Research Article

Impact of Hydroxychloroquine, on QTc Interval, in Patients with Rheumatologic Diseases

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Abstract

Background: Hydroxychloroquine (HCQ) has been historically used for treatment of autoimmune diseases and more recently, it is used for treatment of COVID-19 patients. Using HCQ in COVID-19 patients resulted in corrected QT(QTc) prolongation which has potential to deteriorate into Torsades de Pointes and sudden cardiac death. As it is used chronically by rheumatologic patients so this study was designed to establish effect of HCQ on QTc in rheumatic patients.

Methods: A cross sectional comparative study conducted in Rheumatology Department Shaikh Zayed hospital, Lahore. Non-probability consecutive sampling technique was used. Duration of study was 169 days. 45 patients used HCQ for three months and 45 patients did not use HCQ. ECG was done at induction in the study and after three months. Serum calcium, potassium and magnesium were also checked at onset. QTc was calculated by Bazett's formula.

Results: QTc did not raise in 21(46%) patients, in both groups. QTc raised between 1- 50msec in 20(44.4%) and 23(51.1%) patients in HCQ exposed and unexposed patients, respectively. QTc rise more than 50msec in 4(8.88%) and 1(2.2%) patient in HCQ exposed and unexposed patients, respectively (p-value=0.344). The QTc change is associated with heart rate showing 75.0% chances of increased QTc among those with increased heart rate.

Conclusion: HCQ did not increase QTc interval in 46% study. 8.88% of HCQ exposed population and 2.22% of HCQ unexposed population had significant change in QTc. However, no adverse cardiac events were observed in study duration.

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Introduction

Hydroxychloroquine (HCQ) was launched in 1955 for use in malaria. Later on, it was used as a disease modifying anti rheumatic drug (DMARD) and anti-inflammatory drug in various rheumatic disorders i.e., systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), antiphospholipid syndrome (APLS). HCQ has demonstrated survival benefits in SLE, RA and APLS by reducing morbidity. HCQ use is associated with improved cardiac profile and reduced cardiovascular incidents by improving lipid profile, reducing

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thrombosis and ischemic heart disease. It has demonstrated its benefit in preventing thrombotic events in APLS.[1–3] Recently, HCQ use in diabetic population has resulted in clinically meaningful improvement in diabetic control.[4] HCQ has shown to attenuate risk of developing diabetes in RA.[5] The most common side effects are related to gastrointestinal tract e.g., abdominal discomfort nausea, vomiting and diarrhea.[6] Retinal toxicity is most threatening complication. In addition, HCQ associated skin pigmentation, myopathy, cardiac toxicity including rhythm disorders such as a prolong corrected QT interval (QTc), which can convert into Torsades de pointes (Tdp); a potentially life-threatening condition and sudden cardiac death (SCD) are also well-known side effects.[7]

The QT interval reflects depolarization then repolarization of the ventricles. QT is adjusted for heart rate to calculate QTc. Several formulas like Bazett, Fridericia, Framingham, Hodges and Rautaharju have been developed to calculate the QTc interval. Till late adolescence, QTc intervals are almost similar in both genders (370 msec upto 440 msec). In adults, the normal QTc interval is slightly longer in females (<460msec) as compared to males (< 450msec). When the QTc interval is 470–500 msec for males, or 480–500msec for females, or the QTc interval increases 60 msec or more from pretreatment values, the risk of arrythmia is increased so reasons behind should be sought.[8-9] Risk factors involved in QTc prolongation include female gender, advanced age, recent conversion from atrial fibrillation, congestive cardiac failure, left ventricular hypertrophy, subclinical LQTS, drugs, electrolyte disturbances (hypokalemia, severe hypomagnesemia), and diseases e.g. (diabetes mellitus, hypertension, cerebrovascular accidents, chronic kidney disease).[10]

