Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial

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Summary: Compared with usual care, early treatment with HCQ failed to reduce the RNA viral load in nasopharyngeal swabs after 3 and 7 days of treatment and shorten the time to complete resolution of symptoms in adults with PCR-confirmed mild Covid-19.

ABSTRACT

BACKGROUND: No therapeutics have yet been proven effective for the treatment of mild-illness caused by SARS-CoV-2. We aimed to determine whether early treatment with hydroxychloroquine (HCQ) would be more efficacious than no-treatment for outpatients with mild Covid-19.

METHODS: We conducted a multicenter, open label, randomized controlled trial in Catalonia (Spain) between March 17, and May 26, 2020. Eligible Covid-19 cases were non-hospitalized adult patients with recently confirmed SARS-CoV-2 infection and less than five days of symptoms. Patients were assigned to receive HCQ (800 mg on day 1, followed by 400 mg once daily for 6 days) or no antiviral treatment (not-placebo controlled). Study outcomes were the reduction of viral RNA load in nasopharyngeal swabs up to 7 days after treatment start, patient disease progression using the WHO scale 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 (SD 1.82) Log_{10} copies/mL, and median time from symptom onset to randomization was 3 days. No significant 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; difference 0.01 [95% CI -0.28;0.29]) or at day 7 (-3.37 vs. -3.44; d –0.07 [-0.44;0.29]). This treatment regimen did not reduce risk of hospitalization (7.1%, control vs. 5.9%, intervention; RR 0.75 [0.32;1.77]) nor shortened the time to complete resolution of symptoms (12 days, control vs. 10 days, intervention; $p = 0.38$). No relevant treatment-related AEs 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

INTRODUCTION

Since the emergence of the novel SARS-CoV-2 coronavirus in December 2019, various drugs have been proposed as antiviral agents for treating the coronavirus disease-2019 (Covid-19), including the aminoquinolines chloroquine and hydroxychloroquine (HCQ) [1]. At the time this work started, the US FDA and EU EMA 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], but a high-level assessment suggested that calculated extracellular lung concentrations are well below the in vitro efficacy values and therefore the drug has low potential for in vivo activity at standard dosing regimens [8]. As of June 20, 2020, publicly available clinical data on the effectiveness of chloroquine and HCQ for treating Covid-19 were limited to two small randomized clinical trials [9,10] and six 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 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 physician's 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 WHO recently agreed on a minimal outcome set to facilitate study design and data sharing, including viral burden (i.e., quantitative viral RNA or cycle threshold from nasopharyngeal swabs), clinical outcome (i.e., progression scale: ambulatory, hospitalized, death) and survival (i.e., 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 March 17, 2020 to May 26, 2020 in three health administrative regions in Catalonia (Spain) covering 4,206,440 inhabitants (i.e., 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 all patients tested positive for Covid-19 in any of the designated diagnostic laboratories to be notified to the SUVEC [18]. Trained physicians identified from that registry and selected for study participation non-

hospitalized patients of any kind (health worker, household contact, etc.) recently diagnosed. Reasons for non-enrollment were recorded.

Adult patients aged 18 years or more were eligible if they had mild symptoms of Covid-19 (i.e., fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, or influenza-like-illness) for less than five days before enrollment, were non-hospitalized, 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 (e.g., required hospitalization), any condition that might preclude following the study procedures safely (e.g., mental disability), known allergy or hypersensitivity to study drugs, known retinal and severe liver or renal diseases, history of cardiac arrhythmia, known QT prolongation or other diseases that could be exacerbated by study drugs (e.g., psoriasis), active treatment with medications that are contraindicated with study drugs, or known HIV infection. Females who were pregnant (verbally declared or positive pregnancy test) or breastfeeding were also excluded.

