Hydroxychloroquine cardiotoxicity: a case-control study comparing patients with COVID-19 and patients with systemic lupus erythematosus

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Abstract

Objective

Antimalarials have been associated with QT prolongation in COVID-19 patients but are generally safe in systemic lupus erythematosus (SLE).We compared the prevalence of QTc prolongation between COVID-19 and SLE patients treated with hydroxychloroquine (HCQ).

Methods

We included patients with SARS-CoV-2 infection confirmed by nasopharyngeal swab and patients taking HCQ for SLE. A prolonged QTc was defined as an increase in QTc intervals >60 ms (compared with baseline) or as a QTc of ≥500 ms. We performed the univariate and multivariate logistic regression to investigate the risk factors for QTc prolongation in COVID-19 patients.

Results

We enrolled 58 COVID-19 patients (median age 70.5 years, IQR 25), grouped into group A (patients with HCQ) group B (patients with HCQ + azithromycin) and group C (not received either drug). Fifty (26%) COVID-19 patients presented a QTc prolongation (12 QTc≥500 ms, 3 patients ΔQTc>60 ms). We did not find any differences in QTc prolongation among the three treatment groups. Baseline QTc (OR 111.5) and D-dimer (OR 78.3) were independently associated to QTc prolongation. Compared to the 50 SLE patients (median age 38.5 years, IQR 22), chronically treated with HCQ, COVID-19 patients showed significantly longer QTc (p<0.001).

Conclusion

This is the first study demonstrating that, unlike COVID-19 patients, patients with SLE are not susceptible to HCQ-induced long QT syndrome and arrhythmia. The combined arrhythmogenic effect of SARS-CoV-2 infection and HCQ could account for the excess of QTc prolongation and fatal arrhythmias described in patients with COVID-19.

Key words

hydroxychloroquine, QT prolongation, COVID-19, rheumatologic diseases; systemic lupus erythematosus

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Introduction

The spread of Severe Acute Respiratory Syndrome (SARS) Coronavirus-2 (SARS-CoV-2) has imposed the search for effective treatments for the SARS-CoV-2 pneumonia (*i.e.* Coronavirus Disease 19 - COVID-19). Chloroquine (CQ) and hydroxychloroquine (HCQ) were included among the anti-viral drugs being able to inhibit the entry of the SARS-CoV-2 virus through its receptor, the angiotensin-converting enzyme 2 (ACE2) (1-3).

Although new data are available every day, the scientific evidence is not robust enough and doubts of the efficacy of antimalarials (AMs) outweigh certainties. Results from randomised clinical trials (RCTs) revealed that HCQ does not prevent COVID-19 when used as post-exposure prophylaxis within 4 days after exposure (4) and does not improve severity of symptoms over 14 days in outpatients with early, mild COVID-19 patients (5). Although AM do not prevent COVID-19, a recent Italian study encourages clinicians to maintain anti-rheumatic drugs, including AMs, in patients with SLE, and in fact in their cohort they have not recorded any cases of SARS-CoV-2 infections (6). Furthermore, HCQ does not improve clinical status at 15 days in mild-to-moderate COVID-19 hospitalised patients. Finally, prolongation of corrected QT (QTc) interval was more frequent in patients receiving HCQ (7) and, HCQ did not result in a significantly higher probability of negative conversion (8). On June 15, 2020 FDA revoked the emergency use authorisation to use HCQ and CQ to treat COVID-19 in certain hospitalised patients when a clinical trial is unavailable or participation is not feasible.

On the other hand, concerns about the potential cardiac toxicity of AM drugs are arising. A systematic review of the literature reported a prolongation of QTc in 10% of COVID-19 patients treated with HCQ or CQ (9). Moreover, a recent multicentric international retrospective study on HCQ suggested increased risk of ventricular arrhythmias and death without any beneficial effect (10). However, this large study was retracted after publication.

These emerging findings could have an impact on the management of autoimmune rheumatic diseases (ARDs) patients, that are chronically treated with AM. Particularly for SLE patients, in which HCQ is still the anchor drug.