The evidence is piling up which shows QTc prolongation in HCQ users[11] and occasional case reports of ventricular arrhythmia and Tdp while taking HCQ therapeutically for SLE treatment and other disorders.[12–14] However, this phenomenon of ventricular arrhythmias is very uncommon. HCQ use is associated with significantly low risk of cardiovascular events in RA population.[15] HCQ has been used extensively in COVID-19 without proper establishment of antiviral activity although it has shown no survival benefit.[16] But HCQ overwhelming use has resulted in reports of cardiac adverse events. Although treatment regimen is comprised of high doses of HCQ, as compared to 200-400mg HCQ daily, for a comparatively short period. Some studies have suggested patients receiving HCQ are at higher risk of various cardiac adverse effects including QTc prolongation, Tdp, cardiomyopathy and heart failure.[17] Recently, a large study of COVID-19 patients, treated with chloroquine/HCQ, with or without azithromycin, shown a marked increase in the QTc intervals. Increase in QTc was more pronounced in patients treated with combination therapy of HCQ and azithromycin as compared to HCQ monotherapy.[18] On the other hand, a recent study in COVID-19 patients, who received HCQ, demonstrated that none of the patients developed any sustained ventricular tachyarrhythmia.[19] Rather COVID-19 patients have conflicting evidence of improvement in cardiovascular profile in those patients who use HCQ. HCQ have been found to reduce arterial thrombosis, cardiac arrhythmia and hypercholesterolemia in recent peer-reviewed studies.[20]

As this drug is used extensively in rheumatologic diseases for years RA, SLE, MCTD, APLS and overlap syndrome. Therefore, because of conflicting observation and absence of guidelines about cardiac monitoring in patients on HCQ it is pertinent to study whether it effects QTc, in Pakistani population in long term (03 months). Primary objective of this study is to determine absolute QTc prolongation in patients taking HCQ for period of three months. Secondary objective of the study would be assessment of frequency of QTc prolongation in study population.

Methods

This study was performed in department of Rheumatology, Shaikh Zayed hospital, Lahore. It was a cross sectional comparative study. Non-probability consecutive sampling technique was used. Duration of study was 169 days w.e.f. 28 march 2021 to 12 September 2021. Sample size of 45 patients was estimated by using confidence interval of 95%, 90% power with expected QTc before start of HCQ as 424±45 and after 6 months as 449±55. 45 control patients were also be taken as control group. This study was given IRB approval on 28-03-2021, with IRB ID SZMC/IRB/internal/0061/2021. Approval number/reference number of the study was SZMC/IRB/0090/2021.

Two resting 12-lead ECGs were taken with time gap of three months. R-R interval, heart rate, QT and QTc were recorded in limb leads II, V5 or V6. Multiple consecutive ECG beats were measured for QT interval and largest one was taken. Measurement of QT interval was done from start of Q wave until the end of T wave where it joins again isoelectric line. Definition of the end of the T-wave is a tangent that will be drawn from the last limb of the T-wave, to its intersection with the isoelectric line. Large U-wave more than 1mm, joined with T-wave were regarded as a part of QT interval. QT interval was defined as time from the starting of the Q wave (first negative deflection of QRS on ECG wave form) to the point where T wave (upstroke of ecg following QRS complex on ECG waveform) ends. QTc interval was adjusted for QT interval against R-R interval by Bazett's formula: QTC = QT / √ RR. Normal QTc intervals 460msec in females and 450msec in male were taken as the upper limits of normal, respectively. Time interval more than these is considered as prolong QTc interval.

Patients of both gender with age between 16 to 65 years were included. Patients were divided in two groups; Without HCQ: HCQ naïve patients who did not take HCQ at all and With HCQ: HCQ Naïve patients of any rheumatologic disease who would take HCQ according to weight 6.5mg/kg (maximum 400mg) for at least three months were included. Patients were tested for serum calcium, magnesium and potassium levels those who were found having normal values were included in this study. Patients with past medical history of cardiac diseases, any arrhythmia, comorbid severe illnesses stroke, end stage renal disease, decompensated chronic liver disease and severe chronic obstructive pulmonary disease were excluded from the study. Patient taking tricyclic antidepressant, SSRI and SNRI which are known to be a risk factor for QTc prolongation, were also excluded from study.

