DOI: 10.1002/jmv.26004

LETTER TO THE EDITOR

JOURNAL OF MEDICAL VIROLOGY WILEY

Conduction abnormalities in hydroxychloroquine add on therapy to lopinavir/ritonavir in COVID-19

To the Editor,

We read with interest the systematic review and meta-analysis by Sarma et al[1] on the use of hydroxychloroquine (HCQ) in coronavirus disease-2019 (COVID-19). They concluded that more evidence is required for definitive conclusions and recommended electrocardiography (ECG) monitoring. Currently, the role of HCQ in COVID-19 remains controversial but continued to be used in the absence of effective therapy.[2,3] We like to add on our experience with use of HCQ as add on therapy for COVID-19.

To date, we have 138 reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed COVID-19 cases, of which 48 have received treatment following our treatment protocol. Mild cases were monitored and given symptomatic treatment whereas moderate/severe cases or with any of the followings; chest radiograph (CXR) changes, age more than 60 years with comorbidities (diabetes, immunocompromised, pulmonary, or cardiovascular disease), persistent fever and/or diarrhea, lymphopenia, neutrophil to lymphocyte ratio greater than or equal to 3.1 and National Early Warning Score (≥5) were started on treatment. Our treatment consist of lopinavir-ritonavir (400/100 mg; twice daily at least 14 days) as the first line. HCQ (400 mg twice daily day-1 and 200 mg twice daily day-2-5) was added if there was no response to lopinavir/ritonavir. Patients also received Tamiflu (75 mg twice daily; 5 days), and antibiotics when indicated. Other medications associated with QTc prolongation (defined as > 450 ms for male and >470 ms for female) were not used. ECG were done at baseline (before the first dose of HCQ), day-2, day-4, and when indicated. Laboratory investigations were done on admission and as required. Patients were discharged after recovering with two consecutive negative RT-PCR 24 hours apart after 13 days from diagnosis.

Eleven patients had HCQ added on at a median of 2 days (range, 0-6) after starting lopinavir/ritonavir (Table 1). Two patients (18%) had acute kidney failure (case-1 and case-10) on admission and none had any known cardiac disease. Baseline (pre-HCQ) ECGs were normal apart from two (18%) patients who had QTc prolongation. Case-4 was started on HCQ as the QTc prolongation was not critical (defined as QTc >500 ms) and in case-1 due his critical nature and disease progression despite lopinavir/ritonavir. After starting HCQ, there were five (45.5%) new events; prolonged QTc in three including one associated with right bundle brunch block, one with bradycardia, and one with thrombocytopenia. HCQ was discontinued in five (45.5%) patients (Table 1). All conduction abnormalities normalized after HCQ discontinuation. Two patients continued on HCQ despite prolonged QTc; case-4 had mild increase in QTc (noncritical) and case-1 had improvement of QTc (Δ − 23 ms). There were no electrolytes abnormalities on the days of ECGs abnormalities except for mild hypocalcemia (2.14 mmol/L; normal range 2.23-2.58) in case-8. To date, eight (72.7%) patients have recovered and discharged after virological clearance (negative RT-PCR two consecutive times), two (18.8%) remain unwell (ventilation and extracorporeal membrane oxygenation [ECMO] support) and one death (case-1: admitted with coexisting *Staphylococcus aureus* bacteremia progressing to septicemia needing ventilatory, renal, and ECMO support).

Our experience showed that potentially significant cardiac side effects were common in patients treated with HCQ add on therapy to lopinavir/ritonavir. Three patients (27.3%) developed prolonged QTc (WHO-UMC system; certain) after starting HCQ including two critical (18.2%) with additional development conduction blocks in two patients at cumulative HCQ dose of 1200 mg. Molina et al[4] reported one (9.1%) QTc prolongation, while Chorin et al[5] reported 30% ($_{\Delta}$QTc of > 40 ms from baseline) with 11% having critically prolonged QTc interval (> 500 ms). These studies had used HCQ and azithromycin combination. Literature on HCQ use in rheumatic disorders also reported common cardiac side effects.[6] On the other hand, study has also shown HCQ and chloroquine to be associated with reduction cardiovascular risk in patients with rheumatic disorders.[7] However, this was likely due to the reduction in atherosclerosis-related events. Our patient with bradycardia was possibly related to HCQ (WHO-UMC system; possible), which resolved several days after discontinuation of HCQ, whereas the case with thrombocytopenia was not.

