prednisone 3 years before ECG (each 100 grams)	1.05 (1.01, 1.09)	0.0147
	Cumulative AM prior to ECG higher than median dose (1207 grams)	0.42 (0.22, 0.77)	0.0057

List of univariate variables: Sex, Caucasian, age at ECG, hypertension, diabetes, cardiovascular disease, pulmonary hypertension, thyroid disease, smoking, alcohol consumption, Adjusted Mean SLEDAI-2K 2 years prior to ECG, CPK elevation unrelated to statin treatment, anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-RNP, dsDNA, anti-depressant treatment, anti-epileptic treatment, sedative/ hypnotics / anxiolytics / anti-psychotics, N calcium antagonist/beta-blocker at ECG, cumulative prednisone, immunosuppressives within 3 years before ECG, cumulative AM dose, cumulative AM dose higher than median dose, AM treatment ≥5 yrs after SLE diagnosis before ECG. All variables are at ECG or prior to ECG.
*N-CCB: non-dihydropyridine calcium channel blocker.

conduction abnormalities. Also similar to the finding from the main analysis was the result that a cumulative AM dose higher than median was non-significantly associated with structural ECG abnormalities (OR 1.57; 95% CI: 0.77–3.21, *p*=0.215. The association of non-dihydropyridines and beta blockers with conduction abnormalities was also seen (OR 2.50; 95% CI: 1.14–5.50, *p*=0.02).

Discussion

Our study is the largest to date, that we know of, evaluating ECG abnormalities related to anti-malarials and specifically, the association between these drugs and ECG findings indicating structural and conduction abnormalities. In our female predominant (89.8%) study population, conduction abnormalities were more prevalent *than structural abnormalities (15.7% vs*. 12.8%) and 26.0% of patients had structural or conduction abnormalities. We found a cumulative antimalarial dose above the median (1207 g) to be a statistically significant predictor of structural ECG abnormalities in univariate analysis but in multivariable analysis, although there was still increased risk (OR=1.82), the finding was not statistically significant (*p*=0.07). Higher cumulative anti-malarial dose decreases the odds of ECG conduction abnormalities (OR 0.42; *p*=0.006). This was also seen in the nested case-control study (OR 0.36; *p*=0.0007). Patients with higher than median cumulative doses of anti-malarial had a similar frequency of hypertension as those at or below the median; 174/252 (69.0%) and 122/201 (60.7%) (*p* 0.06). Furthermore, hypertension was not associated with LVH in those with structural abnormalities compared to those without (72.2% *vs*. 62.3%, *p* 0.38). Duration of anti-malarial use >5 years was not a statistically significant predictor of either conduction or structural ECG abnormalities in multivariable analysis.

Non-dihydropyridine calcium channel blockers and beta blockers were independently associated with conduction abnormalities and this was confirmed by the nested case-control (OR 2.50; *p*=0.02). This association is likely specific for the cases of bradycardia identified (2.6%) and is expected based on the mechanism of action of these drugs. There was no association between ENA profile or antiphospholipid antibodies and abnormal ECGs.

Our study findings are consistent with those of other SLE cohorts as regards the prevalence of conduction abnormalities. Godeau *et al*. reported conduction abnormalities to be present in 17.5% of lupus patients after a 10-year follow up (36). The prevalence of conduction abnormalities in our study were also similar to those of Costetedoat-Chalumeau *et al*. whose study population had a similar AM (HCQ) mean cumulative dose (1090g) (37). They concluded that the rate of conduction abnormalities was similar to what is expected in the general population, and contrasted with prior results indicating increased frequency of these abnormalities in CQ-treated patients.