The enrolled patients were examined for their ECG at baseline and at interval of three months and data such as gender, age, disease, heart rate, QT, RR and QTc intervals were tested at baseline and at three months interval. Serum calcium, potassium and magnesium were tested at the baseline. Data were entered and analyzed by using IBM Statistics, SPSS version 20.0. Data for age, calcium, potassium and magnesium, 1st heart rate, 2nd R-R interval, QTc interval 1st and 2nd reading, QTc interval absolute and percentage changes were described by using mean ± Sd as normally distributed and 1st and 2nd QT intervals, 2nd heart rate and 1st R-R interval were described by using median (IQR). Comparison of all normally distributed variables were performed by using independent sample t-test and others by using Mann Whitney U test, between two groups; "without HCQ exposure" and "with HCQ exposure". Absolute change and percentage change in QTc interval were also calculated. Data for gender, rheumatologic disorder, absolute change and percentage change of QTc interval, was presented by using frequency and percentage. Prolong QTc was regressed to HCQ, taking age, gender, and change in heart rate as confounding variables through binary logistic regression and results were presented by using adjusted odds ratio with 95% confidence interval. P-value ≤ 0.05 was considered significant.

Results

The group without HCQ exposure had 14(31.1%) cases with Ankylosing spondylitis (AS), 7(15.6%) cases with JIA and 6(13.3%) with mechanical backache as most prevalent patients' diseases. In group with HCQ exposure, most of the cases 38(84.4%) were of RA and SLE,

Table 1: *The Distribution of Cases by Disease and Hydroxychloroquine Status*

Disease	Group					
	Without HCQ		With HCQ		Total	
	N	%	N	%	N	%
RA	0	0.0	28	62.2	28	31.1
AS	14	31.1	0	0.0	14	15.6
SLE	0	0.0	10	22.2	10	11.1
JIA	7	15.6	0	0.0	7	7.8
Mechanical Backache	6	13.3	0	0.0	6	6.7
OA	4	8.9	0	0.0	4	4.4
PsA	3	6.7	0	0.0	3	3.3
PM	3	6.7	0	0.0	3	3.3
Overlap Syndrome	0	0.0	3	6.7	3	3.3
MCTD	0	0.0	3	6.7	3	3.3
Fibromyalgia	3	6.7	0	0.0	3	3.3
SS	2	4.4	0	0.0	2	2.2
ITP	1	2.2	0	0.0	1	1.1
APLS	0	0.0	1	2.2	1	1.1
AOSD	1	2.2	0	0.0	1	1.1
ANCA vasc	1	2.2	0	0.0	1	1.1
Total	45	100.0	45	100.0	90	100.0

while only 1(2.22%) with APLS. Disease distribution of both groups is given (Table 1).

There were 25(55.55%) males in group without HCQ exposure while 16(35.55%) in group with HCQ exposure but gender difference was insignificant between two groups, with p-value 0.090. There were 21(46%) cases in each group whom QTc did not increase at three months interval. There were 20(44.4%) cases in group with HCQ exposure with raised QTc between 1- 50msec, while 4(8.88%) had raised QTc by more than 50msec. Group without HCQ exposure had 23(51.1%) with increased QTc between 1- 50msec while only 1(2.22%) case with QTc raise of more than 50msec. This difference was also found insignificant with p-value 0.344. This is reflected in figure1 given below;

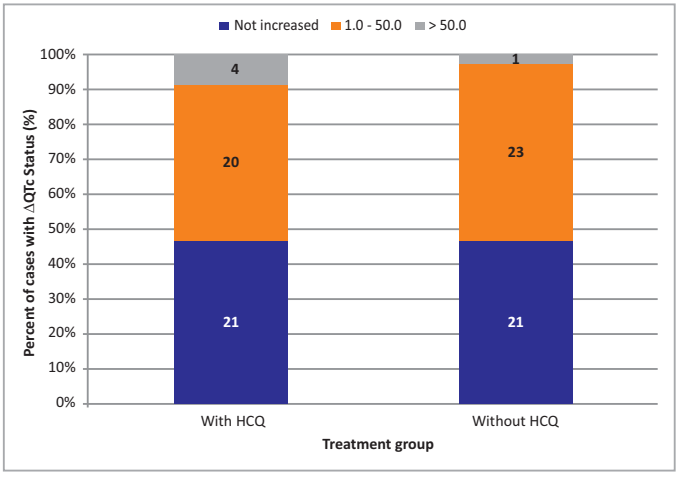

Figure 1: Percentage of cases with change in QTc in HCQ exposed ND unexposed groups

