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Hydroxychloroquine for Early Treatment of Adults With Mild Coronavirus Disease 2019: A Randomized, Controlled Trial

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Background. No effective treatments for coronavirus disease 2019 (COVID-19) exist. We aimed to determine whether early treatment with hydroxychloroquine (HCQ) would be efficacious for outpatients with COVID-19.

Methods. Multicenter open-label, randomized, controlled trial conducted in Catalonia, Spain, between 17 March and 26 May 2020. Patients recently diagnosed with <5-day of symptom onset were assigned to receive HCQ (800 mg on day 1 followed by 400 mg once daily for 6 days) or usual care. Outcomes were reduction of viral load in nasopharyngeal swabs up to 7 days after treatment start, disease progression up to 28 days, and time to complete resolution of symptoms. Adverse events were assessed up to 28 days.

Results. A total of 293 patients were eligible for intention-to-treat analysis: 157 in the control arm and 136 in the intervention arm. The mean age was 41.6 years (SD, 12.6), mean viral load at baseline was 7.90 $\log_{10}$ copies/mL (SD, 1.82), and median time from symptom onset to randomization was 3 days. No differences were found in the mean reduction of viral load at day 3 (−1.41 vs −1.41 $\log_{10}$ copies/mL in the control and intervention arm, respectively) or at day 7 (−3.37 vs −3.44). Treatment did not reduce risk of hospitalization (7.1% control vs 5.9% intervention) nor shorten the time to complete resolution of symptoms (12 days, control vs 10 days, intervention). No relevant adverse events were reported.

Conclusions. In patients with mild COVID-19, no benefit was observed with HCQ beyond the usual care.

Keywords. hydroxychloroquine; SARS-CoV-2; COVID-19; therapy; randomized controlled trial.

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019, various drugs have been proposed as antiviral agents for treating coronavirus disease 2019 (COVID-19), including the aminoquinolines chloroquine and hydroxychloroquine (HCQ) [1]. At the time this work started, the US Food and Drug Administration and EU European Medicines Agency had given emergency approval for the use of chloroquine and HCQ in COVID-19 patients [2, 3].

Chloroquine and HCQ have been extensively used for treating malaria and various autoimmune diseases, although other therapeutic effects, including antiviral effects, have been increasingly recognized [4, 5]. In vitro studies showed that both drugs can block the viral replication of SARS-CoV-2 in cell cultures [6, 7]. However, a high-level assessment that became available after the start of our study suggested that calculated extracellular lung concentrations are well below the in vitro efficacy values; therefore, the drug has low potential for

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in vivo activity at standard dosing regimens [8]. As of 20 June 2020, publicly available clinical data on the effectiveness of chloroquine and HCQ for treating COVID-19 were limited to 2 small randomized clinical trials [9, 10] and 6 observational studies [11–16]. Several studies were seriously flawed in important methodological respects and lacked internal validity [9, 11–13, 15]. A randomized trial with 150 patients found that HCQ administration did not result in a significantly higher polymerase chain reaction (PCR) negative conversion (85% vs 81%) by 28 days [10]. However, the trial design raised concerns about the long delay between the onset of symptoms and the initiation of treatment (median, 16.6 days) because antiviral therapy needs to be initiated early to have an impact on viral shedding. Two large observational studies of hospitalized patients with COVID-19 treated with HCQ at physicians' discretion found no significant reduction in the risk of death/intubation compared with no specific treatment [14, 16]. Because the metrics for each trial were chosen rapidly due to the emerging threat, the measured outcomes were different from one study to the next. The Clinical Characterization and Management Working Group established by the World Health Organization (WHO) recently agreed on a minimal outcome set to facilitate study design and data-sharing, including viral burden (ie, quantitative viral RNA or cycle threshold from nasopharyngeal swabs), clinical outcome (ie, progression scale: ambulatory, hospitalized, death), and survival (ie, all-cause mortality) [17].

We assessed the efficacy and safety of HCQ initiated early for treating outpatients with mild COVID-19 using the WHO core outcome set.