The study protocol and subsequent amendments were approved by the institutional review board of Hospital Germans Trias Pujol, and the Spanish Agency of Medicines and Medical Devices. Written informed consent was obtained from all patients. This trial was a secondary study of the Barcelona Postexposure Prophylaxis Study against SARS-CoV-2 (BCN PEP CoV-2 Study) 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 six days). Initially, the protocol included the use of HCQ and cobicistat-boosted darunavir (DRVc) combined treatment, but 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 home visited for baseline assessment and patient enrollment. Outbreak field teams verified the selection criteria for eligibility, obtained patients' 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), 14 and 28 (phone visits). Compliance was assessed using self-reports in a telephone interview (e.g., number of doses taken between interviews). Adverse events (AE) were defined as any new symptom or worsening of pre-existing symptoms and were followed until complete resolution of symptoms or up to day 28 after enrollment. Serious adverse events (SAE) 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 RT-PCR positive cases (all time points collected). Details on laboratory methods for SARS-CoV-2 identification and quantification are provided in 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 by 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-days 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 AE that occurred during treatment, SAE, AE of special interest (i.e., cardiac), and premature discontinuation of therapy. AE were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. All unexpected SAE were notified through Eudravigilance.

Statistics

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 two-sided significance level of $\alpha = 0.05$, assuming an expected standard deviation 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 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 per mL (i.e., lower limit of detection) for the purpose of statistical analysis. The secondary clinical outcome regarding between-group differences in disease progression were assessed using risk ratio (RR) for the predefined events. The time to clinical improvement was analyzed using Kaplan-Meier survival functions and hazard ratios (HRs), 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 two-sided α level of 0.05 unless otherwise indicated, and all analyses were conducted in R version 3.6.2 [25].

RESULTS

Patients

Between March 17 and April 28, 2020, we assessed for eligibility 753 confirmed Covid-19 patients. Figure 1 summarizes the recruitment and follow-up flowchart of study participants. Four-hundred (53.1%) of 753 did not meet the selection criteria and were therefore not enrolled. Additionally, 60 (8.0%) participants were finally 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 failure due to history of more than five 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 PP population.

The two study arms had similar characteristics at baseline (ITT population), including age, gender, comorbidities, frequency of symptoms, and nasopharyngeal viral load (Table 1). The mean age of patients was 41.6 years (SD 12.6), and 201 (68.6%) of them were women. The median time from symptom onset to enrollment was 3 days (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 (SD 1.82) Log_{10} copies/mL. Most patients were healthcare workers (254 [86.7%] of 293).

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 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 arm, respectively (difference [d] 0.01 [95% CI –0.28; 0.29]) (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 arm, respectively (d –0.07 [–0.44; 0.29]). The sensitivity analysis in the PP population also showed no difference between groups (Table S1, Supplementary Material). Sub-group analysis comparing the viral loads of patients treated with HCQ plus DRVc did not reveal differences compared with HCQ alone (Table S2).

Secondary outcomes

The clinical outcome of risk of hospitalization was similar in the control arm (7.1%, 11/157) and the intervention arm (5.9%, 8/136; RR 0.75 [95% CI 0.32; 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, IQR 4–18; log-rank-test for survival analysis $p = 0.38$; Figure 3).

Safety

In the safety population 16/184 (8.7%) patients in the control group and 121/169 (72.0%) in the intervention group experienced at least one AE during the 28 days of follow-up (Table 3). The most frequent treatment-related AEs among participants given HCQ were gastrointestinal (e.g., diarrhea, nausea, and abdominal pain) and nervous system disorders (e.g., drowsiness, headache, and metallic taste). Twenty SAE were reported, 12 in the control arm and 8 in the intervention arm, none of them related to HCQ (Table S3).