All ECG measures were found insignificantly different between two groups with p-values >0.05. The only significant difference was observed for age. Group with HCQ exposure had a significantly higher average age of 36.8±14.7 years as compared to 30.4±13.4 for the group without HCQ exposure and the p-value for age was 0.032. The absolute change in QTc for group with HCQ exposure was 0.58±39.0 while group without HCQ exposure was 4.0±25.3, when measured relatively the change for two groups were 0.63±8.8 and 1.28±6.1 percent respectively. The serum potassium levels had no significant difference between two groups with p-value 0.136, having all values in normal range. The magnesium and potassium levels, though had a statistically significant difference between two groups at baseline with p-values 0.023 and <0.001, but the mean and individual values were all in normal range so could not be considered clinically significant. (Table 2).

Mann Whitney U test is used for (1st QT interval, 2nd QT Interval, 2nd HR and 1st RR), Independent sample t-test is used for all other measures

The change in QTc (ΔQT) was related to age, gender, HCQ and change in heart rate (ΔHR) and was observed that except ΔHR all had no association with ΔQT. The odds ratios of group without HCQ were 1, age 1.74, male gender 0.82 but for ΔHR was found 11.0(4.10 – 29.45) for raised QTc. When binary logistic regression analysis was applied it revealed that the HCQ exposure has no association with raised QTc in the presence of

Table 2: *Status and Comparison of Age, ECG Parameters Electrolytes between Two Groups*

	Group						P-value
	With HCQ			Without HCQ			
	Mean	SD	Median (IQR)	Mean	SD	Median (IQR)	
Age	36.8	14.7		30.4	13.4		0.032
1st QT interval			360 (320 – 360)			360 (320 – 360)	0.428
2nd QT interval			360 (360 – 400)			360 (320 – 360)	0.194
1st HR	85.8	15.1		85.8	17.4		1.000
2nd HR			81 (76 – 88)			83 (75 – 90)	0.689
1st RR			710 (630 – 800)			750 (610 – 810)	0.981
2nd RR	735.8	92.8		714.9	100.0		0.307
QTc 1st	423.7	40.4		415.4	34.7		0.296
QTc 2nd	424.3	36.1		419.4	26.8		0.465
Δ QTc (absolute)	0.58	39.0		4.0	25.3		0.621
Δ QTc (percent)	0.63	8.8		1.28	6.1		0.682
S. Potassium (mmol/L)	4.34	0.38		4.46	0.37		0.136
S. Magnesium (mg/dl)	2.05	0.16		1.98	0.12		0.023
S. Calcium (mg/dl)	8.83	0.15		9.05	0.10		<0.001

age, gender and heart rate as confounding variables. The adjusted odds ratio was 0.78(0.27 – 2.22) showing an equal exposure to HCQ for those with raised QTc as compared to not raised. However, the heart rate increase had a significant association with QTc raised showing 12.77 times higher exposure to increased heart rate among those with raised QTc as compared to those not experiencing increased QTc. The gender and age also had no significant effect on raised QTc. The accuracy of this regression model was overall 76.7% showing reasonably good. The predictability of model with raised heart rate to predict raised QTc was 75.0% and for those with no rise in heart rate to predict no rise in QTc was 78.6%. (Table 3)

Table 3: *Relation of Change in QTc with Change in HR by Taking age, Gender and HCQ as Confounding Variables with Prediction Accuracy Binary Logistic Regression Model*

		ΔQT					P-value	Odds ratio	Adjusted Odds ratio
		Raised		Not raised		Total			
		N	%	N	%	N			
Group	With HCQ	24	53.3	21	46.7	45	0.635	1(0.44 – 2.29)	0.78(0.27 – 2.22)
	Without HCQ	24	53.3	21	46.7	45		Ref	Ref
Age	> 35	21	61.8	13	38.2	34	0.410	1.74(0.73 – 4.13)	1.56(0.54 – 4.46)
	. . .	27	48.2	29	51.8	56		Ref	Ref
Sex	Female	25	51.0	24	49.0	49	0.188	0.82(0.35 – 1.88)	0.49(0.17 – 1.42)
	Male	23	56.1	18	43.9	41		Ref	Ref
ΔHR	Increased	36	80.0	9	20.0	45	<	11.0(4.10 – 29.45)	12.77(4.44 – 36.68)
	Not Increased	12	26.7	33	73.3	45	0.001	Ref	Ref

