Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open label non-randomized clinical trial

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BACKGROUND	
Background	In late 2019 an outbreak of an emerging infectious disease due to a novel coronavirus (SARS-CoV-2) started in Wuhan China. In March 2020 the World Health Organization classified the epidemic as a pandemic anticipating widespread infection and mortality. A recent study from Wuhan hypothesized that 80% of infections are considered mild but in patients with comorbidities or advanced age infection can be more severe and reach an 8% fatality rate.[2] SARS-CoV-2 also known as COVID-19 has no proven treatment and thus it is imperative that an effective treatment is found.
Previous trials	A recent paper reported an inhibitor effect of remdesivir and chloroquine on the growth of SARS-CoV-2 in vitro.[3] An early clinical trial conducted in COVID-19 Chinese patients, showed that chloroquine had an effect in terms of clinical outcome and viral clearance when comparing to controls groups.[4]
Why this study?	Hydroxychloroquine (HCQ) usage has increased for both hospitalized patients and outpatients based on in vitro results, but the clinical efficacy remains ill defined.

GENERAL STUDY OVERVIEW		
	Summary	**Critique**
Trial design	Open-label **non-randomized** clinical trial	N/A
Objectives	Efficacy of HCQ on viral load & clinical progression (body temp, respiratory rate, length of stay at hospital and mortality) and adverse events in patients infected with SARS-CoV-2	N/A
Enrollment	20 patients in the experimental arm 16 patients in the control arm	**Limited sample size makes interpretation difficult** 10/16 control patients were managed at different institutions, the others refused treatment at main site
METHODS		
Inclusion criteria	**Patients age >12 years with PCR documented SARS-CoV-2 carriage in nasopharyngeal samples at admission.**	Per results 2 patients were included who were 10 years of age. An additional 2 patients did not have NP swabs performed on day 0 or day 1, both of which were in the control arm.

Exclusion criteria	Patients were excluded if they had a known allergy to HCQ or chloroquine or had another known contraindication to treatment with the study drug, including retinopathy, G6PD deficiency and QT prolongation. Breastfeeding and pregnant patients were excluded based on their declaration and pregnancy test results when required.	Although not stated in the exclusion criteria, patients had to be "evaluable" at day 6 otherwise they were excluded, this led to the exclusion of 6 HCQ patients. The six reasons were ICU transfer (3), death (1), left hospital (1), and discontinuation due to ADE (nausea, 1). These exclusions could be considered treatment failures (which would represent 23% of HCQ patients). No control patients were excluded in this manner.
Interventions	**HCQ 200mg Q8H (n=20) x10 days vs. supportive care (n =16)** **Six patients received concomitant azithromycin (AZ) (500 mg day 1, then 250 mg 2 - 5) with HCQ based on clinical judgment to prevent bacterial superinfection.**	N/A
Primary Endpoints	**Virological clearance at day-6 post-inclusion via specific RT-PCR from nasopharyngeal swabs** Clearance defined as Cycle Threshold (C_T > 35)	Unclear relevance of 6-day viral eradication endpoint Per trials site was to measure 1, 4, 7, 14-day eradication Other analyses require CT > 40 to define negative samples
Secondary Endpoints	Virological clearance overtime during the study period, clinical follow-up (body temperature, respiratory rate, length of stay at hospital and mortality), and occurrence of side effects	No clinical endpoints have been reported to date
RESULTS		
Baseline characteristics	**Patient population:** 16 patients in the control (4 asymptomatic, 10 upper respiratory tract infection, 2 lower respiratory tract infections) 20 patients in HCQ arm (2 asymptomatic, 12 upper respiratory tract infections, 6 lower respiratory tract infections) 42% of the cohort were male, and the average time from symptom onset to inclusion was 4.0 ± 2.6. These were similar between the groups. HCQ patients were older 51.2 ± 18.7 vs 37.3 ± 24.0; p = 0.06	
Primary Outcome	**At day 6 post-inclusion:** Viral eradication occurred in 14/20 (70%) HCQ patients vs 2/16 (12.5%) control p = 0.01 **Viral eradication rates in subgroup of HCQ patients at day 6:** HCQ monotherapy 8/14 (57%) vs. HCQ + AZ 6/6 (100%); p = 0.11	Small patient population so difficult to discern effects of HCQ on "virological cure". Also, the clinical relevance of viral eradication at a given time point from NP swabs is unclear. Patients on HCQ monotherapy had higher viral loads than those on HCQ and AZ. When patients with similar starting viral loads are compared,

		eradication rates similar with HCQ monotherapy (7/9, 78%) and combination therapy 6/6 (100%). Significant concern for selective reporting as eradication at day 6 was not a pre-defined endpoint per trial site, and one patient in HCQ + AZ group who was PCR negative at day 6 was PCR positive at day 8. 10/16 control patients were managed at different institutions which had less rigorous testing procedures (not done daily) and reporting strategies
Secondary Outcomes	Not reported	Clinical outcomes and safety are more relevant than viral eradication. Concern raised for selective reporting of positive results

AUTHORS' CONCLUSIONS

Despite the study's small sample size, the authors concluded that HCQ treatment was associated with viral load reduction/disappearance in COVID-19 patients. The authors speculated that these effects were further reinforced by the addition of AZ despite small sample size of combination therapy (N=6).

GENERALIZABILITY/CRITIQUE/DISCUSSION

Unfortunately, these data are uninformative to clinical practice. The authors selectively report data of questionable clinical relevance and seemingly only share data points that support their conclusions. As stated above the relevance of viral eradication, according to a cycle threshold definition inconsistent with the SARS CoV-2 literature, at day 6, is unclear. This was not the initial primary outcome, nor was it a pre-defined time frame for analysis. This is highlighted by the fact that one patient who was PCR negative on day 6 was positive on day 8. When this is combined with other methodological issues including different testing and reporting strategies for control patients, the exclusion of six patients on HCQ of which 5 should most likely be considered failures, and the failure of the authors to report on clinical outcomes these data become of no value to clinicians. Furthermore, the authors use this finding to support combination therapy with azithromycin. It is important for readers to note that outside of this analysis there is no data that would support that the addition of azithromycin to HCQ would have any benefit over HCQ monotherapy for the management of SARS CoV-2 and that azithromycin was added in these patients for different reasons. As the perceived differences in viral eradication between HCQ monotherapy and HCQ + AZ combination therapy are no longer demonstrated once differences in viral load and selective reporting at day 6 are removed, these data should not be seen as supportive for the combination over monotherapy alone. This is particularly important given the additive toxicity risk of these agents. Further, given the failure to account for the exclusions in the HCQ arm, and the differences in testing of the control patients, these data are not overly informative to the role of HCQ on viral eradication either.

CITATIONS

1. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949.
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