METHODS

Study Design and Participants

This was a multicenter, open-label, randomized, controlled trial conducted from 17 March 2020 to 26 May 2020 in 3 health administrative regions in Catalonia, Spain, covering 4 206 440 inhabitants (ie, 60% of the Catalan population): *Catalunya central*, *Àmbit Metropolità Nord*, and *Barcelona Ciutat*. Study candidates were identified from the electronic registry of the Epidemiological Surveillance Emergency Service of Catalonia (SUVEC) of the National Department of Health. During the COVID-19 epidemic in Catalonia, a public health ordinance required that the SUVEC be notified of all patients who tested positive for COVID-19 at any of the designated diagnostic laboratories [18]. From that registry, trained physicians identified and selected recently diagnosed nonhospitalized patients of any kind (eg, health worker, household contact) for study participation. Reasons for nonenrollment were recorded.

Adult patients aged ≥18 years were eligible if they had mild symptoms of COVID-19 (ie, fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, or influenza-like illness) for fewer than 5 days before enrollment, were nonhospitalized, and had a positive PCR test for SARS-CoV-2 in the baseline nasopharyngeal swab. Patients were excluded if they had moderate to severe COVID-19 disease (eg, required hospitalization), any condition that might preclude following the study procedures safely (eg, mental disability), known allergy or hypersensitivity to study drugs, known retinal and severe liver or renal diseases, history of cardiac arrhythmia, known electrocardiographic QT interval prolongation or other diseases that could be exacerbated by study drugs (eg, psoriasis), active treatment with medications that are contraindicated with study drugs, or were living with human immunodeficiency virus (HIV). Females who were pregnant (verbally declared or positive pregnancy test) or breastfeeding were also excluded.

The Hospital Germans Trias Pujol Institutional Review Board and the Spanish Agency of Medicines and Medical Devices approved the study protocol and subsequent amendments. Written informed consent was obtained from all patients. This trial was a secondary study of the Barcelona Postexposure Prophylaxis Study against SARS-CoV-2 registered in ClinicalTrials.gov (NCT04304053).

Procedures

Participants were randomized (1:1) using a computer-generated random-number list to either the control arm (no treatment aside from usual care) or the intervention arm (HCQ; Dolquine®, 800 mg on day 1 followed by 400 mg once daily for 6 days). Initially, the protocol included the use of HCQ and cobicistat-boosted darunavir (DRVc) combined treatment. However, it was adapted to HCQ alone after the recommendation of the pharmaceutical company not to use DRVc for the treatment of COVID-19 due to lack of activity in vitro [19, 20] and the negative results in human clinical trials of closely related HIV protease inhibitors [21].

The study medications were dispensed by the hospital pharmacy and provided free of charge to the patients at the first home visit by dedicated outbreak field teams of trained nurses aided by trained paramedical staff. Random allocation was done remotely by a member of the study team not involved in participants' enrollment. Masking was not possible because a placebo could not be prepared due to the emergency nature of the trial. Laboratory technicians were unaware of participants' treatment allocation, treatment response, and previous PCR results at all time points.

Participants were assessed on day 1 (baseline, HCQ was started) and days 3, 7, 14, and 28. On day 1, patients were visited at home for baseline assessment and patient enrollment. Outbreak field teams verified the selection criteria for eligibility, obtained patient-signed informed consent, assessed specific symptoms associated with COVID-19, and collected relevant epidemiological information from a structured interview. Disease progression, safety, and self-reported treatment compliance were monitored by the Clinical

Trials Unit (CTU) of Hospital Germans Trias Pujol at days 3 and 7 (home visits) and days 14 and 28 (phone visits). Compliance was assessed using self-reports in a telephone interview (eg, number of doses taken between interviews). Adverse events (AEs) were defined as any new symptom or worsening of preexisting symptoms and were followed until complete resolution of symptoms or up to day 28 after enrollment. Serious adverse events (SAEs) were defined as any medical event that required hospitalization or caused patient death. SAEs were graded for causality and expectedness and reported immediately to the Contract Research Organization of the study sponsor and the trial pharmacovigilance consultancy (Asphalion, Barcelona) for independent adjudication of relatedness. Study data were recorded electronically by the CTU during phone interviews and on paper case record forms by the outbreak field teams during home visits and then entered into an electronic database by the data entry team of the sponsor. Data validation and cleaning were done by trial researchers with the support of a trial data management consultancy (Trial Form Support, Barcelona).

