Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19

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BACKGROUND – THE STUDY QUESTION?	
Background	• Hydroxychloroquine (HCQ) is FDA approved for the treatment of Lupus erythematosus, malaria, and rheumatoid arthritis[1,2] • IDSA and NIH guidelines recommend the use of HCQ for the treatment of SARS-CoV-2 in the setting of a clinical trial[3,4] • The FDA has approved the use of HCQ with an emergency use authorization for adults in the hospital with COVID-19 that are not eligible for a clinical trial or for whom a clinical trial is not feasible[5] • Chloroquine and HCQ have the same mechanism of action but hydroxychloroquine is considered better tolerated[6]
Previous trials (Only selected trials are reviewed here)	• Wang et. al demonstrated in-vitro efficacy of HCQ against SARS-CoV-2 with two proposed mechanisms of action including (1) alkalization of endosomes blocking the virus from fusing with the cell, and (2) inhibiting glycosylation of cell receptors.[7] • A subset of six patients in a French study received the combination of HCQ and azithromycin (AZ) and had 100% viral clearance by day six. This article has significant limitations but the results have been spurring interest in the combination.[8] • Preliminary results from the CloroCovid-19 study by Borba et. al, a phase 2b RCT, found that high dose chloroquine as 600mg PO bid x 10 days caused a non-statistically significantly increase in deaths and QTc elevations compared to low dose chloroquine as 450mg PO bid x 1 day then 450mg PO daily. The trial was terminated early.[9] • Tang et al. conducted an open-label RCT in China with standard of care (SOC) vs SOC + HCQ. Before the study could reach power, the trial was discontinued due to a perceived but not statistically significant difference in symptom alleviation and anti-inflammation effect reported to the data safety monitoring board (DSMB). While there was no statistically significant difference in efficacy outcomes, there was a statistically significant increase in ADRs (8.8% SOC, 30% SOC+ HCQ, p = 0.001).[10] • A routine care observational study evaluating the initiation of HCQ 600mg PO daily within the first 48 hrs of hospitalization found no difference in rates of death or transfer to the ICU within 7 days when compared to patients that did not receive HCQ (20.5% vs 22.1% respectively, RR 0.93, 95% CI 0.48 – 1.81). However, 9.5% of patients that were started on HCQ were discontinued at a median of 4 days (3-9) due to EKG changes.[11]
Why this study?	• This is the first US study evaluating the efficacy and safety of HCQ for COVID-19. Given the large sample size, robust nature of VA data, and the fact that it was conducted in US patients, there has been considerable interest in the results of this study.
Null Hypothesis	• There is no difference in clinical outcomes of hospitalized patients with SARS-CoV-2 whether they received HCQ, HCQ + AZ, or HCQ un-treated

GENERAL STUDY OVERVIEW		
	Summary	Critique
Funding	• NIH University of Virginia grant (R01EY028027 and R01EY029799) • Some of the authors have received consultant fees or grants from various healthcare companies but claim no competing interest. One author is an inventor or has a patent related to COVID-19 but unrelated to this study.	• The authors claim no conflicts of interest but there does seem to be some potential for bias given that at least two of the authors have other projects directly related to the disease state being studied.
Trial design	• National retrospective cohort study (United States Veterans Health Administration Clinical Data Warehouse) • Study index date = date of hospitalization with a positive SARS-CoV-2 test between 03/09/2020 – 04/11/2020 • Baseline period = any time before the study index date • Follow – up period = Index date + any time after the index study date	• Not a randomized control trial so it cannot demonstrate causality. However, given the limited and evolving data currently available, the efforts of the authors for this study are appreciated. • Weaknesses: retrospective design, index date is date of hospitalization and not day of symptom onset where viral load might be lower, vital sign data were from the initial

	• Patients were followed until hospital discharge or death • Drug administration data collected through barcode system • ICD-10-CM codes were used for comorbidities and the Charlson comorbidity index • All vital sign data were initial hospitalization values	hospitalization values and not the worst during the hospitalization, did not include chest imaging, did not include clinical diagnosis or severity of COVID-19. • The trial also did not state the normal COVID-19 testing and diagnosis procedure across the VHA, which may have led to severity bias where only the severe were tested. This may also lead to treatment bias. • Strengths: followed until discharge or death, population is US veterans which are generally older males and more closely represents the high risk US population, propensity score adjustments for baseline comorbidities
Objectives	• Not explicitly stated other than clinical outcomes associated with hydroxychloroquine and azithromycin use	• Vague primary objective. The primary endpoints were results of hospitalization (mortality or discharge) and whether mechanical ventilation was required. Retrospective database limits the ability to exam more granular outcomes. •
Enrollment	• Identified by inpatient lab result positive for SARS-CoV-2	• There have been reports of false negative results so a clinical diagnosis may have been more encompassing.[12] • Enrollment of patients from March 9 to April 11, very short time frame during initial phase of outbreak where laboratory testing may be inadequate.
METHODS		
Inclusion criteria	• Inpatient lab + for SARS-CoV-2 at a US VA hospital	• Does not include patients with a clinical diagnosis of COVID-19 that may have a false negative test result. Also did not include when lab tests were indicated.
Exclusion criteria	• BMI, vital signs, and discharge status were not all available	• This is a common limitation of a retrospective design
Interventions	• HCQ vs HCQ + AZ vs None	• Potential selection bias for sicker patients to be exposed to HCQ given retrospective design. • Patients were categorized based on receipt of HCQ (+/- AZ) however, there was no mention of the required duration of exposure of duration of overlap of exposure between HCQ and AZ so misclassification bias may occur. • Unclear guidance for when HCQ vs HCQ + azithromycin was recommended for the VA or if per the discretion of the clinical team. • Dosing for the HCQ was not provided
Primary Endpoints	• Result of hospitalization represented by either discharge or death or need for mechanical ventilation	• Competing primary endpoints

