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LETTER TO THE EDITOR

WILEY

QTc evaluation in COVID-19 patients treated with chloroquine/hydroxychloroquine

In late December 2019, a cluster of pneumonia cases caused by a novel coronavirus occurred in Wuhan, China, and has spread rapidly initially throughout Europe and later in the United States.[1] The pathogen was originally called 2019 novel coronavirus (2019-nCoV) and later named severe acute respiratory syndrome coronavirus 2 (SARS-nCoV-2) by the World Health Organization (WHO). Although most human infection linked by coronavirus are mild, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) were responsible for 8422 and 1600 infections with 916 and 574 deaths, with a mortality rate of 10% and 37%, respectively.[2,3,4,5] SARS-CoV-2 shares many similar clinical symptoms with SARS-CoV and MERS-CoV, including fever, dry cough, fatigue and worsening dyspnoea with interstitial pneumonia that in up to 3%-5% might unfortunately evolve in a severe acute respiratory distress syndrome (ARDS).[6,7] By 26 April 2020, 2 940 979 confirmed cases have been reported globally, with 203 822 deaths. The infection is now spread in 210 countries, with a median mortality rate up to 7%.[8] The rapid worldwide diffusion of SARS-CoV-2 prompted the WHO to proclaim the state of pandemic on 11 March 2020.[9] While social-distancing measures were rapidly implemented, a safe and effective vaccine is likely to take many months or years.

Up to now, since no effective SARS-CoV-2 therapy is available, patients are treated with several nonspecific drugs. Despite poor real clinical evidence of unequivocal beneficial effect of chloroquine/hydroxychloroquine (CQ/HCQ), the absence of an effective COVID-19 treatment and the social pressure raised the demand of these drugs for its compassionate use, both in hospital and outpatient settings.[10]

High-dosed HCQ showed promising potential effect in reducing SARS-CoV-2 viral load in COVID-19 patients with enhanced effects in combination with azithromycin or several antiviral drugs.[11]

CQ/HCQ are two old anti-malarial drugs also used in long-term treatment of connective tissue disease making both drugs widely available and economically sustainable.

Nevertheless, cardiac toxicity may occur following QT prolongation and sodium-channel inhibition, resulting in ventricular arrhythmias, conduction blockade and cardiovascular collapse Figure 1. ECG QT interval prolongation could reflect prolongation of ventricular repolarization and thus the effective refractory period. Many factors affect the duration of ventricular repolarization, and the QT interval varies from beat-to-beat, day-to-day and daytime to night-time. It is affected by several factors such as age, sex, electrolyte concentrations, autonomic tone, myocardial ischaemia and importantly by several different classes of drugs. This pharmacological property is used to prevent ventricular arrhythmias, but it could also cause them predisposing to intraventricular circuits of depolarization that manifest as potentially lethal polymorphic malignant ventricular tachyarrhythmias (torsades de pointes).[12] Chloroquine/Hydroxychloroquine provoke sodium and calcium channel blockades, which lead to membrane-stabilizing effects that might result in conduction disturbances with atrioventricular block, and QRS interval widening and a dangerous QT prolongation Figure 1. This side effect might be even enhanced in the setting of COVID-19 setting because of drug-to-drug interaction (azithromycin, antivirals, etc) and the clinical setting of acute infection that usually sees fever, dehydration and electrolyte abnormalities. Finally, SARS-CoV-2 is primarily responsible for an acute respiratory infection that might present a trigger for acute cardiovascular events like myocarditis or acute coronary syndrome.[13,14]

QTc prolongation and cardiotoxicity closely correlate with CQ/HCQ dose and duration, and a recently published review of complications affecting patients treated with a long time high cumulative dose of CQ showed that cardiac conduction disorders were the main side effects with an incidence reported up to 85% of all complications.[15]

Considering this, it could be argued that an incautious use of CQ/HCQ might be responsible of a certain amount of undiagnosed arrhythmic deaths improperly attributed to COVID-19 itself. In so forth, we believe that is probably time to have prospective clinical trials that will evaluate the safety and efficacy of HCQ during treatment of COVID-infected patients.

In the meantime, if pneumologist, internal doctor or specialist in infective disease will recommend HCQ, especially