For each patient, serial oral and nasopharyngeal swab samples were planned to be obtained on days 1 and 3. However, preliminary analyses revealed a possible delay for a significant viral load reduction beyond day 3. Therefore, we amended the study protocol to extend the collection of nasopharyngeal swabs to an additional sample on day 7 (a 3-day window was allowed for patients who could not be assessed on day 7). The presence of SARS-CoV-2 was investigated from nasopharyngeal swabs, and viral load was quantified in all reverse-transcription (RT)-PCR–positive cases (all time points collected) following Centers for Disease Control and Prevention's (CDC) guidelines [22]. Details on laboratory methods for SARS-CoV-2 identification and quantification are provided in the Supplementary Material.

Outcomes

The primary outcome was the reduction of viral RNA load in nasopharyngeal swabs at days 3 and 7 after treatment start. The secondary outcomes were clinical progression measured using a simplified version of the WHO progression scale [17] (1, not hospitalized with or without resumption of normal activities; 2, hospitalized, requiring supplemental oxygen; 3, hospitalized, requiring invasive mechanical ventilation; and 4, death) and time from randomization to complete resolution of symptoms within the 28-day follow-up period. Resolution of symptoms was assessed sequentially using a symptoms questionnaire designed to gather information on the type of symptom and last day experienced; complete resolution was considered when no COVID-19–related symptoms were reported at all. Safety outcomes included AEs that occurred during treatment, SAEs, AEs of special interest (ie, cardiac), and premature discontinuation of therapy. AEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. All unexpected SAEs were notified through Eudravigilance.

Statistical Analyses

We estimated that a sample size of 280 patients would provide the trial with 80% power to detect a difference of 0.5 $\log_{10}$ in the mean reduction of SARS-CoV-2 viral load at a 2-sided significance level of $\alpha = 0.05$, assuming an expected standard deviation (SD) of 1.5 [23]. A 0.5 $\log_{10}$ copies/mL difference in reduction was chosen to represent the minimal threshold for a biologically relevant change for our analyses [24]. Considering the open-label design and the possibility of side effects caused by the study medication, the primary efficacy analysis was performed on the intention-to-treat (ITT) population. Sensitivity analyses were performed with the per-protocol (PP) population. Safety was assessed in the safety population, which included all participants who received any therapy including usual care.

Efficacy was determined by comparing the mean reduction of the viral load from baseline to days 3 and 7, with the use of a mixed effects regression model and taking into account the randomization group and repeated measures within each individual. The viral load was provided in logarithmic scale; specimens with undetectable viral load at a given follow-up assessment were assigned a value of 3 $\log_{10}$ copies/mL (ie, lower limit of detection) for the purpose of statistical analysis. The secondary clinical outcome regarding between-group differences in disease progression was assessed using risk ratio for the predefined events. The time to clinical improvement was analyzed using Kaplan-Meier survival functions and hazard ratios, calculated using a Cox proportional hazards regression model based on the assumptions of proportional risks. Kaplan-Meier estimates were compared using the log-rank test. The significance threshold was set at a 2-sided α level of 0.05 unless otherwise indicated, and all analyses were conducted in R version 3.6.2 [25].

RESULTS

Patients

Between 17 March 2020 and 28 April 2020, we assessed 753 confirmed COVID-19 patients for eligibility. Figure 1 summarizes the recruitment and follow-up of study participants. A total of 400 (53.1%) of 753 participants did not meet the selection criteria and were therefore not enrolled. Additionally, 60 (8.0%) participants were excluded from ITT analysis because of negative RT-PCR at baseline, missing RT-PCR at all follow-up visits, or consent withdrawal, yielding an ITT population of 293 COVID-19 patients. During follow-up, 23 participants had a protocol deviation (8 were screening failures due to a history of more than 5 days since start of symptoms, 1 was severely ill at baseline, 3 were taking contraindicated medication, 8 were lost to follow-up, and 3 had treatment compliance under 80%) and were excluded from the PP population.