Secondary Endpoints	• Result of hospitalization (discharge or death) when a ventilator was required	• Secondary endpoints seem reasonable given the retrospective design and this still allows a general picture of rates of improvement in some of the sickest patients. It would have been ideal if they could have also provided information about improvement on the 7-point scale from the WHO R&D blueprint so that it could be more easily compared to other studies.[13] This would have helped provide more information on clinical outcomes which was the intent of the study but may not have been feasible given the study design.
Statistical analyses	• Descriptive data for baseline demographics, comorbidities, and clinical characteristics. • Differences between the three exposure groups were evaluated through the use of an ANOVA F-test for continuous variables or chi-square test for categorical variables. • To assess time to event (death or need for mechanical ventilation) Cox proportional hazard regression was performed. The Fine and Gray method was used to account for competing risk between the two co-primary endpoints. • Propensity scores to model the probability of receipt of HCQ and HCQ + AZ were created using multinomial logistic regression. These propensity scores where then included in the above outcome models.	• • Appropriate statistical testing with respect to the use of the proportional hazards model (assessment of underlying assumptions was completed) and use of methodology to account for the competing risk of the co-primary endpoints. Unclear if there was any form of censoring of events. • All baseline variables were included in the propensity scores, it is unclear based on the information presented in the text if this resulted in an appropriate model (i.e. model did not suffer from overfitting). • Use of propensity scores in multivariable regression model is not inappropriate, however, as opposed to matching, the results of the use of these scores can be more obfuscated in the final presented results.
RESULTS		
Enrollment	• 385 patients were initially enrolled but since only 17 were female, those patients were excluded. The below results only pertain to the remaining 368 male patients (HCQ 97, HCQ + AZ 113, no HCQ 158)	• Largest American population treatment study to-date • It's unfortunate there were so few women in the study and they were excluded. However, given that COVID-19 seems to affect men more than women and this was done in VA hospitals, it is not unexpected. In addition, excluding women likely decreased skewing the data to less severe outcomes.

Baseline characteristics	• Median age was similar across all arms (HCQ 70, HCQ+AZ 68, no HCQ 69, p = 0.665) • Notable areas with a lack of a statistical difference: race, BMI, ACEI/ARB, procalcitonin, ESR, charlson comorbidity index, history of smoking, history of diabetes, history of renal disease, history of COPD, history of immunosuppressing conditions (ex: HIV/AIDS, cancer, etc.) • Statistically significant differences: ALT, AST, serum albumin, tbili, RBCs, HCT, leukocytes, lymphocytes, plts, CRP, troponin, cerebrovascular disease • 31.7% of patients in the no HCQ arm received azithromycin	• Age and BMI are consistent with the highest risk population • BMI, COPD, diabetes, and renal disease have all been associated with a high risk for COVID-19 or worse outcomes so it is appreciated that there were no differences in these risk factors between treatment arms • There is ongoing debate about the role and impact of ACEI/ARBs so it's good that there was no statistical difference regarding the utilization between the treatment arms.[14] • Other than the history of cerebrovascular disease, the differences in labs between treatment arms is difficult to interpret given one p-value provided and multiple strata for each lab. Looking purely at percentages, it appears that patients that were exposed to HCQ (HCQ or HCQ + AZ) had more classical signs of COVID-19 with labs consistent with clinical characteristics previously presented in the literature.[15-17] Having a clearer diagnosis of COVID-19 with signs rather than just exposure in the setting of community transmission could explain why the patients were prescribed treatment with HCQ or HCQ+AZ. This might also explain why almost a third of the patients in the no HCQ arm received AZ (presume atypical pneumonia instead of HCQ for COVID-19 but not reported in the article).
Monitoring	• N/A	• N/A

