EDITORIAL COMMENTARY

COVID-19 treatments, QT interval, and arrhythmic risk: The need for an international registry on arrhythmias

Lia Crotti, MD, PhD,*†‡ Elena Arbelo, MD, PhD, MSc§¶‖

*From the *Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Milan, Italy, †Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy, ‡Istituto Auxologico Italiano, IRCCS, Center for Cardiac Arrhythmias of Genetic Origin, Milan, Italy, §Arrhythmia Section, Cardiology Department, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain, ¶Institut d'Investigació August Pi i Sunyer (IDIBAPS), Barcelona, Spain, and ‖Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain.*

In December 2019, the Chinese public health authorities reported several cases of acute respiratory syndrome in the city of Wuhan caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] In our hyperconnected world, the initial outbreak underwent unprecedented dissemination and has now become this century's worst pandemic, with more than 8 million people infected and almost 450,000 deaths to date.[3]

To manage the emergency situation, several "off-label" treatment options have been implemented worldwide based on limited *in vitro* or small observational studies. These drugs include chloroquine/hydroxychloroquine, protease inhibitors, remdesivir, azithromycin, glucocorticoids, and biological agents such as tocilizumab, among others.[4]

One major concern with these drugs is the possibility of QTc prolongation and torsades de pointes/sudden death. This risk is amplified by drug-to-drug interactions (which may increase bioavailability and, consequently, side effects), concomitant use of other QTc-prolonging drugs, and/or the presence of ion dysbalances (hypokalemia, hypomagnesemia, and/or hypocalcemia). A second concern is the risk of conduction disturbances; however, these seem to be rare and mostly linked to long-term treatment.[4] Consequently, at an early stage in the coronavirus disease 19 (COVID-19) pandemic, it became apparent that in order to prevent drug-induced proarrhythmia, standardized protocols were needed, and several guidance documents by international associations and arrhythmia/QTc experts have been published.[4–7]

In a study reported in this issue of *Heart Rhythm Journal,* Jain et al[8] retrospectively analyzed 2006 electrocardiograms (ECGs) collected during a 2-week period from 524 unique patients, most of them with a diagnosis of COVID-19. Almost 20% of the patients showed QT prolongation, defined as QTc >470 ms for QRS <120 ms, or QTc >500 ms in case of prolonged QRS. Whenever QT prolongation was identified, the electrophysiology consult service was activated, and support was given to the primary team caring for the patient. The support was mainly based on recommendations for electrolyte supplementation, discontinuation of nonessential QT-prolonging drugs, and a discussion on the risks and benefits of continuing COVID-19 treatment. In one-third of the patients, COVID-19 treatments (most commonly hydroxychloroquine, rarely in association with atazanavir or azithromycin) were discontinued. None of the patients developed torsades de pointes, and only 1 patient had sustained ventricular tachycardia but in the setting of an acute myocardial infarction. Not all patients were monitored, and, as clearly highlighted by the authors, some arrhythmias may not have been identified; however, these data still are reassuring. The authors are confident that their monitoring system played a major role in the low incidence of arrhythmic events observed. Although this may be true, no ECG data are available to directly view the QT response to the electrophysiologists' recommendations, and a control group is missing. Furthermore, their data do not show a clearly reduced event rate compared to other observational studies performed to date. Indeed, a few studies already have evaluated QTc and arrhythmic risk in hospitalized COVID-19 patients treated with different QT-prolonging drugs (ie, hydroxychloroquine/chloroquine, azithromycin, lopinavir/ritonavir). The first study by Chorin et al[9] showed that in a population of 85 COVID-19 patients treated with hydroxychloroquine/azithromycin, QT prolongation was present in most treated patients. In 30% of patients QTc increased by >40 ms, and 11% of patients had severe prolongation (QTc >500 ms). Even so, none of these patients developed torsades de pointes.[9] Saleh et al[10] evaluated 201 COVID-19 patients who during hospitalization received chloroquine/hydroxychloroquine either as monotherapy (61%) or in association with azithromycin (59%). Similar

Address reprint requests and correspondence: Dr Lia Crotti, Istituto Auxologico Italiano IRCCS, Piazzale Brescia 20, 20149 Milan, Italy. E-mail address: l.crotti@auxologico.it.