The two study arms had similar characteristics at baseline (ITT population), including age, gender, comorbidities,

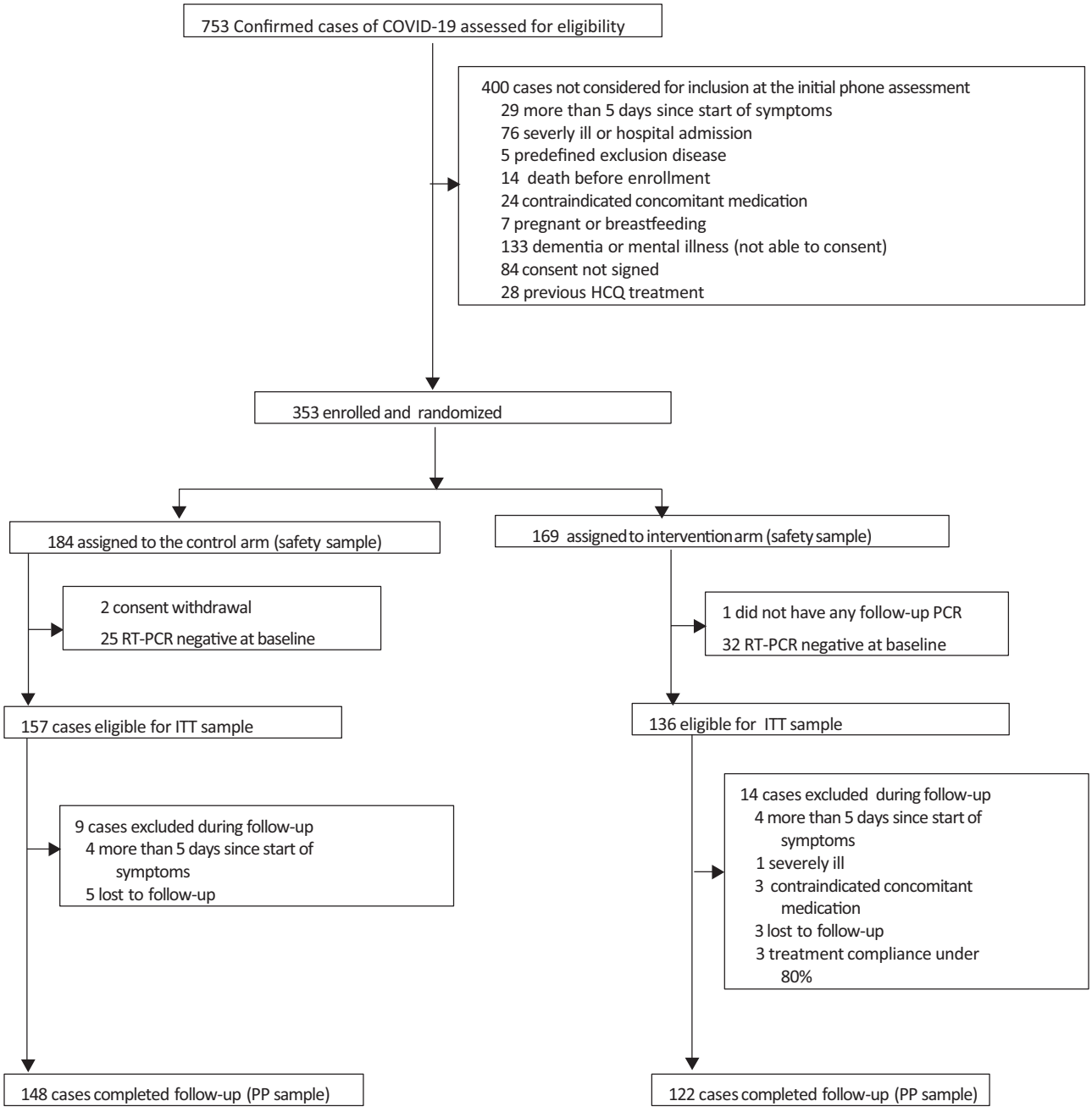

Figure 1. Flow diagram of participant selection and allocation. Abbreviations: COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; ITT, intention to treat; PP, per protocol; RT-PCR, reverse-transcription polymerase chain reaction.

frequency of symptoms, and nasopharyngeal viral load (Table 1). The mean age of patients was 41.6 years (SD, 12.6), and 207 (70.6%) of them were women. The median time from symptom onset to enrollment was 3 days (interquartile range [IQR], 2–4). A total of 53.2% of the patients (156 of 293) reported chronic health conditions. Fever, cough, and sudden olfactory loss were the most common presenting symptoms. The mean viral load in the nasopharyngeal swab at baseline was 7.90 $\log_{10}$ copies/mL (SD, 1.82). Most patients were healthcare workers (252 of 293; 86%).

