Treating COVID-19 With Hydroxychloroquine (TEACH): A Multicenter, Double-Blind Randomized Controlled Trial in Hospitalized Patients

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Background. Effective therapies to combat coronavirus 2019 (COVID-19) are urgently needed. Hydroxychloroquine (HCQ) has in vitro antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but the clinical benefit of HCQ in treating COVID-19 is unclear. Randomized controlled trials are needed to determine the safety and efficacy of HCQ for the treatment of hospitalized patients with COVID-19.

Methods. We conducted a multicenter, double-blind randomized clinical trial of HCQ among patients hospitalized with laboratory-confirmed COVID-19. Subjects were randomized in a 1:1 ratio to HCQ or placebo for 5 days and followed for 30 days. The primary efficacy outcome was a severe disease progression composite end point (death, intensive care unit admission, mechanical ventilation, extracorporeal membrane oxygenation, and/or vasopressor use) at day 14.

Results. A total of 128 patients were included in the intention-to-treat analysis. Baseline demographic, clinical, and laboratory characteristics were similar between the HCQ (n = 67) and placebo (n = 61) arms. At day 14, 11 (16.4%) subjects assigned to HCQ and 6 (9.8%) subjects assigned to placebo met the severe disease progression end point, but this did not achieve statistical significance ($P = .350$). There were no significant differences in COVID-19 clinical scores, number of oxygen-free days, SARS-CoV-2 clearance, or adverse events between HCQ and placebo. HCQ was associated with a slight increase in mean corrected QT interval, an increased D-dimer, and a trend toward an increased length of stay.

Conclusions. In hospitalized patients with COVID-19, our data suggest that HCQ does not prevent severe outcomes or improve clinical scores. However, our conclusions are limited by a relatively small sample size, and larger randomized controlled trials or pooled analyses are needed.

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

Coronavirus disease 2019 (COVID-19) is an acute pneumonia syndrome caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is currently responsible for over 25 million infections and 850 000 deaths worldwide [1]. Effective therapies combating SARS-CoV-2 are urgently needed to prevent severe outcomes related to COVID-19.

The antimalarial and immunomodulatory drug hydroxychloroquine (HCQ) is one candidate to treat SARS-CoV-2. In vitro data show that HCQ has antiviral effects against SARS-CoV-2 [2]; Possible mechanisms include decreased SARS-CoV-2 binding due to HCQ interference with terminal glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor [3] and increased endosomal pH interfering with proteolytic enzymes involved in SARS-CoV-2 processing [4]. In addition to a direct antiviral effect, HCQ also reduces in vitro T-cell activation [5] and cytokine expression [6] during SARS-CoV-2 infection, leading to the hypothesis that HCQ may decrease the cytokine storm associated with severe outcomes in COVID-19. Hydroxychloroquine is approved by the US Food and Drug Administration (FDA) for treatment of lupus and

rheumatoid arthritis and has an established safety profile for those conditions [7, 8].

As the COVID-19 pandemic intensified, HCQ was widely adopted as off-label treatment and was recommended in treatment guidelines by the Chinese government [9], some US hospital systems [10], and professional societies [11]. On March 28, 2020, HCQ gained emergency use authorization (EUA) by the FDA for the treatment of COVID-19 [12]. Despite early adoption of HCQ as COVID-19 therapy, the existing clinical data do not clearly show whether HCQ is beneficial, has no effect, or causes harm in hospitalized patients with COVID-19. Early in the pandemic, a small (n = 36) open-label, nonrandomized study in France suggested that HCQ decreased viral shedding [13], and a randomized trial (n = 62) in China suggested a possible time-to-recovery benefit from HCQ in addition to standard care [14]. More recently, large retrospective inpatient COVID-19 cohorts from US (n = 2541) and French (n = 3737) health systems suggested a mortality benefit associated with the use of HCQ [10, 15]. Conversely, other large observational studies of hospitalized patients with COVID-19 failed to show improved outcomes associated with HCQ administration [16, 17] and found that HCQ treatment of COVID-19 is associated with an increased risk of QT interval prolongation [18, 19]. In light of these data, the Infectious Diseases Society of America published guidelines recommending that the use of HCQ for COVID-19 be limited to clinical trials [20], and the FDA rescinded the EUA on June 15, 2020 [21]. A recent meta-analysis concluded that the evidence regarding HCQ therapy for COVID-19 is "very weak and conflicting" [22], and a call for well-designed randomized controlled trials (RCTs) is prominent in the literature.