Patients with ARDs have been treated long-term with AMs for more than 70 years and only few cases of severe arrhythmia have been reported (11-14). In particular, antimalarials are included in the recommendations for the management of patients with systemic lupus erythematosus (SLE) (15). In the context of SARS-CoV-2 infection, concurrent administration of pro-arrhythmic drugs and severe inflammation may contribute to the arrhythmic events described in critically ill COVID-19 patients.

The aim of the study was to compare the prevalence of QTc prolongation in COVID-19 patients treated or not with HCQ and patients with SLE chronically treated with HCQ.

Methods

This is single-centre, cross-sectional, case-control study on consecutive COVID-19 patients hospitalised at Policlinico Umberto I, Sapienza University of Rome included all patients with SARS-CoV-2 infection confirmed by naso-pharyngeal swab for SARS-CoV-2 on real-time-reverse-transcriptase-polymerase-chain-reaction (RT-PCR) admitted between March and April 2020.

We included hospitalised patients with available electrocardiograms (ECG) at baseline, before starting any treatment, and during the follow-up. Bazett formula was used to calculate QTc intervals and prolonged QTc was defined as an increase in QTc intervals of more than 60 milliseconds (ΔQTc >60 ms) compared with baseline or as a QTc of ≥500 ms (16). We also calculated the Tisdale score, a prognostic score validated for hospitalised patients (17).

As a control group, we enrolled SLE patients, according to 2019 EULAR/ACR classification criteria (18), taking HCQ, with available ECG and attending the Sapienza University of Rome, Rheumatology Unit. Data from inpatient were recorded by medical records before SARS-CoV-2 pandemic (rang-

Table I. Clinical and demographic features of 58 COVID-19 patients.

Features	Patients n=58 (%)	Group A Hydroxychloroquine n=26 (44.8)	Group B Hydroxychloroquine and azithromycin n=15 (25.9)	Group C No Hydroxychloroquine and azithromycin n=17 (29.3)	A-B-C *p*-value	A-B *p*-value	B-C *p*-value	A-C *p*-value
Age years (IQR)	70.5 (25)	75 (21.5)	66 (19)	73 (42.5)	NS	-	-	-
Female	23 (39.7)	14 (53.8)	5 (33.3)	6 (35.3)	-	NS	NS	NS
Comorbidities	50 (86)	23 (88.5)	12 (80)	15 (88)	-	NS	NS	NS
Baseline laboratory values, median (IQR)								
Lymphocyte count, cells/L	1045 (855)	880 (610)	1114 (900)	1070 (1020)	0.05			-
Lactate dehydrogenase, U/L	287 (121)	290 (114.8)	274 (136)	289 (151)	NS	-	-	-
Ferritin ug/L	403 (625)	596 (556)	301 (423)	397 (610)	0.16	-	-	-
D-dimer mg/L	1059 (1557)	1173 (3439)	1180 (1626)	571 (813)	NS	-	-	-
Complications								
Arrhythmia	4 (6.9)	2	2	0	-	NS	-	-
ARDS	6 (10.3)	5	1	0	-	NS	-	-
ALI	17 (29.3)	11	3	3	-	NS	NS	NS
Tisdale score at treatment Initiation								
<7	50 (86.2)	24	13	13	-	NS	NS	NS
7-10	8 (13.8)	2	2	4	-	NS	NS	NS
>10	0	0	0	0	-	-	-	-
1 QTc-prolonging agent	17 (29.3)	8	2	7	-	NS	NS	NS
≥2 QTc-prolonging agents	7 (12)	0	2	5	-	-	NS	-
Loop diuretic	8 (13.8)	4	2	2	-	NS	NS	NS
Baseline QTc ≥450 ms	13 (22.4)	4	3	6	-	NS	NS	NS
Heart failure	7 (12)	3	1	3	-	NS	NS	NS
Acute coronary syndrome	2 (3.5)	0	1	1	-	-	NS	-
Serum potassium <3.5 mEq / magnesium <2.0 mg/dl at QTc peak	0	0	0	0	-	-	-	-
Baseline QTc, median (IQR)	413 (47)	409 (69)	418 (49.8)	-	0.03	NS	-	-
During treatment QTc, median (IQR)	432 (52)	442.5 (57.5)	420 (65)	-	-	NS	-	.
Post-treatment/follow-up QTc peak, median (IQR)	432 (36.25)	436 (60)	421 (54)	444 (52)	NS	-	-	-
QTc prolongation	15 (25.9)	8 (30.8)	2 (13.3)	5 (29.4)	-	NS	NS	NS