Classification Table (Nagelkerke R^2 = 0.377)

Observed		Predicted		
		ΔQT		Percentage Correct
		Raised	Not Raised	
ΔQT	Raised	36	12	75.0
	Not Raised	9	33	78.6
Overall Percentage				76.7

Discussion

With the discovery of COVID-19, started a race, of finding novel solution for this pandemic that resulted in use of medication which lack strong scientific evidence. The drugs like HCQ and Azithromycin were used in COVID-19 patients. As a result, COVID-19 patients surfaced having higher QTc values. Studies in COVID-19 patients showed combination therapy with HCQ and Azithromycin prolongs QTc interval more than monotherapy with HCQ, in patients with COVID-19. But there were no adverse cardiac events observed.[21–23] Despite the fact that COVID-19 patients took these drugs for short period of time, LQTS was observed quite frequently and quickly.[24] This unusual frequency was not observed in rheumatic patients as frequently despite the fact that HCQ had been in use more than 70 years in rheumatologic patients. i.e. RA SLE, MCTD.

In this study we applied HCQ as per indication in patients like RA, SLE, MCTD, APLS, overlap syndrome. Made patient assessment at the baseline and after 03 months interval when patients had used HCQ, side by side we collected data of another group of rheumatic patients, for whom HCQ was not indicated, so they never used HCQ. Findings of this study suggested that in rheumatologic patients there is no change in QTc in 21(46.66%) patients in both HCQ exposed and unexposed groups, however, there is insignificant change of less than 50msec in 20 (4.44%) and 23(51.11%) patients in group with HCQ exposed and unexposed patients respectively. There is significant change of >50msec in 4(8.88%) patients with HCQ exposure and 1(2.22%) patient with HCQ non exposure but there is no conversion into Tdp or life-threatening event as in other studies. Patients' mean age was 36.8 with SD 14.7 in group-1 and 30.4 with SD 13.4 in group-2. Age was only significant variable in patient characteristics as reflected by P-value of 0.032.

This finding is in accordance to studies in past which shown impact of advanced age on QTc.

Using HCQ in treatment of rheumatic disorders SLE, rheumatoid arthritis, and others shown promising results. There was reduced risk of CVD, improved diabetic control and lipid profile as opposed to its usage in COVID-19 patients.[25] Whereas, it is observed to result in QTc prolongation and TdP even in patients with no underlying cardiovascular comorbidity.[4,11] In literature, the normal range of QTc is 350–440msec, it is often underestimated that 10–20% of healthy adults have prolong QTc values beyond this described normal range. So, 10–20% of the human population has borderline QT prolongation as per aforementioned definitions, guidelines and cut-offs values.[26]

COVID-19 patients presenting with prolong QTc had high morbidity and mortality because of heart lung interaction in the form of thrombotic microangiopathy, damage of pulmonary circulation and severe heart failure much more frequently than rheumatologic involvement of heart.[27-28] Insignificant increase in QTc while taking HCQ in rheumatologic patients and absence of cardiac events suggest that drug have direct beneficial effect on rheumatologic diseases which outweigh cardiac risks.[29] Those patients who have no baseline clinical factors associated with subsequent QTc prolongation and whom frequent monitoring can be done (including continuous QTc interval monitoring by ECGs, serum electrolytes and renal function tests), complications including drug-induced Tdp can be avoided. So with no baseline QTc prolonging factors, continuous ECG monitoring, lab testing for renal function, serum electrolytes, hydroxychloroquine is a safe drug in rheumatologic patients and should be encouraged for its beneficial effects in rheumatic diseases. The study period was small and could recruit only small sample size because of low frequency of HCQ naive rheumatic patients and difficulty in registration and follow up of patients during COVID-19 pandemic. So it needs further research in a larger cohort of rheumatologic patients for longer follow up duration, to strengthen the results and make them more applicable.