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 five days from symptom onset (median 3 days) was not effective in reducing viral shedding compared with no antiviral therapy. The quantification of the viral load in the upper respiratory tract provides strong evidence on the capacity of the treatment to affect the pathogen burden. Furthermore, this treatment regimen did not reduce the risk of hospitalization—though the trial was underpowered for this outcome—nor shortened 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 eight patients presented a SAE within 28 days of HCQ treatment initiation, all related to disease progression. No cardiovascular events nor 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 and therefore the number of patients analyzed for viral positivity at this time point was lower compared to 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 the time for viral load reduction assessment to be long enough to capture a relevant decrease—ideally, 7 days or longer—and the significant reduction threshold to be set at 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 therapeutic effect on SARS-CoV-2 [27] and the better safety profile compared to other HIV protease inhibitors. However, in-vitro results showing no activity that 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 expect 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 AE declared (AEs are less often reported in a control, non-placebo group). Nevertheless, it did not affect the attrition numbers in the control arm. Moreover, to minimize the detection bias of the primary outcome (i.e., 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 using HCQ for treating Covid-19 that includes 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 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 policymakers with essential insights on the inefficacy of HCQ as a therapeutic candidate for SARS-CoV-2, at least in similar settings and conditions to ours.

NOTES:

CONTRIBUTORS

OM, LB, VC, CV, RMV, MVM conceived, designed, and wrote the manuscript,
MC, CGB, PA, AA, CAP, GC, AE, AF, GFM, PL, NN SN, AN, NP, JP, CQ, NRM, AS CS, MU contributed to the recruitment, clinical care, and follow-up of patients,
CT, AT, EM, JR, AS analyzed and managed data
JA, JMA, JC, RF, MF analyzed data and reviewed the manuscript
EB, PC, ER, LR did all laboratory tests
JM, MC, MS, SG directed and managed the planning and execution of the project
All authors reviewed and approved the final version of the manuscript

ACKNOWLEDGMENTS

We thank Gerard Carot-Sans, PhD, for providing medical writing support during the revisions of the subsequent drafts of the manuscript, the personnel from the Fights Aids and Infectious Diseases Foundation for their support in administration, HR and supply-chain management, Eric Ubals (Pierce AB) and Òscar Palao (Opentic) for website and database management, Óscar Camps and OpenArms Non-governmental organization for nursing home operations, Anna Valentí and the human resources department of the Hospital Germans Trias i Pujol for telephone monitoring. We are very grateful to Marc Clotet and Natalia Sánchez who coordinated the JoEmCorono crowdfunding campaign. We thank the institutional review board of Hospital Germans Trias Pujol and the Spanish Agency of Medicines and Medical Devices (AEMPS) for their prompt action for consideration and approvals to the protocol.

FUNDING

This work was mainly supported by the crowdfunding campaign JoEmCorono (https://www.yomecorono.com/) with the contribution of over 72,000 citizens and corporations. The study also received financial support from Laboratorios Rubió, Laboratorios Gebro Pharma, Zurich Seguros, SYNLAB Barcelona, and Generalitat de Catalunya. Laboratorios Rubió also contributed to the study with the required doses of hydroxychloroquine (Dolquine®).

CONFLICTS OF INTEREST

We declare no conflicts of interest

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Figure legends

Figure 1. Flow diagram of individual selection and allocation.

Figure 2. Change from baseline in SARS-CoV-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 RT-PCR. Boxes represent median and IQR 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

Figure 3. Time to clinical improvement from randomization (intention-to-treat)

Survival curve of participants in the control arm (blue line, median [IQR] 12.0 [6.0-21.0]) and in the intervention arm (red line, median 10.0 [4.0-18.0], log rank test p =0.38)

Tables

Table 1. Baseline characteristics of index cases in each study arm (intention-to-treat)