COPD: Chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; ALI: acute lung injury.

ing from September 2019 to February 2020). Outpatient data and ECG were collected during the examinations performed between January and April 2020. In the control group, we excluded COVID-19 patients through a questionnaire that assessed contacts with certain or suspected cases of COVID-19 or the presence of signs or symptoms suggestive of SARS-CoV-2 infection.

Each subject gave their informed consent in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The local Ethic Committees approved the protocol.

Data are expressed as mean±standard deviation or median (interquartile range) according to the variable distribution. χ^2 test or Fisher's exact test was used to compare categorical variables. The differences between the continuous variables among the three groups A-B-C have been previously evaluated with Kruskal-Wallis, subsequently binary with the Mann-Whitney U-test. We performed the univariate and multivariate logistic regression for examining the relationship of a binary (or dichotomous) outcome to investigate the risk factors associated to QTc prolongation. In the univariate and multivariate analyses we included: sex, age, baseline QTc, D-dimer level, lymphocytes count, ferritin level, LDH level, acute lung injury (ALI) and (Acute respiratory distress syndrome) ARDS.

The SPSS software automatically calculates anti-logs or the exponentials (Exp) of the regression coefficients (β); these provide adjusted ORs (aOR) (Expβ=aOR); for having the outcome of interest, while adjusting for the effect of other predictor factors. *p*-values <0.05 were considered statistically significant. SPSS 20.0 statistical software package (SPSS Inc., Chicago, IL, USA) was utilised.

Results

We enrolled 58 hospitalised patients affected by COVID-19 (32 males and 26 females, 55 Caucasian, 3 Hispanic) with a median age of 70.5 years (IQR 25.3). As control we recruited 50 Non-COVID-19 patients affected by SLE (7 males and 43 females, all Caucasian) with a median age of 45 years (IQR 17) and a median disease duration of 110 months (IQR 193). Clinical and demographic characteristics of both groups are reported in Tables I and II.

SLE patients were further divided into two groups according to the possibility of calculating Tisdale score: 25 inpatients and 25 outpatients. Clinical and demographic characteristics of inpatients have been reported in Table III.

COVID-19 patients

Of the 58 hospitalised patients affected by SARS-CoV-2 infection, 50 (86%) reported at least one comorbidity (Ta-

ble I). The most common symptoms at disease onset were fever (42 [72.4%]), dyspnea (28 [48.3%]) and cough (21 [36.2%]); the median time from first symptoms to hospital admission and positive nasopharyngeal swab for SARS-CoV-2 on RT-PCR assay was 4 days (IQR 8.25). Chest high resolution computed tomography (HRCT) showed bilateral distribution of patchy shadows or ground-glass opacity in 49 out of 58 patients (84.5%). Fifty patients (86.2%) had a low-risk Tisdale score at the baseline, 8 out 58 (13.8%) a moderate risk and no patients presented a high risk. Twenty-four patients (41.4%) were taking at least 1 QTc-prolonging agent. The median baseline QTc value was 413 (IQR 47).

Clinical and demographic features of COVID-19 patients are summarised in Table I.

The 58 COVID-19 patients were grouped into group A (patients with HCQ) group B (patients with HCQ + azithromycin) and group C (not received either drug).

HCQ and azithromycin were prescribed at 200 mg twice per day and 500 mg daily, respectively, for seven consecutive days. Prolonged QTc was observed in 15 out of 58 (26%) COVID-19 patients, 12 patients showing a QTc ≥500 ms and other 3 patients ΔQTc >60 ms.