We performed a multicenter, placebo-controlled RCT during the peak of the pandemic in New York to evaluate the efficacy and safety of HCQ in hospitalized patients with COVID-19. We hypothesized that HCQ is superior to placebo in preventing severe outcomes among hospitalized COVID-19 patients.

METHODS

Regulatory
This study was approved by the New York University Grossman School of Medicine Institutional Review Board (s20-00463), the Bellevue STAR Research Review Committee (STUDY00002403), and the SUNY Downstate Institutional Review Board (Study #1590355). The NYU Langone COVID-19 Data Safety and Monitoring Board (DSMB) provided oversight throughout the study period. ClinicalTrials.gov registration (NCT04369742) was initiated by the study team on April 15, 2020, but due to administrative delays during COVID-19, the NYU Office of Science and Research submitted the registration to ClinicalTrials.gov on April 27, 2020.

Study Sites
We enrolled patients at NYU Langone Health (Tisch Hospital and Kimmel Pavilion, NYU Langone—Brooklyn Hospital, and NYU Winthrop Hospital), NYC Health and Hospitals/Bellevue Hospital Center (BHC), and State University of New York (SUNY) Downstate Medical Center.

Trial Design
Enrolled subjects were randomized 1:1 to study drug or placebo and followed for 30 days. Randomization was stratified by age (>60 years old) and study site. Subjects and investigators were blinded to the treatment assignment, but in cases of rapid COVID-19 progression meeting our primary end point, or at the request of the treating physician, we allowed for subject unblinding. Subject visits were performed by study personnel at baseline, day 6 (or day of discharge if discharge occurred before day 6), day 14, and day 30. Vital signs, laboratory results, clinical scores, and monitoring for the primary outcome were performed by electronic medical record (EMR) review. Concomitant antibacterial therapy and off-label agents for SARS-CoV-2 were allowed. The protocol was amended to allow for co-enrollment in other COVID-19 therapeutic trials and for the enrollment of children and pregnant women. Adverse events (AEs) were captured throughout the study period; AEs of interest were defined by the study team and included common AEs attributed to HCQ [23]. The full protocol is provided in the Supplementary Data.

Population
To identify potential participants, the EMR at each site was screened daily to identify hospitalized patients with a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR). To enhance recruitment at NYU Langone Health, providers could refer patients directly from the EMR as part of admission orders (Supplementary Figure 1). In addition to a positive RT-PCR within 72 hours of enrollment, inclusion criteria required at least one COVID-19 symptom (eg, fever, cough, dyspnea, nausea, diarrhea, myalgia, anosmia, dysgeusia) and the subject's (or legally authorized representative's) written informed consent. We excluded subjects who met the primary end point (admitted to the intensive care unit [ICU], mechanical ventilation, extracorporeal membrane oxygenation [ECMO], and/or vasopressor use) at enrollment, had received any doses of HCQ or chloroquine (CQ) within 30 days, were unable to take oral medications, were allergic to HCQ or CQ, had a baseline corrected QT (QTc) interval >500 ms, were on concomitant therapy with antiarrhythmic medications (flecainide, amiodarone, digoxin, procainamide, propafenone, thioridazine, or pimozide), and those who had a history of cardiac arrest, retinal disease, or glucose-6-phosphate dehydrogenase deficiency.