Primary Outcome

For the primary outcome of reduction of the viral load in nasopharyngeal swabs, there were no significant differences between the control arm and the intervention arm at day 3 or day 7. The mean differences in viral load from baseline to day 3 were −1.41 and −1.41 $\log_{10}$ copies/mL in the control and intervention arms, respectively (difference [d], 0.01; 95% confidence interval [CI], −.28 to .29; Table 2 and Figure 2). The comparative analysis of the reduction of the viral load followed a similar trend at day 7: −3.37 and −3.44 in the control and intervention arms,

Table 1. Baseline Characteristics of Index Cases in Each Study Arm (Intention to Treat)

	Assigned to Control Arm	Assigned to Intervention
N = 293	N = 157	N = 136
Individual characteristic		
Age, mean (SD), years	41.7 (12.6)	41.3 (12.4)
Gender, n (%), female	103 (65.6)	104 (76.5%)
Time from onset of symptoms to PCR result, median (IQR), days	2.00 (1.00 to 3.00)	2.00 (1.00 to 3.00)
Time from onset of symptoms to enrollment, median (IQR), days	3.00 (2.00 to 4.00)	3.00 (2.00 to 4.00)
Coexisting comorbidities		
Any coexisting disease, n (%)	85 (54.1%)	71 (52.2%)
Cardiovascular disease, n (%)	15 (9.6%)	20 (14.7%)
Respiratory disease, n (%)	10 (6.4%)	7 (5.1%)
Metabolic disease, n (%)	11 (9.0%)	9 (6.6%)
Nervous system disease, n (%)	21 (13.4%)	19 (14.0%)
Symptoms at baseline		
Dyspnea, n (%)	22 (14.1)	21 (15.4)
Fever, n (%)	96 (61.5)	88 (64.7%)
Cough, n (%)	104 (66.7)	85 (62.5)
Sudden olfactory or gustatory loss, n (%)	67 (42.9)	58 (42.6)
Rhinitis, n (%)	13 (8.3)	15 (11.0)
Laboratory data		
Viral load (RT-PCR $\log_{10}$ copies/mL), mean (SD)	7.83 (1.89)	7.99 (1.74)
Main risk factor of exposure to coronavirus disease 2019		
Healthcare worker, n (%)	132 (84.1)	104 (76.5%)
Nursing home worker, n (%)	8 (5.1)	8 (5.9)
Household contact of a case, n (%)	1 (0.6)	5 (3.7%)
Unknown, n (%)	16 (10.2)	19 (14.0%)

No statistically significant differences were found between groups.

Abbreviations: IQR, interquartile range; RT-PCR, reverse-transcription polymerase chain reaction; SD, standard deviation.

respectively (d, −0.07; 95% CI, −.44 to .29). The sensitivity analysis in the PP population also showed no difference between groups (Supplementary Table 1, Supplementary Material). Subgroup analysis comparing the viral loads of patients treated with HCQ plus DRVc did not reveal differences compared with HCQ alone (Supplementary Table 2).

Secondary Outcomes

The clinical outcome of risk of hospitalization was similar in the control arm (7.1%, 11 of 157) and the intervention arm (5.9%, 8 of 136; risk ratio, 0.75; 95% CI, .32 to 1.77; Table 2). No patients required mechanical ventilation or died during the study period. Median time from randomization to the resolution of COVID-19 symptoms was not significantly different in the control arm (12.0 days; IQR, 6–21) and the intervention arm (10.0 days; IQR, 4–18; log-rank test for survival analysis $P = .38$; Figure 3).

Safety

In the safety population, 18 of 184 (9.8%) patients in the control group and 122 of 169 (72.2%) in the intervention group experienced at least 1 AE during the 28 days of follow-up (Table 3). The most frequent treatment-related AEs among participants given HCQ were gastrointestinal (eg, diarrhea, nausea, and abdominal pain) and nervous system disorders (eg, drowsiness, headache, and metallic taste). Twenty SAEs were reported, 12 in the control arm and 8 in the intervention arm, none of them related to HCQ (Supplementary Table 3).