Out of 26 patients belonging to group A, 7 (26.9%) developed prolonged QTc ≥500 ms and 1 (3.8%) had ΔQTc >60 ms. Among 15 patients of group B, 2 (13.3%) had QTc ≥500 ms. Three patients (17.6%) of the group C had QTc ≥500 ms and 2 (11.8%) had ΔQTc >60 ms. The QTc length and the percentage of patients with QTc prolongation were similar among the three groups either at baseline and during the follow-up (Table I).

We evaluated the risk factors for QTc prolongation (Tisdale score) (17) and the negative prognostic factors for COVID-19 (lymphocytes <800/L, D-dimer >0.6 mg/L, lactate dehydrogenase level (LDH) >323 U/L and hyperferritinaemia) (19, 20). Baseline QTc showed the highest odds ratio (OR, 111.5), followed by D-dimer >0.6 mg/L (OR 78.3) (Table IV). Four patients developed arrhythmic complications, 2 new-onset atrial fibrillation, both with QTc prolongation, and 2 supraventricular tachyarrhythmias, one with QTc prolongation. Two patients reported an acute coronary syndrome (ACS) with ST-segment elevation, one of them presenting QTc prolongation.

Table II. Difference in clinical and demographic features between systemic lupus erythematosus (SLE) and COVID-19 patients.

Demographic features	SLE patients	COVID-19 patients	*p*-value
n	50	58	
Female	43	23	<0.001
Age (years)	45 (17)	70.5 (25)	<0.001
Comorbidities n %			
Hypertension	15 (30)	24 (48)	NS
Cardiovascular diseses	8 (16)	13 (22.4)	NS
COPD	1 (2)	9 (15.5)	0.016
Thyroid disease	8 (16)	8 (13.8)	
Chronic kidney disease	4 (8)	5 (8.6)	NS
Population characteristics			
Median (IQR)			
HCQ (mg/die)	400 (125)	400	<0.001
HCQ Time (days)	3255 (5790)	7	<0.001
QTc (ms)	432 (36.25)	395 (80)	<0.001
SLEDAI-2K	0 (4)	-	-
SDI	0	-	-

COPD: chronic obstructive pulmonary disease; HCQ: hydroxychloroquine.

Table III. Clinical and demographic features of 25 non-COVID-19 inpatients affected by systemic lupus erythematosus.

Systemic lupus erythematosus inpatients	
n	25
Age	38.5 (22)
Female	19
Comorbidities	**n (%)**
Hypertension	7 (28)
Cardiovascular diseses	6 (24)
COPD	1 (4)
Thyroid disease	7 (28)
Chronic kidney disease	4 (16)
Population characteristics	**median (IQR)**
HCQ (mg/die)	400 (200)
HCQ Time (months)	75 (200)
Tisdale score at treatment initiation	**n (%)**
<7	25 (100)
7-10	0
>10	0
1 QTc-prolonging agent	3 (12)
≥2 QTc-prolonging agents	2 (8)
Loop diuretic	3 (12)
Baseline QTc ≥450 ms	1 (4)
Heart failure	0 (0)
Acute coronary syndrome	0 (0)
Serum potassium <3.5 mEq / Magnesium <2.0 mg/dl at QTc peak	0 (0)

COPD: chronic obstructive pulmonary disease; HCQ: hydroxychloroquine.

Systemic lupus erythematosus patients

The 50 SLE patients were treated with HCQ with a median dosage of 400 mg daily (IQR 125) and a median HCQ treatment duration of 108.5 months (IQR 193). All hospitalised SLE patients (25 out of 50) were retrospectively evaluated for the risk of QTc prolongation. All patients showed low risk of QTc prolongation according to Tisdale score (Table III). Five of the 25 hospitalised patients (20%) were taking at least 1 QTc-prolonging agent other than HCQ. None of the 50 SLE patients showed a QTc prolongation. Inpatients and outpatients were compared for disease activity, comorbidities, dose of HCQ, QTc and resulted in higher disease activity in inpatients (median SLEDAI 6, IQR 2) compared to outpatients (median SLEDAI 0, IQR 0).