N=293	**Assigned to control arm** N=157	**Assigned to intervention** N=136
Individuals' characteristics		
Age (years), *mean (SD)*	41.7 (12.6)	41.6 (12.4)
Gender (female), *n (%)*	103 (65.6%)	98 (72.1%)
Time from onset of symptoms to PCR result (days), *median (IQR)*	2.00 [1.00;3.00]	2.00 [1.00;3.00]
Time from onset of symptoms to enrolment (days), *median (IQR)*	3.00 [2.00;4.00]	3.00 [2.00;4.00]
Coexisting disease		
Any coexisting disease	85 (54.1%)	71 (52.2%)
Cardiovascular disease	15 (9.6%)	20 (14.7%)
Respiratory disease	10 (6.4%)	7 (5.1%)
Metabolic disease	11 (9.0%)	9 (6.6%)
Nervous system disease	21 (13.4%)	19 (14.0%)
Symptoms at baseline		
Dyspnea, *n (%)*	22 (14.1%)	21 (15.4%)
Fever, *n (%)*	96 (61.5%)	91 (66.9%)
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 Covid-19		
Healthcare worker, *n (%)*	132 (84.1%)	106 (77.9%)
Nursing home worker, *n (%)*	8 (5.1%)	8 (5.9%)
Household contact of a case, *n (%)*	1 (0.6%)	4 (2.9%)
Unknown, *n (%)*	16 (10.2%)	18 (13.2%)

IQR: interquartile range. **SD:** standard deviation.
No statistically significant differences were found between groups.

Table 2. Effects of the intervention on SARS-CoV-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)**	**d****	**(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	(-0.28, 0.29)
At day 7	211	-3.37 (0.18)	-3.44 (0.19)	-0.07	(-0.44, 0.29)
	N	**Events (%)**	**Events (%)**	**RR**	**(95% CI)**
Secondary endpoint					
Not hospitalized with resolution of symptoms at home	290	143 (92.3)	128 (94.1)	0.75	(0.32, 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 PCR (undetectable viral load) were assigned a value of 3 Log_{10} copies per mL for the purpose of statistical analysis.
**Estimated using a mixed effects regression model.
None of the estimated mean differences and risk ratios were statistically significant.
d: mean difference. **RR:** risk ratio. **SD:** standard deviation. **SE:** standard error.

Table 3: Incidence of adverse events in the safety population.

N = 351	**Control arm** (N=184)	**Intervention arm** (N=169)
Any AE	16 (8.7%)	121 (72.0%)
None	167 (91.3%)	47 (28.0%)
1	16 (8.7%)	42 (25.0%)
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%)
Grade 2	1 (0.5%)	22 (13.1%)
Grade 3	0 (0.0%	1 (0.6%)
Grade 4	12 (6.5%)	8 (4.8%)
Grade 5	0	0
Serious AE *	12 (6.6%)	8 (4.8%)
Hospitalization	12 (6.6%)	8 (4.8%)
Deaths	0	0
Treatment-related Serious AE	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%)

*None of the serious adverse events (SAE) were adjudicated as related to HCQ by the pharmacovigilance consultants.