Conclusion

HCQ did not increase QTc interval in 46% study population both HCQ exposed and unexposed groups. 8.88% of HCQ exposed population and 2.22% of HCQ unexposed population had significant change in QTc. However, no adverse cardiac events like cardiac arrhythmias, Torsades de Pointes or sudden cardia death were not observed in three months duration. As benefits of HCQ in rheumatologic patients outweigh risk of Long QTc syndrome, HCQ should remain in use among rheumatologic patients but monitoring of QTc with ECG should be done regularly at least three months interval to avoid any untoward events.

Ethical Approval: The Institutional review board approved the study vide letter No. SZMC/IRB/-Internal/ 0061/2021.

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FA: Conception, design, analysis, interpretation, of data, drafting and critical revision

TM: Supervised all steps and critical revision of the article

AR: Conception, design, drafting, critical review

UH: Design, analysis, critical review and drafting

AA: Conception, drafting and literature review

RG: Design, critical review and drafting

References

1. dos Reis Neto ET, Kakehasi AM, de Medeiros Pinheiro M, Ferreira GA, Marques CDL, da Mota LMH, et al. Revisiting hydroxychloroquine and chloroquine for patients with chronic immunity-mediated inflammatory rheumatic diseases. Advances in Rheumatology. 2020;60(1):32.
2. Dima A, Jurcut C, Arnaud L. Hydroxychloroquine in systemic and autoimmune diseases: Where are we now? Joint Bone Spine. 2021 ;88(3):105143.
3. Arunachalam K, Lakshmanan S, Maan A, Kumar N, Dominic P. Impact of Drug Induced Long QT Syndrome: A Systematic Review. J Clin Med Res. 2018;10(5):384–90.
4. Wondafrash DZ, Desalegn TZ, Yimer EM, Tsige AG, Adamu BA, Zewdie KA. Potential Effect of Hydroxychloroquine in Diabetes Mellitus: A Systematic Review on Preclinical and Clinical Trial Studies. Journal of Diabetes Research.

2020;2020(1):e5214751..