Primary Outcome	• Death: HCQ 27 (27.8%), HCQ+AZ 25 (22.1%), no HCQ 18 (11.4%), p = 0.003
	  • Adjusted HR for death comparing HCQ vs no HCQ was 2.61 (95% CI 1.1 – 6.17, p = 0.03)
	  • Adjusted HR for death comparing HCQ+AZ vs no HCQ was 1.14 (95%Ci 0.56 – 2.32, p = 0.72)
	• No significant differences in risk of mechanical ventilation in either HCQ group compared to no treatment
	• Mechanical ventilation: HCQ 12 (13.3%), HCQ+AZ 7 (6.9%), no HCQ 25 (14.1%) p = 0.547
	  • Adjusted HR for a ventilator comparing HCQ to no HCQ was 1.43 (95% CI 0.53 – 3.79, p = 0.48)
	  • Adjusted HR for a ventilator comparing HCQ+AZ to no HCQ = 0.43 (95%CI 0.16-1.12)
	•
		• Given the information in the background provided, it is somewhat expected that there be no difference between the HCQ+AZ arm from the no HCQ arm for all outcomes.
		• The results table for adjusted hazard ratios does not provide the unadjusted measures to compare the effects of the propensity score
		• The study design makes it impossible to determine why there were higher rates of HCQ death compared to no HCQ. Three possible reasons for the association include (1) HCQ has known ADRs which could have contributed to the cause of death, and (2) the patients in the HCQ arm had more signs associated with COVID-19 and therefore may have had more severe disease skewing the patient distribution, and (3) the dose of the HCQ was not provided and there have been studies indicating that higher doses are associated with increased harm.[1,2,9]

Secondary Outcomes	• Death after ventilation:
	  • Adjusted HR comparing HCQ vs no HCQ = 4.08 (95%CI 0.77 – 21.7)
	  • Adjusted HR comparing HCQ+AZ vs no HCQ = 1.20 (95%CI 0.25 – 5.77)
	  • Discharge: HCQ 70 (72.2%), HCQ+AZ 88 (77.9%), no HCQ 140 (88.6%)
		• There does not appear to be any statistical difference in rates of mechanical ventilation or death after ventilation which is consistent with the idea that HCQ does not improve patient outcomes when used for the treatment of COVID-19.
		• However, if this is the case, it does not explain the difference in the primary outcome being statistically significant.

Other Clinical events	• N/A	• N/A

AUTHORS' CONCLUSIONS

- There is no evidence that HCQ or HCQ + AZ decreased the risk of requiring a ventilator
- HCQ is associated with an increase in overall mortality
- We need results from prospective RCTs but until then caution should be exercised around HCQ, especially without concomitant AZ

GENERALIZABILITY/CRITIQUE/DISCUSSION

- Good generalizability to the high risk population in the US
- Did not include information on exposure, patient symptoms, viral load, or duration of SARS-CoV-2 positivity which makes it impossible to determine if treatment was started early enough for the patient to still be in the viral phase of the disease or if it was started later in the inflammatory stage where the treatment would be unlikely to help regardless of the anti-viral therapy.
- The dose of HCQ nor AZ were provided. Higher doses of HCQ have been associated with increased risk of ADRs which could explain the high rate of mortality in this study though causality is not possible due to the trial design.[9,10]
- Almost of a third of the no HCQ arm received AZ despite being SARS-CoV-2 positive possibly indicating milder disease in the eyes of the clinical practice team. There is also an unclear role of asymptomatic or presymptomatic carriers given the lack of reporting on the VA screening process. It is also unknown which test was used and the sensitivity and specificity of that test. This would help determine the positive predictive value and if the PCR test was enough for these patients to be diagnosed with COVID-19 instead of representing community transmission and/ or viral shedding.
- The original intent of combining HCQ with AZ in the Gautret study was to cover for atypical co-infection.[8] It would have been interesting to have provided rates of co-infection for all arms in this study. There have also been critiques that the AZ provides anti-inflammatory support and that could be a possible reason for why there was no statistically significant difference between HCQ+AZ from no HCQ in any outcome. The argument can also be made that since 1/3 of the no HCQ received AZ that really the treatment arms represent HCQ+AZ vs AZ so it may, in actuality just be that HCQ has no impact on the virus.
- HCQ has known adverse effects that can increase a patient's risk for mortality and significant morbidity.[1,2] There have also been significant concerns about the combination of two QTc prolonging agents in the form of HCQ + AZ. While the study did not provide information on changes in QTc intervals, at the very least it did not seem to be associated with an increase in death in this study.
- The role and/or impact of azithromycin in this study cannot be interpreted.
- While this study cannot determine that HCQ was a cause of death, this study does show a signal that HCQ could potentially cause harm in patients with COVID-19. Therefore, if HCQ is going to be utilized for COVID-19, the results of this study support the IDSA and NIH guidelines to only be given in the setting of a clinical trial (preferably a RCT).[3,4]

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