No arrhythmic complications or ACS was recorded among SLE hospitalised patients. When comparing the peak of QTc detected in COVID-19 patients with the QTc interval of SLE patients we observed longer length in the first group (p<0.001) (Table II).

Discussion

This is the first study aimed to compare the frequency of QTc prolongation in

Table IV. Univariate and multivariate analysis for risk of corrected QT (QTc) interval prolongation in COVID19 patients. ODDs ratio estimates for multivariate analysis.

Features	Univariate	Multivariate	Odds ratio (CI 95%)
Female	NS	NS	-
Age >68 y	NS	NS	-
Baseline QT ≥450 ms	0.01	0.004	111.5 (4.5-2752)
D-dimer >0.6 mg/L	0.04	0.03	78.3 (1.5-4112)
Tisdale score 7-10 (moderate risk QT prolongation)	NS	NS	-
Lymphocytes <800/L	NS	NS	-
Ferritin >200 ug/L	NS	NS	-
LDH >323 U/L	NS	NS	-
ALI	0.04	NS	-

LDH: lactate dehydrogenase level; ALI: acute lung injury.

patients with COVID-19 and patients with SLE. The results of our study confirm that HCQ can be associated to QTc interval prolongation in up to 17% of patients hospitalised for COVID-19 but not in SLE patients; moreover, none of the patients with COVID-19 with prolonged QTc developed fatal arrhythmias.

Early enthusiasm for HCQ in the management of COVID-19 was dampened by safety concerns about the risk of drug-induced QTc interval prolongation, an ECG marker of delayed ventricular repolarisation that can trigger a potentially fatal ventricular arrhythmia known as torsades de pointes (TdP). Indeed, the structure of HCQ resemble that of class IA antiarrhythmic, a class of drug that can lead to a QTc prolongation by inhibiting voltage-gated sodium and potassium channels (21).

Given their *in vitro* anti-viral activity, CQ and HCQ have been used in patients with COVID-19 from the beginning of the pandemic. Later on, data on their cardiotoxicity have emerged and a QTc prolongation has been reported in a high percentage of COVID-19 patients, ranging from 5.9% to 36% (22-24). A systematic review of the literature reported that 10% of COVID-19 patients treated with HCQ or CQ developed QTc prolongation (9).

Rosenberg *et al*. reported data on a large population consisting in 1438 hospitalised COVID-19 patients. QT prolongation was observed in 11% of patients treated with HCQ plus azithromycin, in 14% receiving HCQ alone, in 7.1% of those treated with azithromycin alone and in 5.9% of patients who had not received either drug (24). Nonetheless, in adjusted logistic regression models, there were no significant differences in the relative likelihood of abnormal electrocardiogram findings through the groups. On the contrary, cardiac arrest was more likely in patients receiving HCQ plus azithromycin, but not HCQ alone (24). In line with the report by Rosenbreg, showing QTc prolongation in all COVID-19 patients regardless their treatment, we did not find any difference between patients who were treated with HCQ either alone or in combination with azithromycin and those who did not. These data suggest that COVID-19 may account for QTc prolongation more than the drugs used to treat this condition.

However, the recent studies had raised safety concerns about the use of HCQ with or without azithromycin for patients with COVID-19, particularly when both drugs are administered together. Mehra et al. described efficacy and cardiovascular toxicity of CQ and HCQ in a large population of patients with COVID-19; overall, 96.032 hospitalised patients were evaluated. The authors demonstrate an increased risk of new onset ventricular arrhythmias and in-hospital mortality (9). This study led the WHO to pause the clinical trials with HCQ in COVID-19 patients. Later, the paper was retracted and clinical trials were resumed.

Beyond the recent concern related to the management of COVID-19, the analysis of Food and Drug Administration's Adverse Event Reporting System (FAERS) does not demonstrate any safety signal related to TdP/QTc prolongation for HCQ and CQ in patients treated with antimalarials and azithromycin for common indications (SLE and upper respiratory tract infections). On the contrary, azithromycin was associated with a potential safety signal (25).