Anti-malarial induced heart conduction disorders seem to progress slowly from bundle-branch block (including left anterior hemiblock) or 1st and 2nd AVB to complete AVB (37). We found a low prevalence of these disorders in our cohort, with 2.4% having 1st degree AVB and no 2nd degree AVB. Only 3 patients (0.7%) demonstrated prolonged QTc in our study. Prolonged QTc, which indicates a disorder of myocardial repolarisation predisposing to life-threatening ventricular arrhythmias, particularly torsades de pointes, has been documented in patients treated with HCQ (28, 30). However a previous analysis of ECGs from 85 unselected patients with connective tissue diseases on HCQ showed QTc to be no different from normal values (37). Our study confirms the low prevalence of prolonged QTc in SLE patients on HCQ.

Similar to retinal toxicity, it has been suggested that cardiotoxicity may be enhanced by older age, pre-existing cardiac disease and renal insufficiency (38-40). Additionally, longer disease duration (>5 years), as an independent factor, and elevated per-kilogram daily dose of anti-malarials have been

recently confirmed to be the main risks factors for retinal toxicity (2). In this study population, the mean age was 49.2 years and the mean SLE duration at ECG was 19.8 years reflecting a relatively older population with long disease duration who would therefore be at higher risk of cardiovascular disease and thus more likely to demonstrate abnormal ECGs. We found SLE duration to be a statistically significant predictor of both conduction and structural ECG abnormalities in multivariable analysis. The nested case-control analysis also found this relationship between SLE duration and both conduction and structural ECG abnormalities. Age at ECG had a moderate correlation (r=0.60) with SLE duration at ECG test. Costedoat-Chalumeau *et al*. documented that the duration of antimalarial use varied widely in patients with cardiac toxicity, ranging from 3 months to 27 years, with a similarly wide range of cumulative dose of antimalarial drugs (270–9125 g) (27). The median cumulative anti-malarial dose in our study was 1027 grams after converting CQ to equivalent doses of HCQ (2). Hypertension, which was significantly correlated with cardiovascular disease, predicted both conduction and structural ECG abnormalities. We also found that higher eGFRs protected against structural ECG abnormalities.

Inflammation and immunity have been increasingly recognised as novel factors crucially involved in modulating arrhythmic risk in diseases like lupus (32). Our interesting finding that cumulative anti-malarial dose is protective against conduction abnormalities may speak to the drug's immunomodulation effect. We theorise that before significant abnormal structural changes are induced by anti-malarials, the drugs may be protective against conduction abnormalities. Thereafter, these anti-malarial induced structural changes may provide the substrate for the later development of conduction abnormalities.

A limitation of this study is the lack of baseline ECGs prior to the initiation of anti-malarials in order to identify ECG changes not likely to be attributable to anti-malarials. The lack of a control group of SLE patients without anti-malarial exposure to better delineate potential anti-malarial related ECG changes is another limitation. A strength of this study is the use of conversion of CQ to HCQ for analysis of cumulative doses. This approach is important in longitudinal cohort settings such as ours in which some patients have been switched from CQ to HCQ with the emergence of data indicating the relative safety of HCQ to CQ as regards toxic retinopathy

Cardiac toxicity after long-term therapy with HCQ is likely an underdiagnosed condition (20). There is significant inter-individual variability in its clinical manifestations. However, HCQ-induced cardiomyopathy is potentially reversible (22). There are multiple reports of normalisation or improvement of antimalarial cardiomyopathy from as early as three months post drug discontinuation in patients exposed for as long as 31 years. In some of these cases of endomyocardial biopsy confirmed cardiomyopathy, atrial and ventricular sizes and dimensions and ejection fraction normalised (18, 20, 26, 39, 41). Therefore, early identification of affected patients and withdrawal of the drug might be especially important.

Conclusion

In summary, this study suggests an association between cumulative anti-malarials dose above the median (1207 g) and structural ECG abnormalities. More importantly, cumulative AM dose, above the median (1207 g), decreases the odds of ECG conduction abnormalities.

Key messages

- Cumulative AM dose above the median (1207 g) can be associated with structural ECG abnormalities.
- Cumulative AM decreases the odds of ECG conduction abnormalities.

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