Most medications currently used for COVID-19 (HCQ, chloroquine, lopinavir/ritonavir, and azithromycin) are associated with QTc prolongation. Two of our patients with pre-HCQ QTc prolongation were on lopinavir/ritonavir. However, there were other factors such as acute renal failure and critical illness (case-1). Off major concern is the potential widespread use of HCQ and chloroquine due to recommendation for treatment or as prophylaxis for COVID-19.[8] As recommended by Sarma et al[1] monitoring (ECG) is essential if HCQ is to be considered. In addition, risk score should be considered.[9] HCQ is also associated with many noncardiac adverse effects (ie, metabolic such as hypo and hyperglycemia, gastrointestinal, ophthalmic, neurological, musculoskeletal, dermatological, and psychiatric).[10,11] In the meantime, we have currently held off using HCQ for treating patients with COVID-19.

TABLE 1 Details of patients with COVID-19 treated with hydroxychloroquine add on therapy to lopinavir/ritonavir

Case	Age/sex	Comorbid	Admission eGFR (mL/min)	Admission to HCQ add on (d)	Stage of disease when started on HCQ	Baseline (pre-HCQ) ECG	QTc[a]	Reasons for stopping HCQ (d)	Cumulative dose of HCQ	Latest RT-PCR	Outcomes
1	64/M	HT/DLD/overweight	27.8	11	Severe	Long QTc 538 ms	515 ms (d-2)	…	2200 mg	+ve	Died from MOF *Staphylococcus aureus* septicemia RT-PCR+ve
2	42/F	HT/DM/overweight	117.4	6	Moderate	Normal	…	…	2400 mg	−ve	Alive (discharged) RT-PCT−ve
3	43/M	Overweight	130.9	2	Moderate	Normal	490 ms (d-2)	QTc prolongation & left fascicular block (d-2)	1000 mg	−ve	Alive (discharged)
4	41/M	HT/overweight	107.1	1	Moderate	Long QTc 458 ms	469 ms (d-4)	…	2400 mg	−ve	Alive (discharged)
5	56/M	Ex-smoker/ overweight	90.6	1	Severe	Normal	…	…	2400 mg	−ve	Alive (ventilation & ECMO)
6	27/M	…	95.9	5	Moderate	Normal	…	…	2000mg	−ve	Alive (discharged)
7	51/F	HT/overweight	109.4	3	Moderate	Normal	514 ms (d-3)	QTc prolongation (d-3)	1200 mg	−ve	Alive (discharged)
8	60/F	HT/DLD/overweight	82.1	3	Severe	Normal	631 ms (d-4)	RBBB & QTc prolongation (d-4)	1400 mg	−ve	Alive (discharged) ventilation, treatment for pulmonary embolism
9	50/F	…	99	3	Moderate	Normal	…	…	2400 mg	−ve	Alive (discharged)
10	67/M	DLD	34.5	1	Severe	Normal	…	Bradycardia (d-2)	1000 mg	+ve	Alive (ventilation & ECMO)
11	66/M	HT (new)/overweight	78.2	8	Moderate	Normal	…	Thrombocytopenia (d-3)	1200 mg	−ve	Alive (discharged)

Abbreviations: COVID-19, coronavirus disease-2019; DLD, dyslipidemia; DM, diabetes mellitus; ECG, electrocardiography; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; F, female; HCQ, hydroxychloroquine; HT, hypertension; M, male; MOF, multi organ failure; RBBB, right bundle brunch block; RT-PCR, reverse transcriptase-polymerase chain reaction.
[a]QTc prolongation >450 ms for male and >470 ms for female.

CONFLICT OF INTERESTS

All the authors declare that there are no conflict of interests.

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