DISCUSSION

The results of this randomized, controlled trial convincingly rule out any meaningful virological or clinical benefit of HCQ in outpatients with mild COVID-19. We found that HCQ initiated within 5 days from symptom onset (median, 3 days) was not effective in reducing viral shedding compared with no HQC therapy. The quantification of the viral load in the upper respiratory tract provides strong evidence of the capacity of the treatment to affect the pathogen burden. Furthermore, this treatment regimen did not reduce the risk of hospitalization, although the trial was underpowered for this outcome, and it did not shorten the time to complete resolution of symptoms.

The much higher proportion of participants with AEs in the HCQ arm suggests poor tolerability of the treatment; however, no major AEs related to the study drug were observed. Of participants who were treated with HCQ, 70% self-reported mild to moderate side effects that were mainly gastrointestinal. Only 8 patients presented with a SAE within 28 days of HCQ treatment initiation, all related to disease progression. No

Table 2. Effects of the Intervention on Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load and Disease Progression (Intention-to-Treat Population)

N = 293	Total Tested	Assigned to the Control Arm (N = 157)	Assigned to the Intervention Arm (N = 136)		
	n	**Mean (SD)**	**Mean (SD)**		
Primary endpoint*					
Viral load in nasopharyngeal swabs (log_{10} copies/mL)					
At day 1	293	7.83 (1.89)	7.99 (1.74)		
At day 3	271	6.39 (1.83)	6.61 (1.64)		
At day 7	211	4.31 (1.30)	4.22 (1.26)		
		Mean (SE)	**Mean (SE)**	**Mean Difference[a]**	**(95% CI)**
Viral load reduction in nasopharyngeal swabs from baseline (log_{10} copies/mL)					
At day 3	271	−1.41 (0.14)	−1.41 (0.15)	0.01	(−.28 to .29)
At day 7	211	−3.37 (0.18)	−3.44 (0.19)	−0.07	(−.44 to .29)
	n	**Events (%)**	**Events (%)**	**Risk Ratio**	**(95% CI)**
Secondary endpoint					
Not hospitalized with resolution of symptoms at home	290	143 (92.3)	128 (94.1)	0.75	(.32 to 1.77)
Hospitalization not requiring mechanical ventilation	290	11 (7.1)	8 (5.9)	…	…
Hospitalization requiring mechanical ventilation	290	0 (0.0)	0 (0.0)	…	…
Death	290	0 (0.0)	0 (0.0)	…	…

*Specimens with negative polymerase chain reaction (undetectable viral load) were assigned a value of 3 log_{10} copies/mL for the purpose of statistical analysis. None of the estimated mean differences and risk ratios were statistically significant.

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error.

[a]Estimated using a mixed effects regression model.