Study Drug

Hydroxychloroquine sulfate 200-mg tablets (Amneal Brand, Ahmedabad, India) were provided by the New York State Department of Health. The placebo agent, calcium citrate 200-mg tablets (Major Pharmaceuticals, Livonia, MI, USA), was obtained by the NYU Langone Health Investigational Pharmacy. Dosing of both HCQ and calcium citrate was 400 mg (2 tablets) by mouth 2 times per day (day 1) and 200 mg (1 tablet) by mouth 2 times per day (days 2–5); the 5-day course was based on in vitro projections to optimize HCQ tissue levels against SARS-CoV-2 [24]. If the subject was discharged before completing the 5-day course, the remaining doses were provided for home therapy, and compliance was assessed at the day 14 telephone follow-up.

Outcomes

The primary efficacy outcome was the proportion of subjects meeting a severe COVID-19 progression composite end point (death, ICU admission, mechanical ventilation, ECMO, and/or vasopressor use) at day 14. The primary safety outcome was the cumulative incidence of serious adverse events (SAEs), grade 3 or 4 adverse events, and/or discontinuation of therapy at day 30.

Secondary clinical outcomes included changes in an 8-point ordinal COVID-19 clinical severity score (defined in Table 2), the primary composite outcome and mortality at day 30, hospital length of stay (LOS), fever-free days, and oxygen-free days (defined as 7 [the maximum number of days with vital signs captured] minus the number of days with temperature ≥100.4°F or requiring supplemental oxygen). Secondary laboratory outcomes included SARS-CoV-2 viral clearance on nasopharyngeal PCR, clinically significant changes from baseline to follow-up (day 6, or day 3 if day 6 was unavailable) creatinine [25], hepatic and hematology labs [26], and changes in inflammatory markers (C-reactive protein, lactic acid dehydrogenase, ferritin, interleukin-6) and coagulation factors (D-dimer) associated with severe COVID-19 [27, 28].

Sample Size

Based on early internal unpublished data from NYU Langone Health, the primary composite end point was estimated to occur in 30% of COVID-19 admissions. We aimed to detect a 10% reduction in the end point rate, to 20% in the HCQ arm. Using a 2-sided Type I error rate of 0.05, 626 patients would need to be enrolled to provide 80% power to detect this difference. We began enrollment on April 17, 2020, but enrollment decreased substantially as COVID-19 admissions decreased across the region. After consideration with the DSMB, enrollment was paused across all sites on May 12, 2020, before achieving the desired sample size. COVID-19 admission numbers did not increase to an adequate number to resume enrollment.

Statistical Analysis

Data were summarized using mean, median, SD, and range for continuous variables and frequencies for categorical variables. The primary outcome was assessed using a chi-square test comparing the proportion meeting the primary outcome by randomized treatment group. The secondary outcome of the 8-point ordinal COVID-19 severity score was assessed using the Wilcoxon rank-sum test. Primary analyses used the intention-to-treat (ITT) paradigm in which participants are classified according to their randomized treatment assignment, regardless of treatment receipt or compliance. Secondary analyses assessed the safety population (those who received any dose of study medication) and the per-protocol population (those who received at least 80% of their assigned dose).

RESULTS

Study Population

Between April 17 and May 12, 2020, we screened 724 hospitalized patients with a positive RT-PCR test for SARS-CoV-2 and randomized 128 patients, as outlined in Figure 1. The baseline characteristics of the study population are shown in Table 1. Treatment groups did not differ significantly with respect to age, gender, or ethnicity. Although our protocol was amended to allow enrollment of pediatric and pregnant subjects, the youngest participant was 19 years old, and no pregnant patients were enrolled. Subjective fever (n = 72, 56.2%), cough (n = 86, 67.2%), and dyspnea (n = 83, 64.8%) were the most common presenting symptoms, with no statistically significant differences between subjects assigned to HCQ or placebo. Hypertension (n = 74, 57.8%), obesity (n = 46, 35.9%), and diabetes (n = 41, 32%) were the most common comorbidities. Categories of body mass index (BMI) were significantly higher in the placebo arm than subjects receiving HCQ (chi-square $P = .023$). Although 36 subjects (28.1%) reported a history of smoking, only 8 (6.2%) reported active smoking at enrollment. On baseline vital signs, 1 in 3 subjects had documented fever and nearly two-thirds required oxygen supplementation, with no difference between HCQ or placebo in the amount of oxygen needed or type of oxygen delivery device. Baseline laboratory values, radiography results, and COVID-19 ordinal severity scores were similar between participants assigned HCQ and those assigned placebo.