Since 1950, AM are used to treat patients with SLE and other rheumatologic disease, indeed HCQ continues to be the anchor drug for SLE patients due to its effects on preventing flares, decreasing the risk of organ damage and preventing thrombotic complications (11) with an excellent safety profile (26). Thus, nowadays, SLE is one of the main indications for prescribing antimalarials. Antimalarials are included in the recommendations for the management of SLE patients that state that they should be used whenever not contraindicated, moreover, the EULAR recommendation do not suggest any monitoring of ECG (15).

ECG abnormalities were evaluated in 453 SLE patients and only in 0.7% showed a prolongation of QTc (27). Data of the Systemic Lupus International Collaborating Clinics (SLICC) Inception Registry provide further indirect evidence (28). Among 779 SLE patients evaluated for ECG abnormalities, 68% were taking AMs; the mean QTc was 415.3 ms 25.7) and only 5.3% of patients had a QTc >460 ms; factors associated with QTc prolongation at univariate analysis were antihypertensive drug and age (28). A few months ago, a retrospective study evaluating the risk of QT prolongation in 819 patients with autoimmune rheumatologic disease (96% SLE) showed that 8.3% of patients had a QTc >470 ms and 1.5% QTc >500; however, it should be emphasised that the risk of QT prolongation was higher among patients with chronic kidney disease, atrial fibrillation and heart failure (29).

The lack of association between HCQ and QTc prolongation was confirmed in patients with other autoimmune rheumatologic disease. A French study evaluated the heart conduction disorders in 85 connective tissue diseases patients treated with HCQ for at least 1 year showing QTc interval values comparable to that expected in the general population (12). Moreover, a recent Italian study on 645 rheumatoid arthri-

tis (RA) patients enrolled in the Endothelial Dysfunction in Rheumatoid Arthritis study (EDRA) (ClinicalTrials.gov, NCT02341066), showed that patients treated with HCQ for more than 6 months had a mean QTc was within normal limits but longer QTc and a higher prevalence of prolonged QTc compared to those who were treated with disease-modifying anti-rheumatic drugs (30). The EDRA study RA patients were compared with a control group revealing that the QTc was significantly longer in the first one group, even if the QTc prolongation was similar between the two groups (31).

In our study, SLE patients, unlike COVID-19 patients, were treated chronically with HCQ, supporting the hypothesis that QT interval prolongation can be attributed to the inflammatory status driven by SARS-CoV-2 infection more than to the drug alone.

Indeed, the same negative prognostic factors for COVID-19 outcome seems also to predict QTc prolongation. Indeed, we evaluated the association of QTc prolongation with characteristics of a more severe infection (hyperferritinaemia, lymphopenia, elevation of D-dimer and LDH) finding that, besides baseline QTc and D-dimer were independently associated to the prolongation of QTc interval (19, 20). Different from Mercuro *et al*. we did not find any correlation between the Tisdale score and QTc prolongation risk; similarly both detected a correlation with baseline QTc (23).

COVID-19 patients may be a population at greater arrhythmic risk given the high frequency of myocardial injury, heart failure and concomitant use of other QTc-prolonging medications (32, 33). Furthermore, interleukin (IL)-6, a key cytokine in SARS-CoV-2 infection (34), could predispose to QTc prolongation by the inhibiting the rapidly activating repolarising K+ current (34). Moreover, severely ill COVID-19 patients may be more susceptible to a synergistic torsadogenic effect (32, 33).

Zhu *et al*. reviewed the mechanisms of myocardial injury due to direct viral damage and host immune response (36). Firstly, SARS-CoV-2 requires the ACE2 for cellular entry; ACE2 is highly expressed in the heart and SARS-CoV-2 may directly damage cardiomyocytes. Then, proinflammatory signals leading to cytokine storm can indirectly contribute to heart damage (36). On limitation of our study is the discrepancy between the two groups in terms of age and gender; indeed, SLE patients were younger and more frequently female compared with COVID-19 patients as expected considering the epidemiology of the disease. However, according to Mercuro *et al*., age and sex were not independent risk factors for QT prolongation in COVID-19 patients (23).