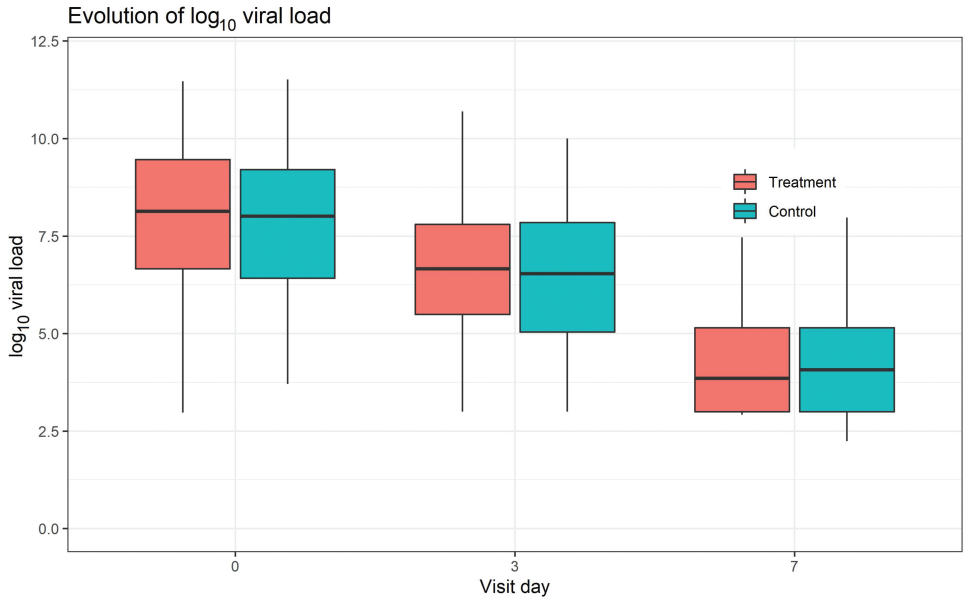

Figure 2. Change from baseline in severe acute respiratory syndrome coronavirus 2 viral RNA on nasopharyngeal swabs (intention to treat). Box plot of viral load of participants in the control arm (blue box) and the intervention arm (red box) at each assessment point (*x*-axis) determined by quantitative reverse-transcription polymerase chain reaction. Boxes represent median and interquartile range for each group. Outliers are plotted as individual points. The number of samples tested are as follows: day 1, 293; day 3, 271; day 7, 211.

cardiovascular events or syncope/palpitation/dizziness suggestive of arrhythmia were reported. This finding is particularly important because it does not corroborate the concern for harm associated with HCQ therapy, particularly cardiac disease [26].

Our study has several limitations. First, clinical assessments on day 7 were not originally scheduled; therefore, the number of patients analyzed for viral positivity at this time point was lower compared with day 3. While WHO has recommended a measure of viral burden in COVID-19 clinical trials, they have neither set up the optimal time for measurement nor the minimal threshold for significant reduction between arms. We recommend that the time for viral load reduction assessment be long enough to capture a relevant decrease, ideally, 7 days or longer, and that the significant reduction threshold be set at a

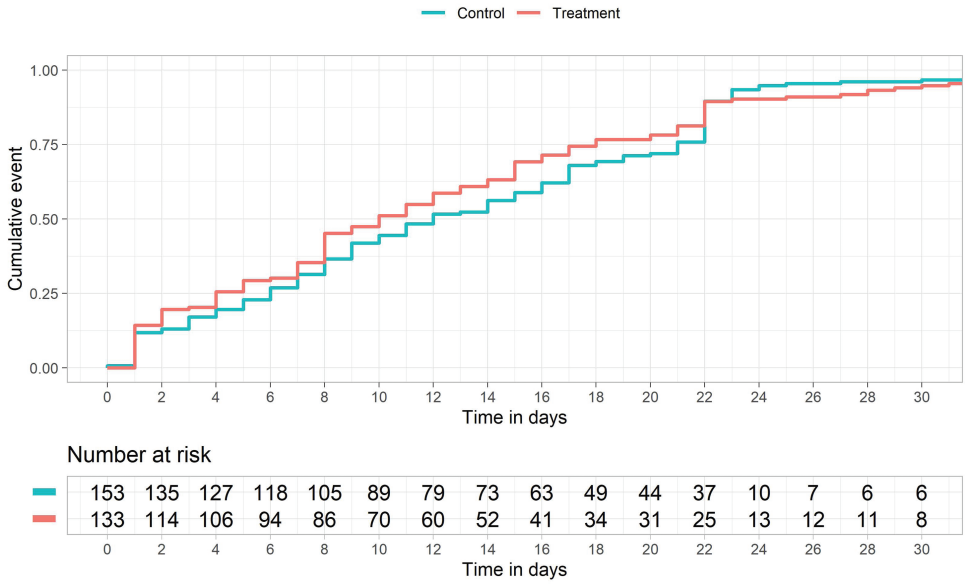

Figure 3. Time to clinical improvement from randomization (intention to treat). Survival curve of participants in the control arm (blue line: median [interquartile range], 12.0 [6.0–21.0]) and in the intervention arm (red line: median, 10.0 [4.0–18.0]; log-rank test $P = .38$).