Outcomes

Primary and secondary outcomes by treatment group are shown in Table 2. Of 128 subjects in the ITT analysis, 17 (13.3%) met the primary efficacy composite end point (death, ICU admission, mechanical ventilation, ECMO, and/or vasopressor use) by day 14. In the HCQ arm, 11 (16.4%) subjects had severe disease progression, compared with 6 (9.8%) subjects assigned to placebo; the difference was not statistically significant ($P = .350$). The primary safety outcome was met by a similar
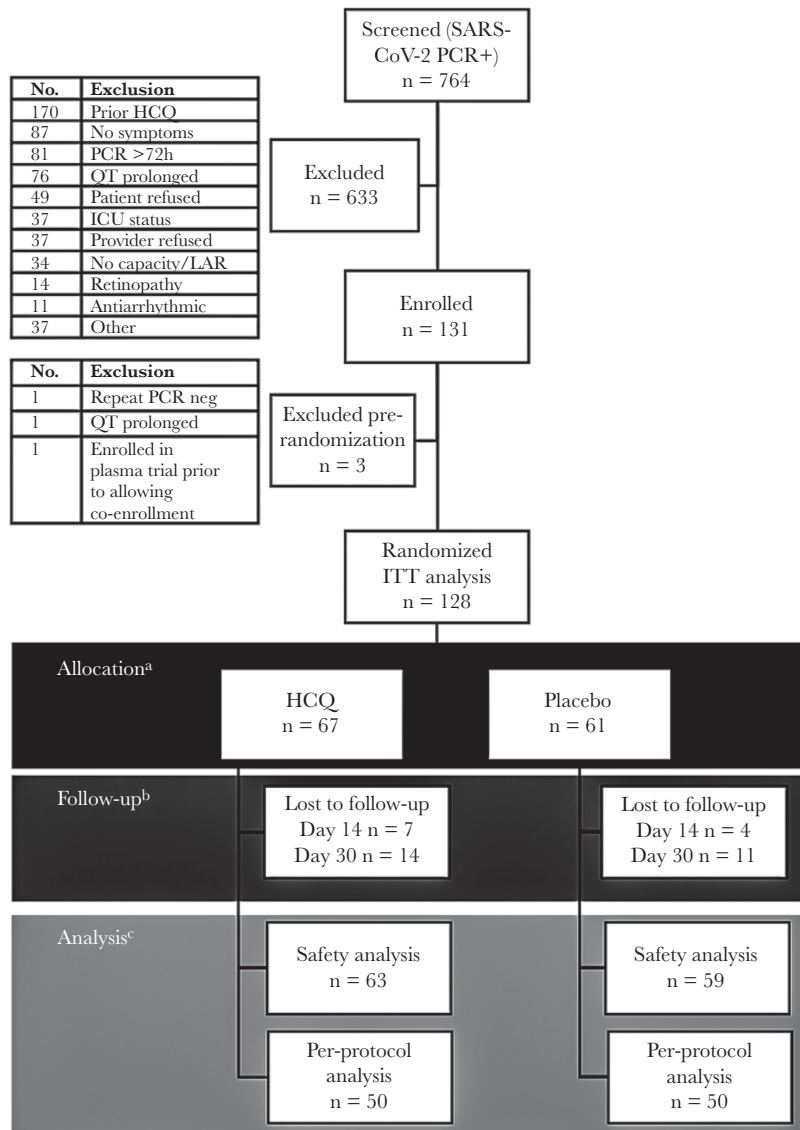
Figure 1. Trial flow diagram. [a]Four patients in the HCQ arm did not receive the study drug (2 voluntarily withdrew, 2 received HCQ outside of the study). Two patients in the placebo arm did not receive the study drug (1 voluntarily withdrew, 1 developed arrhythmia). [b]Two subjects who missing D14 visits were reached on D30, and 4 subjects with D30 follow-up were reached outside of the D30 protocol window but were included in the analysis. [c]Safety analysis = received any study medication. Per-protocol = received at least 80% of assigned doses. Abbreviations: AE, adverse event; ALT alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus 2019; HCQ, hydroxychloroquine; ICU, intensive care unit; ITT, intent-to-treat; LAR, legally authorized representative; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