5. Bili A, Sartorius JA, Kirchner HL, Morris SJ, Ledwich LJ, Antohe JL, et al. Hydroxychloroquine use and decreased risk of diabetes in rheumatoid arthritis patients. J Clin Rheumatol. 2011;17(3):115–20.
6. Lofgren SM, Nicol MR, Bangdiwala AS, Pastick KA, et al. Safety of Hydroxychloroquine Among Outpatient Clinical Trial Participants for COVID-19. Open Forum Infect Dis. 2020 ;7(11):ofaa500. doi: 10.1093/ofid/ofaa500. PMID: 33204764; PMCID: PMC7654376.
7. Jallouli M, Francès C, Piette JC, Huong du LT, et al. Hydroxychloroquine-induced pigmentation in patients with systemic lupus erythematosus: a case-control study. JAMA Dermatol. 2013;149(8):935-40. doi: 10.1001/jamadermatol.2013.709. PMID: 23824340.
8. Ayad RF, Assar MD, Simpson L, Garner JB, Schussler JM. Causes and management of drug-induced long QT syndrome. Proceedings (Baylor University Medical Center). 2010 ;23(3):250.
9. Rochester MP, Kane AM, Linnebur SA, Fixen DR. Evaluating the risk of QTc prolongation associated with antidepressant use in older adults: a review of the evidence. Ther Adv Drug Saf. 2018;9(6):297–308.
10. Kallergis EM, Goudis CA, Simantirakis EN, Kochiadakis GE, Vardas PE. Mechanisms, Risk Factors, and Management of Acquired Long QT Syndrome: A Comprehensive Review. Scientific-WorldJournal. 2012;20(12):212178.
11. Raza HA, Tariq J, Agarwal V, Gupta L. COVID-19, hydroxychloroquine and sudden cardiac death: implications for clinical practice in patients with rheumatic diseases. Rheumatology International. 2021;41(2):257-73.
12. Singh AP, Tousif S, Umbarkar P, Lal H. A pharmacovigilance study of hydroxychloroquine cardiac safety profile: potential implication in COVID-19 mitigation. Journal of clinical medicine. 2020 ;9(6):1867.
13. Saleh M, Gabriels J, Chang D, Soo Kim B, Mansoor A, Mahmood E, Makker P, Ismail H, Goldner B, Willner J, Beldner S. Effect of chloroquine, hydroxychloroquine, and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Circulation: Arrhythmia and Electrophysiology. 2020;13(6):e008662.
14. Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: From Malaria to Autoimmunity. Clin Rev Allergy Immunol. 2012;42(2):145–53.
15. Sharma TS, Wasko MCM, Tang X, Vedamurthy D, Yan X, Cote J, et al. Hydroxychloroquine Use Is Associated With Decreased Incident Cardiovascular Events in Rheumatoid Arthritis Patients. J Am Heart Assoc. 2016;5(1):e002867.
16. Linsell L, Bell J. Effect of hydroxychloroquine in hospitalized patients with COVID-19-preliminary report. New England Journal of Medicine. 2020;383(1):72.
17. McCullough PA, Alexander PE, Armstrong R, Arvinte C, Bain AF, Bartlett RP, et al. Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19). Reviews in Cardiovascular Medicine. 2020;21(4):517–30.
18. Bun SS, Taghji P, Courjon J, Squara F, Scarlatti D, Theodore G, Baudouy D, Sartre B, Labbaoui M, Dellamonica J, Doyen D. QT interval prolongation under hydroxychloroquine/azithromycin association for inpatients with SARS-CoV-2 lower respiratory tract infection. Clinical Pharmacology & Therapeutics. 2020;108(5):1090-7.
19. Satlin MJ, Goyal P, Magleby R, Maldarelli GA, Pham K, Kondo M, Schenck EJ, Rennert H, Westblade LF, Choi JJ, Safford MM. Safety, tolerability, and clinical outcomes of hydroxychloroquine for hospitalized patients with coronavirus 2019 disease. PLoS One. 2020;15(7):e0236778.
20. Prodromos CC, Rumschlag T, Perchyk T. Hydroxychloroquine is protective to the heart, not harmful: a systematic review. New microbes and new infections. 2020;37(1):100747.
21. Cipriani A, Zorzi A, Ceccato D, Capone F, Parolin M, Donato F, Fioretto P, Pesavento R, Previato L, Maffei P, Saller A. Arrhythmic profile and 24-hour QT interval variability in COVID-19 patients treated with hydroxychloroquine and azithromycin. International Journal of Cardiology. 2020;316(1):280-4.
22. Carron J, Sharif Z, Hussein H, Kennedy M, McAdam B, Sheahan R. Clinical guidance for navigating the QTc-prolonging and arrhythmogenic potential of pharmacotherapy during the COVID-19 pandemic. Irish Journal of Medical Science 2021;190(1):403-9.
23. Eftekhar SP, Kazemi S, Barary M, Javanian M, Ebrahimpour S, Ziaei N. Effect of hydroxychloroquine and azithromycin on QT interval prolongation and other cardiac arrhythmias in COVID-19 confirmed patients. Cardiovascular

Therapeutics. 2021;4(1):1-7.

24. Antivalle M, La Paglia G, Ditto MC, Parisi S, Fusaro E, Agosti M, et al. Risk of QT interval prolongation associated with chronic use of hydroxychloroquine in rheumatic patients and the effect of cotreatments. Annals of the Rheumatic Diseases. 2021;8(1)-:254–259.
25. Johnson JN, Ackerman MJ. QTc: how long is too long. Br J Sports Med. 2009;43(9):657.
26. Chen B-H, Shi N-N, Wu C-W, An D-A, Shi Y-X, Wesemann LD, et al. Early cardiac involvement in patients with acute COVID-19 infection identified by multiparametric cardiovascular magnetic resonance imaging. Eur Heart J Cardiovasc Imaging. 2021;22(8):844–51.
27. Dandel M. Heart–lung interactions in COVID-19: prognostic impact and usefulness of bedside echocardiography for monitoring of the right ventricle involvement. Heart Fail Rev. 2021;8(1):1–15.
28. Hooks M, Bart B, Vardeny O, Westanmo A, Adabag S. Effects of hydroxychloroquine treatment on QT interval. Heart Rhythm. 2020 ;17(11):1930.