Since the excess HCQ-associated of pro-arrhythmic changes has emerged during the pandemic, we opted for a retrospective design to include a greater number of patients considering the prevalence of COVID-19 in our region. The small sample size of our study may limit the interpretation of the HCQ safety; however, our data are in line with the literature of the last 50 years demonstrating the good safety profile of antimalarials in patients with SLE and other autoimmune disease.

Conclusion

The arrhythmogenic risk attributed to HCQ during the COVID-19 pandemic was quite surprising, since long-term use of antimalarials for treating Lupus patients had never been associated to such a high risk of QTc prolongation. The results of our study should reassure clinician managing lupus patients since the seems not to be vulnerable to the pro-arrhythmic effect of HCQ, as COVID-19 patients do. While antimalarials are generally safe in SLE patients, the combined arrhythmogenic effect of SARS-CoV-2 infection and pro-arrhythmogenic drugs – including HCQ – could account for the excess of QTc prolongation and fatal arrhythmias described in patients with COVID-19.

References

1. VINCENT MJ, BERGERON E, BENJANNET S *et al*.: Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J* 2005; 2: 69.
2. SAVARINO A, TRANI LD, DONATELLI I, CAUDA R, CASSONE A: New insights into the antiviral effects of chloroquine. *Lancet Infect Dis* 2006; 6: 67-9.
3. DEVAUX CA, ROLAIN J-M, COLSON P, RAOULT D: New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Ag* 2020: 105938.
4. BOULWARE DR, PULLEN MF, BANGDIWALA AS *et al*.: A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *NEJM* 2020; 383: 517-25.
5. SKIPPER CP, PASTICK KA, ENGEN NW *et al*.: Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med* 2020; 173: 623-31.
6. FASANO S, CICCIA F: Incidence of COVID-19 in an Italian cohort of patients with systemic lupus erythematosus: an observational survey. *Clin Exp Rheumatol* 2021; 39 (Suppl. 128): S13.
7. CAVALCANTI AB, ZAMPIERI FG, ROSA RG *et al*.: Hydroxychloroquine with or without azithromycin in mild-to-moderate covid-19. *N Engl J Med*. 2020; 383: 2041-52.
8. TANG W, CAO Z, HAN M *et al*.: Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020; 14: 369.
9. CORTEGIANI A, INGOGLIA G, IPPOLITO M, GIARRATANO A, EINAV S: Update I. A systematic review on the efficacy and safety of chloroquine/hydroxychloroquine for COVID-19. *J Crit Care* 2020; 56: 176-90.
10. MEHRA MR, DESAI SS, RUSCHITZKA F, PATEL AN: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020; 395: 1820.
11. SCHREZENMEIER E, DÖRNER T: Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. *Nat Rev Rheumatol* 2020; 16: 155-66.
12. COSTEDOAT-CHALUMEAU N, HULOT JS, AMOURA Z *et al*.: Heart conduction disorders related to antimalarials toxicity: an analysis of electrocardiograms in 85 patients treated with hydroxychloroquine for connective tissue diseases. *Rheumatology* 2007; 46: 808-10.
13. CHANG ICY; BOIS JP, BOIS MC, MALESZEWSKI JJ, JOHNSON GB, GROGAN M: Hydroxychloroquine- mediated cardiotoxicity with a false- positive 99mTechnetiumlabeled pyrophosphate scan for transthyretin- related cardiac amyloidosis. *Circ Cardiovasc Imaging* 2018; 11: e007059.
14. CHATRE C, ROUBILLE, F, VERNHET H, JORGENSEN C, PERS YM: Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. *Drug Saf* 2018; 41: 919-31.
15. FANOURIAKIS A, KOSTOPOULOU M, ALUNNO A *et al*.: 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78: 736-45.
16. DREW BJ, ACKERMAN MJ, FUNK M *et al*.; American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology, the Council on Cardiovascular Nursing, and the American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology

Foundation. *Circulation* 2010; 121: 1047-60.
17. TISDALE JE, JAYNES HA, KINGERY JR *et al*.: Effectiveness of a clinical decision support system for reducing the risk of QT interval prolongation in hospitalized patients. *Circ Cardiovasc Qual* 2014; 7: 381-90.
18. ARINGER M, COSTENBADER K, DAIKH D *et al*.: 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2019; 71: 1400-12.
19. HUANG C, WANG Y, LI X *et al*.: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506.
20. RUAN Q, YANG K, WANG W, JIANG L, SONG J: Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020; 46: 846-8.
21. WORLD HEALTH ORGANIZATION: The cardiotoxicity of antimalarials: Malaria Policy Advisory Committee Meeting. Published March 24, 2017 (no. WHO/HTM/GMP/MPAC/2017.8).
22. BESSIÈRE F, ROCCIA H, DELINIÈRE A *et al*.: Assessment of QT Intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. *JAMA Cardiol* 2020; 5: 1067-9.
23. MERCURO NJ, YEN CF, SHIM DJ *et al*.: Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020; 5: 1036-11.
24. ROSENBERG ES, DUFORT EM, UDO T *et al*.: Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA* 2020; 323: 2493-502.
25. SARAYANI A, CICALI B, HENRIKSEN CH, BROWN JD: Safety signals for QT prolongation or Torsades de Pointes associated with azithromycin with or without chloroquine or hydroxychloroquine. *Res Soc Adm Pharm* 2020; 17: 483-6.
26. SPINELLI FR, MOSCARELLI E, CECCARELLI F *et al*.: Treating lupus patients with antimalarials: analysis of safety profile in a single-center cohort. *Lupus* 2018; 27: 1616-23.
27. MCGHIE TK, HARVEY P, SU J, ANDERSON N, TOMLINSON G, TOUMA Z: Electrocardiogram abnormalities related to anti-malarials in systemic lupus erythematosus. *Clin Exp Rheumatol* 2018; 36: 545-51.
28. BOURRÉ-TESSIER J, UROWITZ MB, CLARKE AE *et al*.: Electrocardiographic findings in systemic lupus erythematosus: data from an international inception cohort. *Arthritis Care Res* 2015; 67: 128-35.
29. HOOKS M, BART B, VARDENY O, WESTANMO A, ADABAG S: Effects of hydroxychloroquine treatment on QT interval. *Heart Rhythm* 2020; 17: 1930-5.
30. ERRE GL, FERRACCIOLI ES, PIGA M *et al*.: Antimalarial use and arrhythmias in COVID-19 and rheumatic patients: a matter of dose and inflammation? *Ann Rheum Dis* 2020 May 18 [Online ahead of print].
31. ERRE GL, PIRAS A, PIGA M *et al*.: Qt and QT dispersion intervals in long-standing and moderately active rheumatoid arthritis: results from a multicentre cross-sectional study. *Clin Exp Rheumatol* 2020; 38: 516-22.
32. LAZZERINI PE, BOUTJDIR M, CAPECCHI PL: COVID-19, arrhythmic risk and inflammation: Mind the gap! *Circulation* 2020; 142: 7-9.
33. PLANT LD, XIONG D, ROMERO J, DAI H, GOLDSTEIN SAN: Hypoxia produces proarrhythmic late sodium current in cardiac myocytes by SUMOylation of NaV1.5 channels. *Cell Rep* 2020; 30: 2225-36.
34. ZHOU FEI, YU T, DU R *et al*.: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054-62.
35. AROMOLARAN AS, SRIVASTAVA U, ALÍ A, CHAHINE M *et al*.: Interleukin-6 inhibition of hERG underlies risk for acquired long QT in cardiac and systemic inflammation. *PLoS One* 2018; 13: e0208321.
36. ZHU H, RHEE JW, CHENG P *et al*.: Cardiovascular complications in patients with COVID-19: consequences of viral toxicities and host immune response. *Curr Cardiol Rep* 2020; 22: 1-9.