proportion of subjects assigned to HCQ (n = 23, 34.3%) and placebo (n = 19, 31.1%) during the study period (P = .620). Similar to the ITT analysis, there were no statistically significant differences between HCQ and placebo in the primary outcomes using the safety or per-protocol analysis (Supplementary Table 1) or when age-stratified subgroups (≤60 and >60 years) were assessed (Supplementary Table 2).

Thirty-day mortality in the HCQ (n = 7, 10.4%) and placebo (n = 6, 9.8%) arms did not differ significantly (P = 1.00). The mean number of fever-free and oxygen-free days was nearly identical between treatment arms. The average LOS was 9.75 (±10.3) days in the HCQ group and 6.80 (±5.92) days in the placebo group, a trend that approached statistical significance

(P = .053). There were no significant differences in day 14 severity scores between HCQ and placebo (P = .354), with the majority of the cohort (n = 88, 68.8%) having COVID-19 severity scores in the outpatient range (level 7 or 8). Ninety-five (74.2%) subjects improved their COVID-19 severity scores from baseline to day 14 (Figure 2), with no significant difference between HCQ and placebo (P = .274).

We did not observe an increase in acute kidney injury, hepatotoxicity, hypoglycemia, anemia, or thrombocytopenia from HCQ compared with placebo. The mean change in QTc interval was significantly longer (P = .029) in patients treated with HCQ (16 ms ± 30.0 ms) than placebo (2.1 ms ± 25.3 ms), but there was no statistically significant

Table 1. Baseline Characteristics by Treatment Group[a]

