EDITORIAL

Hydroxychloroquine, Coronavirus Disease 2019, and QT Prolongation

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The complex decisions facing clinical teams caring for patients who are critically ill with coronavirus disease 2019 (COVID-19) are compounded by the absence of proven treatment strategies. Lacking robust trial evidence, clinicians are forced to consider all options based on preclinical and small observational studies, often in heart-wrenching settings of patients who are deteriorating in the throes of severe pneumonia, acute respiratory distress syndrome, cytokine storm, and in many cases, cardiovascular complications.

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Among possible therapies, hydroxychloroquine has been advocated and even politicized as a promising therapy because of its anti-inflammatory and potential antiviral properties. The drug, known for its immunosuppressive and antimalarial effects, has risen to the top of many treatment algorithms alone or in combination with azithromycin. Hydroxychloroquine was first approved in 1955 by the US Food and Drug Administration and has been viewed as generally safe and well-tolerated in patients treated for chronic inflammatory conditions. However, hydroxychloroquine prolongs the QT interval because of blockade of inward cellular potassium current and has a known risk of proarrhythmia,[1-3] especially in the setting of other drugs that also prolong the QT interval. Drug-induced QT prolongation has long been considered a surrogate for risk of drug-associated torsades de pointes.[4] Although widely used, azithromycin has also been increasingly recognized for risks of QT interval prolongation and sudden death.[5] Opinions vary regarding the optimal dose of hydroxychloroquine and stopping points based on corrected QT (QTc) prolongation. In patients with COVID-19, there may be greater risk tolerance among clinicians for QTc prolongation and toxicity in patients who are very sick, but at the same time, there may be an increased risk of ventricular arrhythmias because of electrolyte abnormalities, hypoxia, concomitant QT-prolonging medications, and underlying cardiovascular disease.[6,7] The risk-benefit trade off of hydroxychloroquine may also depend on whether other drugs with unclear benefit (such as remdesivir and tocilizumab) are available as alternative therapies.

Given the paucity of evidence of benefit and risk for treating COVID-19 with hydroxychloroquine alone or with azithromycin, the findings of Bessière and coworkers[8] and Mercuro and coworkers[9] are welcome and important. These reports from Lyon, France, and Boston, Massachusetts, provide concordant insights regarding the potential for QTc prolongation with this treatment in patients hospitalized with COVID-19. Excessive prolongation of QTc was observed in 14 of 40 patients (36%) in an intensive care unit, as reported by Bessière et al,[8] with cutoffs defined either as an increase in QTc of 60 milliseconds or more (in 10 patients [25%]) or prolongation of QTc of 500 milliseconds or more (7 patients [18%]). What is most striking, however, are the paired data demonstrating that 37 of 40 patients (93%) manifested an increase in QTc with hydroxychloroquine alone or in combination with azithromycin.[8]

Similarly, in the cohort reported by Mercuro et al,[9] 18 of 90 patients (20%) treated with hydroxychloroquine alone or in combination with azithromycin developed QTc prolongation of 500 milliseconds or more. The magnitude of increase in QTc compared with baseline values was more pronounced in those treated with both agents. One-third of the hospitalized patients in this series were treated in an intensive care unit. As with the observations of Bessière et al,[8] paired data show that QTc increased in most patients, particularly in those treated with concomitant azithromycin.[9]

In patients being treated in the hospital for COVID-19, especially in an intensive care setting, there are a number of confounding factors, noted previously, including electrolyte alterations, other drugs, heart failure, and cardiac ischemia; thus, these findings may not be generalizable to other settings in patients who are less acutely ill, as the authors note.[8,9] The fact that no episodes of torsades de pointes were observed by Bessière et al[8] is likely because hydroxychloroquine (with or without azithromycin) was stopped using generally accepted cut points; however, 1 patient reported by Mercuro et al developed torsades de pointes 3 days after the combination of hydroxychloroquine and azithromycin was discontinued because of a QTc interval of 499 milliseconds.[9] Allowing treatment beyond these limits to even longer QTc intervals in patients with COVID-19 should not be recommended unless there are clear benefits associated with anti-inflammatory or antiviral effects that are yet to be clinically demonstrated.

It is also true that, in an intensive care unit, the QTc can be safely monitored in most patients receiving hydroxycholoroquine and azithromycin. However, the data showing increases in QTc in more than 90% of patients treated with these agents by Bessière et al[8] and in most patients reported by Mercuro et al,[9] coupled with similar findings with chloroquine diphosphate in a Brazilian trial,[10] underscore the potential risk associated with widespread use of hydroxychloroquine and the combination of hydroxycholoquine and azithromycin in ambulatory patients with known or suspected COVID-19.[11] Understanding whether this risk is worth taking in the absence of evidence of therapeutic efficacy creates a knowledge gap that needs to be addressed. Whether signals of potential benefit outweigh signals of harm is unknown until well-controlled clinical trials are completed for the treatment or prevention of COVID-19 infections. Two such studies are the

Outcomes Related to COVID-19 Treated With Hydroxychloroquine Among In-patients With Symptomatic Disease (ORCHID) trial (NCT04332991)[12] and the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial (ISRCTN50189673),[13] which will also have ongoing safety reviews. Until then, treatment decisions for this disease will remain based on clinical judgment and, ideally, in the context of enrolling patients into clinical trials to provide definitive answers.

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