Table 3. Incidence of Adverse Events in the Safety Population

∫	Control Arm (N = 184), n (%)	Intervention Arm (N = 169), n (%)
Any AE	18 (9.8%)	122 (72.2%)
None	166 (90.2%)	47 (28.0%)
1	16 (8.7%)	43 (25.4%)
2	1 (0.5%)	22 (13.1%)
3 or more	1 (0.5%)	57 (33.9%)
Intensity: Grade		
1	5 (2.7%)	90 (53.6%)
2	1 (0.5%)	22 (13.1%)
3	0 (0.0%	1 (0.6%)
4	12 (6.5%)	8 (4.8%)
5	0	0
SAE[a]	12 (6.6%)	8 (4.8%)
Hospitalization	12 (6.6%)	8 (4.8%)
Deaths	0	0
Treatment-related SAE	0	0
Type of AE		
Cardiac disorders	0 (0.0%)	0 (0.0%)
Ear and labyrinth disorders	0 (0.0%)	5 (3.0%)
Eye disorders	0 (0.0%)	5 (3.0%)
Gastrointestinal disorders	7 (3.8%)	148 (88.1%)
General disorders	1 (0.5%)	30 (17.9%)
Infections and infestations	12 (6.6%)	9 (5.4%)
Injury, poisoning, and procedural complications	0 (0.0%)	1 (0.6%)
Metabolism and nutrition disorders	1 (0.5%)	2 (1.2%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	1 (0.6%)
Nervous system disorders	3 (1.6%)	63 (37.5%)
Psychiatric disorders	0 (0.0%)	2 (1.2%)
Renal and urinary disorders	0 (0.0%)	1 (0.6%)
Reproductive system and breast disorders	0 (0.0%)	1 (0.6%)
Respiratory, thoracic, and mediastinal disorders	0 (0.0%)	2 (1.2%)
Skin and subcutaneous tissue disorders	0 (0.0%)	11 (6.5%)
Vascular disorders	0 (0.0%)	1 (0.6%)

Abbreviation: AE, adverse event; SAE, serious adverse event.

[a]None of the SAEs were adjudicated as related to hydroxychloroquine by the pharmacovigilance consultants.

0.5 $\log_{10}$ decrease or greater. Second, we had originally chosen to combine HCQ with the HIV protease inhibitor DRVc because in silico molecular docking studies had predicted that DRVc might have a therapeutic effect on SARS-CoV-2 [27] and a better safety profile compared with other HIV protease inhibitors. However, in vitro results that showed no activity, which became available after the start of our study, prompted the decision to drop DRVc [19, 20]. The concomitant administration of DRV in some participants may have slightly increased plasma levels of HCQ, thereby leading to increased HCQ effect because DRVc is a weak inhibitor of the metabolic enzyme of HCQ, CYP2D6. Therefore, we do not believe that the use of DRVc might have reduced the effect of HCQ. Third, owing to the urgency, the trial could not be masked with a placebo, which may affect the rate of AEs declared (AEs are less often reported in a control, nonplacebo group). Nevertheless, it did not affect the attrition numbers in the control arm. Moreover, to minimize the detection bias of the primary outcome (ie, the viral load), the laboratory staff remained unaware of participants' allocation. Finally, the regional nature of the trial and overrepresentation of healthcare workers (>80%) may limit the generalization of our findings. Therefore, cautiousness should be taken when extrapolating our data to other countries or settings.

HCQ and chloroquine have garnered unprecedented attention as potential therapeutic agents following inconclusive clinical trials in combination or not with azithromycin [9, 12], uncontrolled case series [14], and public figure endorsements [28]. While there is a growing body of scientific data against use of HCQ for treating COVID-19 that include a concern for harm, particularly cardiac disease, the potential for the treatment of mild COVID-19 with HCQ has been explored in this trial to provide definite evidence. Our results indicate no impact of HCQ on viral burden up to 7 days nor symptoms resolution or hospitalization rate up to 28 days following diagnosis. The

added value of our study is the randomized, controlled design and the use of the agreed minimal outcome set for COVID-19 clinical trials, including RT-PCR to conclusively determine the viral burden. Our findings provide the scientific community and policy makers with essential insights on the inefficacy of HCQ as a therapeutic candidate for SARS-CoV-2, at least in settings and conditions that are similar to ours.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. O. M., L. B., V. C., C. V., R. M. V., and M. V. M. conceived, designed, and wrote the manuscript. M. C., C. G. B., P. A., A. A., C. A. P., G. C., A. E., A. F., G. F. M., P. L., N. N., S. N., A. N., N. P., J. P., C. Q., N. R. M., A. S., C. S., and M. U. contributed to the recruitment, clinical care, and follow-up of patients. C. T., A. T., E. M., J. R., and A. S. analyzed and managed data. J. A., J. M. A., J. C., R. F., and M. F. analyzed data and reviewed the manuscript. E. B., P. C., E. R., and L. R. performed all laboratory tests. J. M., M. C., M. S., and S. G. directed and managed the planning and execution of the project. All authors reviewed and approved the final version of the manuscript.

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