	Overall (n = 128)	HCQ (n = 67)	Placebo (n = 61)	P
Demographics				
Age, mean (SD), y	66.2 (16.2)	66.5 (16.4)	65.8 (16.0)	.804
Male sex	76 (59.4)	45 (67.2)	31 (50.8)	.089
Race/ethnicity				
Hispanic	50 (39.1)	25 (37.3)	25 (41.0)	.807
Non-Hispanic African American	26 (20.3)	15 (22.4)	11 (18.0)	.695
Non-Hispanic Asian	10 (7.81)	3 (4.5)	7 (11.5)	.253
Non-Hispanic White	41 (32.0)	23 (34.3)	18 (29.5)	.694
Unknown	1 (0.78)	1 (1.5)	0 (0)	1.000
Temperature				
Afebrile (<100.4°F)	86 (67.2)	46 (68.7)	40 (65.6)	.855
Febrile (≥100.4°F)	42 (32.8)	21 (31.3)	21 (34.4)	
Oxygen supplementation				
Nasal cannula	62 (48.4)	28 (41.8)	34 (55.7)	.162
O2, mean (SD),[b] L	3.17 (1.57)	2.96 (1.79)	3.34 (1.36)	.355
High-flow nasal cannula	1 (0.8)	1 (1.5)	0 (0.0)	1.000
Noninvasive ventilation (CPAP or BiPAP)	1 (0.8)	1 (1.5)	0 (0)	1.000
Non-rebreather	18 (14.1)	11 (16.4)	7 (11.5)	.583
Body mass index[c]				.023
<20 kg/m^2	8 (6.2)	56 (7.5)	3 (4.9)	
≥20–<30 kg/m^2	74 (57.8)	45 (67.2)	29 (47.5)	
≥30–≤40 kg/m^2	34 (26.6)	15 (22.4)	19 (31.3)	
>40 kg/m^2	12 (9.4)	2 (3.0)	10 (16.4)	
COVID-19 symptoms				
Cough	86 (67.2)	42 (62.7)	44 (72.1)	.343
Dyspnea/shortness of breath	83 (64.8)	41 (61.2)	42 (68.9)	.471
Fever	72 (56.2)	36 (53.7)	36 (59.0)	.672
Fatigue	59 (46.1)	33 (49.3)	26 (42.6)	.566
Myalgia	33 (25.8)	13 (19.4)	20 (32.8)	.127
Diarrhea	34 (26.6)	17 (25.4)	17 (27.9)	.905
Nausea/vomiting	22 (17.2)	11 (16.4)	11 (18.0)	.994
Abdominal pain	18 (14.1)	7 (10.4)	11 (18.0)	.328
Chest pain	17 (13.3)	7 (10.4)	10 (16.4)	.466
Headache	17 (13.3)	9 (13.4)	8 (13.1)	1.000
Loss of sense of smell	13 (10.2)	6 (9.0)	7 (11.5)	.858
Loss of sense of taste	16 (12.5)	9 (13.4)	7 (11.5)	.947
Anorexia	16 (12.5)	6 (9.0)	10 (16.4)	.316
Sore throat	12 (9.4)	5 (7.5)	7 (11.5)	.635
Rhinorrhea	7 (5.5)	5 (7.5)	2 (3.3)	.515
Nasal congestion	6 (4.7)	4 (6.0)	2 (3.3)	.763
Other	37 (28.9)	21 (31.3)	16 (26.2)	.658
Symptom duration				
Days since symptom onset, median (IQR)	7.00 (10.0)	6.50 (6.00)	7.00 (10.0)	.091
Comorbidities				
Hypertension	74 (57.8)	36 (53.7)	38 (62.3)	.423
Diabetes	41 (32.0)	19 (28.4)	22 (36.1)	.457
Cardiovascular disease (non-HTN)	34 (26.6)	21 (31.3)	13 (21.3)	.279
Asthma	20 (15.6)	9 (13.4)	11 (18.0)	.637
Cancer	15 (11.7)	8 (11.9)	7 (11.5)	1.000
Hyperlipidemia	13 (10.2)	8 (11.9)	5 (8.2)	.684
Chronic renal disease (nondialysis)	10 (7.8)	7 (10.4)	3 (4.9)	.404
COPD	9 (7.0)	5 (7.5)	4 (6.6)	1.000
Cerebrovascular disease	8 (6.2)	7 (10.4)	1 (1.6)	.091
HIV	7 (5.5)	5 (7.5)	2 (3.3)	.515
Chronic renal disease (dialysis)	4 (3.1)	2 (3.0)	2 (3.3)	1.000
History of solid organ transplant	2 (1.6)	2 (3.0)	0 (0)	.518
Other	45 (35.2)	19 (28.4)	26 (42.6)	.133
None of the above	16 (12.5)	8 (11.9)	8 (13.1)	1.000