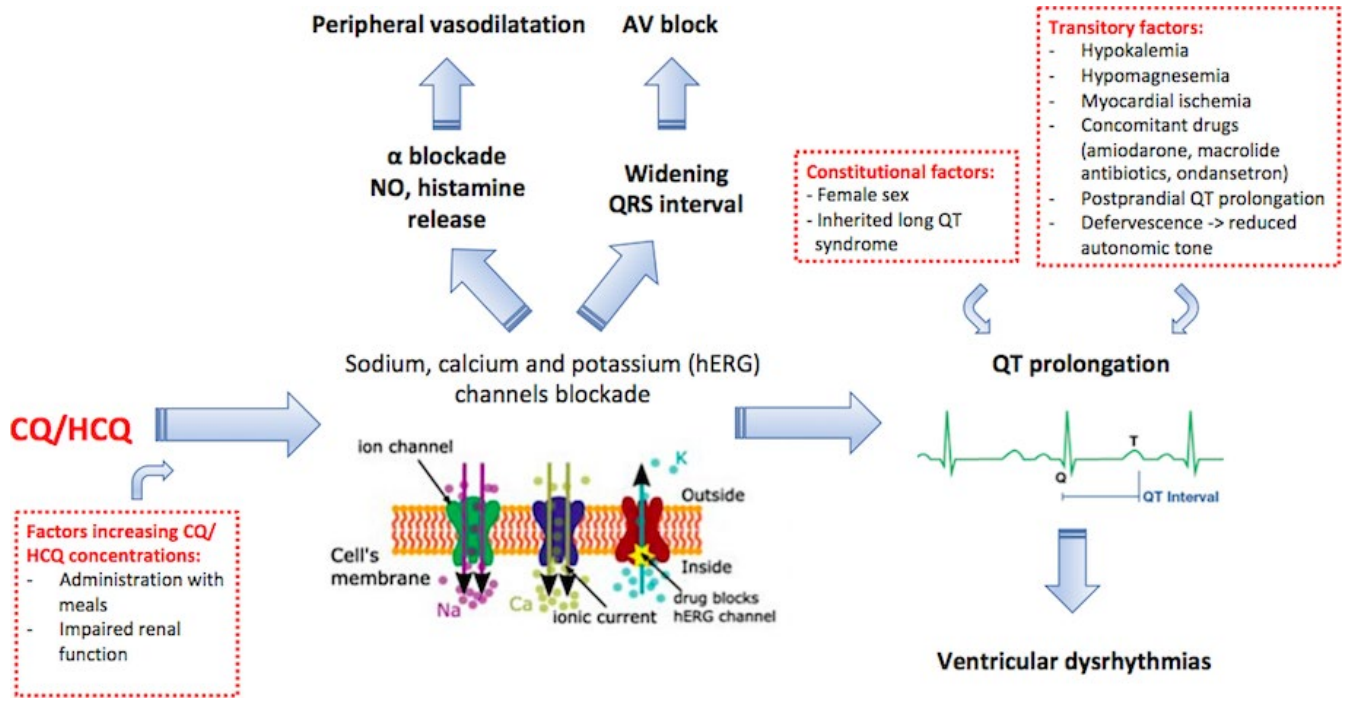

FIGURE 1 Cardiac toxicity related to chloroquine/hydroxychloroquine pathophysiology

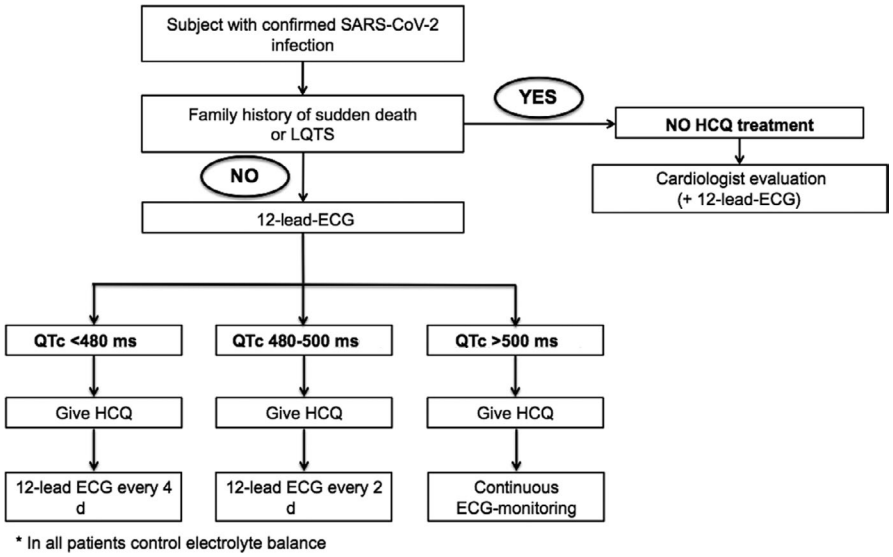

FIGURE 2 Flow chart for QTc monitoring during hydroxychloroquine (HCQ) treatment in subjects with confirmed SARS-CoV-2 infection

in combinations with azithromycin or antivirals we suggest an easy step-by-step flow chart for hospitalized COVID-19 patients that could offer an easy way to control the risk of HCQ cardiotoxicity Figure 2. Firstly, the concomitant use of other drugs that could result in QT prolongation and sodium-channel inhibition should be highly discouraged. Moreover, a careful checklist that will exclude the presence of long-QT genetic disease (both for the patient and for the family) and familiar unexplained sudden cardiac death should be the first anamnestic step. If yes, the patient should be referred to a complete cardiological evaluation. If not, we recommend having a baseline 12-lead ECG and, if possible, a blood sample with evaluation of electrolytes followed by our flow chart for QTc monitoring during HCQ administration. In case of outpatients setting, we recommend an ECG every 7 days. In case of QTc > 500 ms, please consider the need of hospital admission and continuous ECG monitoring.

Nonetheless, the mandatory requirement of a basal ECG would be a considerably limiting requirement for the prescription of HCQ in outpatients, especially in consideration of the limited availability of healthcare professionals and personal protective equipment to protect them in a pandemic situation.

Stay at home is an important message able to contain spreading of the virus, and awaiting the widely availability of telemedicine ECG-telemetry, the use of smartphone-based pocket ECG reliable devices should be highly encouraged and can potentially save healthcare resources in the current situation.

CONFLICT OF INTEREST

None.

Alice Monzani[1]
Giulia Genoni[2]
Alice Scopinaro[3]
Gianfranco Pistis[3]
Daniela Kozel[3]
Gioel Gabrio Secco[3]

[1]*Division of Pediatrics, Department of Health Sciences, Università del Piemonte Orientale, Novara, Italy*
[2]*Neonatal and Pediatric Intensive Care Unit, Azienda Ospedaliero Universitaria Maggiore della Carità, Novara, Italy*
[3]*Department of Cardiology, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy*

Correspondence
Gioel Gabrio Secco, Interventional Cardiology and Cardiac Surgery Unit, Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy.
Email: gioel.gabrio.secco@gmail.com

ORCID

Gioel Gabrio Secco https://orcid.org/0000-0002-9998-7049

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