Figure 1

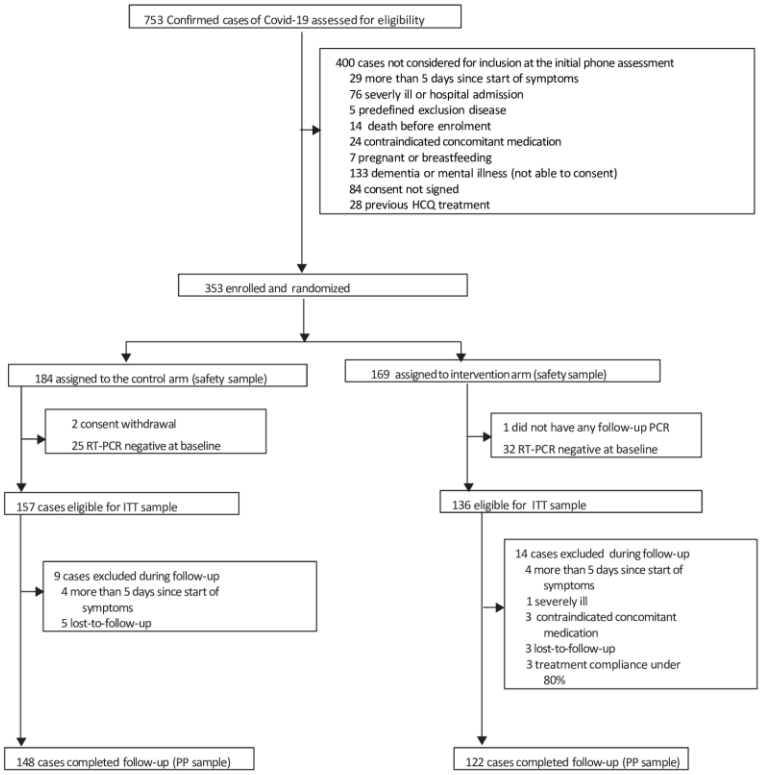

***Figure 1*: Trial profile**

Figure 2

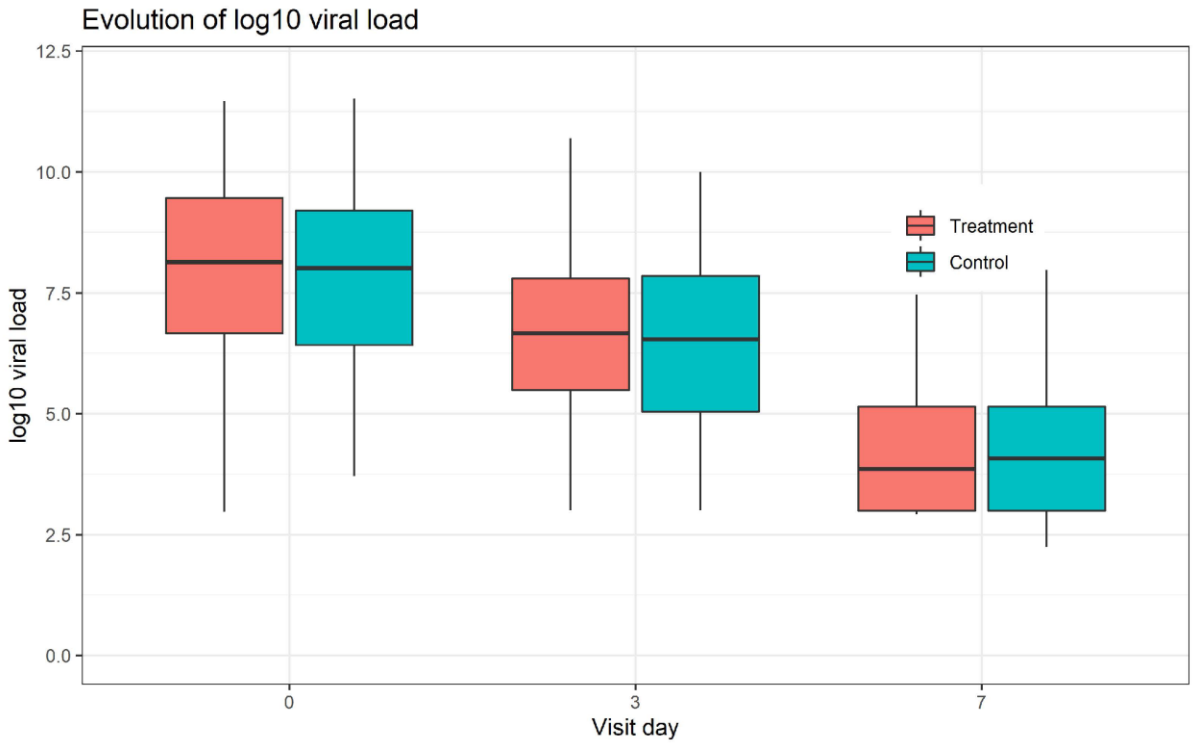

Figure 3