Table 1. Continued

	Overall (n = 128)	HCQ (n = 67)	Placebo (n = 61)	P
Smoking				
Active smoking	8 (6.2)	5 (7.5)	3 (4.9)	.819
Past smoking	36 (28.1)	16 (23.9)	20 (32.8)	.356
Vaporizer use	1 (0.8)	1 (1.5)	0 (0)	1.000
Inhaler use				.199
No inhaler	96 (75.0)	54 (80.6)	42 (68.9)	
Yes, albuterol only	14 (10.9)	7 (10.4)	7 (11.5)	
Yes, albuterol and other long-acting inhalers	18 (14.1)	6 (9.0)	12 (19.7)	
Electrocardiogram				
Corrected QT interval (Bazett formula), mean (SD), ms	441 (22.9)	439 (23.2)	443 (22.6)	.354
Radiography				
Chest x-ray	122 (95.3)	64 (95.5)	58 (95.1)	1.000
Chest CT	11 (8.6)	6 (9.0)	5 (8.2)	1.000
Radiography results				
Opacities	83 (64.8)	41 (61.2)	42 (68.9)	.471
Consolidations	21 (16.4)	10 (14.9)	11 (18.0)	.814
Bilateral	95 (74.2)	47 (70.1)	48 (78.7)	.368
Unilateral	11 (8.6)	6 (9.0)	5 (8.2)	1.000
None of the above	24 (18.8)	14 (20.9)	10 (16.4)	.671
COVID-19 severity score[d]				.777[d]
3: Hospitalized, on noninvasive ventilation or high-flow nasal cannula	21 (16.4)	14 (20.9)	7 (11.5)	
4: Hospitalized, on supplemental oxygen	62 (48.4)	26 (38.8)	36 (59.0)	
5: Hospitalized, not on O2, requiring ongoing medical care	43 (33.6)	26 (38.8)	17 (27.9)	
6: Hospitalized, not on O2, not requiring ongoing care	2 (1.6)	1 (1.5)	1 (1.6)	
SARS-CoV-2 RT-PCR				
Nasopharyngeal	128 (100)	67 (100)	61 (100)	1.000
Days before enrollment, median (IQR)	1.00 (1.00)	1.00 (0.00)	1.00 (1.00)	.184
Laboratory results, mean (SD)				
Creatinine, mg/d	1.57 (2.36)	1.62 (2.54)	1.51 (2.16)	.806
AST, U/L	55.2 (65.8)	62.8 (86.0)	46.9 (30.6)	.180
ALT, U/L	44.9 (49.3)	45.7 (58.4)	44.0 (37.4)	.846
Glucose, mg/dL	123 (54.7)	118 (48.3)	129 (60.9)	.264
WBC, K/µL	7.67 (4.54)	7.80 (4.98)	7.53 (4.03)	.745
Absolute lymphocyte count, K/µL	1.35 (2.21)	1.43 (2.97)	1.27 (0.79)	.682
Hemoglobin, g/dL	12.1 (1.97)	12.1 (2.21)	12.0 (1.69)	.590
Platelet count, K/µL	239 (114)	238 (117)	240 (111)	.911
D-dimer, ng/mL	957 (1500)	782 (960)	1160 (1940)	.168
Ferritin, ng/mL	1070 (2110)	944 (1030)	1200 (2870)	.514
Bilirubin, mg/dL	0.77 (0.89)	0.81 (0.97)	0.73 (0.79)	.612
LDH, U/L	373 (158)	370 (146)	376 (171)	.823
C-reactive protein, mg/L	99.0 (87.1)	92.6 (74.3)	106 (99.4)	.393
Interleukin-6, pg/nL	17.1 (24.9)	18.0 (26.8)	16.1 (22.5)	.755
Interleukin-6 missing	53 (41.4)	25 (37.3)	28 (45.9)	1.000

Abbreviations: ALT alanine aminotransferase; AST, aspartate aminotransferase; BiPAP, bilevel positive airway pressure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus 2019; CPAP, continuous positive airway pressure; CT, computed tomography; HCQ, hydroxychloroquine; HTN, hypertension; IQR, interquartile range; LDH, lactic acid dehydrogenase; O2, oxygen; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; U, units; WBC, white blood cell count.

[a]Unless otherwise specified, data are presented as number of subjects (%).

[b]Liters of oxygen calculated for n = 62 patients on nasal cannula.

[c]BMI categories differ between treatment groups using the chi-square test (P = .023).

