Opinion

Hydroxychloroquine, Coronavirus Disease 2019, and QT Prolongation
Robert O. Bonow, MD, MS; Adrian F. Hernandez, MD, MHS; Mintu Turakhia, MD, MAS

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.

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 coworkers8 and Mercuro et al9 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 hydroxychloroquine 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 sig-
nals 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) and the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial (ISRCTN50189673), 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.

ARTICLE INFORMATION

Author Affiliations: Northwestern University Feinberg School of Medicine, Chicago, Illinois (Bonow); Duke Clinical Research Institute, Durham, North Carolina (Hernandez); Duke University, Durham, North Carolina (Hernandez); Stanford University School of Medicine, Stanford, California (Turakhia); Center for Digital Health, Stanford University School of Medicine, Stanford, California (Turakhia); Veterans Affairs Palo Alto Health Care System, Palo Alto, California (Turakhia); Editor, JAMA Cardiology (Bonow); Associate editor, JAMA Cardiology (Hernandez, Turakhia).

Corresponding Author: Robert O. Bonow, MD, MS, Northwestern University Feinberg School of Medicine, 676 N St Clair St, Ste 600, Chicago, IL 60611 (robert.bonow@nm.org).

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REFERENCES