https://doi.org/10.1016/j.hrthm.2020.05.024

to previous study,[9] 9% of patients showed QTc >500 ms with treatment (3.5% discontinued therapy), but no torsades de pointes or arrhythmic deaths were reported. Whereas Jain et al[8] used a clear strategy to reduce the risk of arrhythmias potentially related to QT prolongation, Chorin et al[9] and Saleh et al[10] did not present any predefined strategies. Nevertheless, it is likely that if QTc was monitored, corrections to avoid excessive QT prolongation (ie, avoiding electrolytes abnormalities and association with additional QT-prolonging drugs when possible) were implemented even without a precise scheme. A major difference between these studies is that one-third of the patients in the study by Jain et al[8] discontinued therapy compared to only 2.5% in the study by Saleh et al.[10] In the presence of a potentially lethal disease, discontinuation of an effective therapy may be dangerous, but this is not the case here. Indeed, the underlying evidence supporting the current COVID-19 treatment is weak, and well-designed clinical trials are critically needed.

As new data with greater levels of evidence emerge, the treatment options for COVID-19 will rapidly evolve. However, whatever the medication, we should always bear in mind the potential risk of QTc prolongation, drug-to-drug interactions, and drug-induced proarrhythmia. Indeed, very recently, several studies have questioned the effectiveness of hydroxychloroquine,[11,12] lopinavir/ritonavir,[13] and remdesivir.[14] Only the lopinavir/ritonavir trial specifically assessed QTc and proarrhythmia, and it showed no significant QTc prolongation or serious arrhythmic events in either arm (95 patients in the lopinavir/ritonavir group and 99 patients in the standard care group).[13] These data clearly are important to better evaluate risks vs benefits (ie, arrhythmic risk in a protected environment vs effectiveness of therapy in reducing mortality and improving outcomes) and therefore should be systematically collected. To facilitate the collection of these data in a large number of affected patients and to monitor the occurrence of arrhythmic events in the context of the SARS-CoV-2 infection, the International Registry on Arrhythmias in COVID-19 (COVIDAR) was recently established and endorsed by EHRA and ERN GUARD-Heart. This registry, if successful, will provide valuable support in the decision-making process.

References

1. Chang D, Lin M, Wei L, et al. Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. JAMA 2020; 323:1092–1093.
2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323:1061–1069.
3. European Centre for Disease Prevention and Control (ECDC). COVID-19 in numbers, https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html. Accessed May 13, 2020.
4. European Society for Cardiology. ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic. Last update June 17, 2020, https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance. Accessed June 18, 2020.
5. Giudicessi JR, Noseworthy PA, Friedman PA, et al. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin Proc 2020;95:1213–1221.
6. Wu C-I, Postema PG, Arbelo E, et al. SARS-CoV-2, COVID-19 and inherited arrhythmia syndromes. Heart Rhythm 2020;17:1456–1462.
7. Roden DM, Harrington RA, Poppas A, et al. Considerations for drug interactions on QTc interval in exploratory COVID-19 treatment. Published online April 14, 2020. Heart Rhythm https://doi.org/10.1016/j.hrthm.2020.04.016.
8. Jain S, Workman V, Ganeshan R, et al. Enhanced ECG monitoring of COVID-19 patients. Heart Rhythm 2020;17:1417–1422.
9. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with SARS-CoV-2 infection treated with hydroxychloroquine/azithromycin. Preprint. Posted online April 3, 2020. medRxiv 2020:2020.04.02.20047050. https://doi.org/10.1101/2020.04.02.20047050.
10. Saleh M, Gabriels J, Chang D, et al. The effect of chloroquine, hydroxychloroquine and azithromycin on the corrected QT interval in patients with SARS-CoV-2 infection. Published online April 29, 2020. Circ Arrhythm Electrophysiol https://doi.org/10.1161/CIRCEP.120.008662.
11. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. Published online May 7, 2020. N Engl J Med https://doi.org/10.1056/NEJMoa2012410.
12. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open 2020;3:e208857e208857.
13. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382:1787–1799.
14. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395:1569–1578.