[d]Wilcoxon rank-sum test is used for COVID-19 score.

difference between HCQ (n = 3, 4.5%) and placebo (n = 1, 1.6%) in follow-up QTc >500 ms (P = .680). Inflammatory laboratory changes were similar between treatment arms, except for an increase in D-dimer in subjects assigned HCQ (+800 ng/dL ± 3550 ng/dL) compared with placebo (−288 ng/dL ± 1700 ng/dL; P = .047). Follow-up SARS-CoV-2 RT-PCR was performed in 67 (52.3%) participants at a median (interquartile range [IQR]) of 6 (4) days, with 8 (11.9%) subjects assigned HCQ and 10 (16.4%) subjects assigned placebo achieving viral clearance (P = .639).

Table 2. Primary and Secondary Outcomes by Treatment Group[a]

	Overall (n = 128)	HCQ (n = 67)	Placebo (n = 61)	P
Primary outcomes				
Severe disease composite (day 14)[b]	17 (13.3)	11 (16.4)	6 (9.8)	.350
Death	8 (6.2)	3 (4.5)	5 (8.2)	.659
ICU admission	14 (10.9)	9 (13.4)	5 (8.2)	.452
Mechanical ventilation	9 (7.0)	5 (7.5)	4 (6.6)	1.000
ECMO	0 (0)	0 (0)	0 (0)	NA
Vasopressor use	6 (4.7)	3 (4.5)	3 (4.9)	1.000
Unknown	11 (8.6)	7 (10.4)	4 (6.6)	.639
Primary safety composite (day 30)[c]	42 (32.8)	23 (34.3)	19 (31.1)	.620
Unknown	18 (14.1)	11 (16.4)	7 (11.5)	.783
Secondary outcomes				
Severe disease composite (D30)	19 (14.8)	13 (19.4)	6 (9.8)	.166
Death	13 (10.2)	7 (10.4)	6 (9.8)	1.000
ICU admission	12 (9.4)	9 (13.4)	3 (4.9)	.153
Mechanical ventilation	8 (6.2)	5 (7.5)	3 (4.9)	.778
ECMO	0 (0)	0 (0)	0 (0)	NA
Vasopressor use	4 (3.1)	2 (3.0)	2 (3.3)	1.000
Lost to follow-up	25 (19.5)	14 (20.9)	11 (18.0)	.853
COVID-severity score at day 14[d]				.354
1: Death	8 (6.2)	3 (4.5)	5 (8.2)	
2: Ventilator or ECMO	2 (1.6)	2 (3.0)	0 (0)	
3: Hospitalized, on NIV or high-flow nasal cannula	9 (7.0)	7 (10.4)	2 (3.3)	
4: Hospitalized, on supplemental oxygen	5 (3.9)	4 (6.0)	1 (1.6)	
5: Hospitalized, not on O2, ongoing medical care	2 (1.6)	2 (3.0)	0 (0)	
6: Hospitalized, not on O2, not requiring ongoing care	3 (2.3)	1 (1.5)	2 (3.3)	
7: Outpatient, limitation on activities or home O2	31 (24.2)	13 (19.4)	18 (29.5)	
8: Outpatient, no limitation on activities	57 (44.5)	28 (41.8)	29 (47.5)	
Unknown	11 (8.6)	7 (10.4)	4 (6.6)	
30-d mortality	13 (10.2)	7 (10.4)	6 (9.8)	1.000
Fever-free days (T <100.4°F), mean (SD)	6.36 (1.13)	6.40 (0.94)	6.31 (1.33)	.631
O2 supplementation–free days, mean (SD)	4.53 (2.41)	4.63 (2.44)	4.43 (2.40)	.640
Length of stay, mean (SD), d				
Admission to discharge	8.34 (8.59)	9.75 (10.3)	6.80 (5.92)	.053
Electrocardiogram changes[e]				
QT interval >500 ms	4 (3.1)	3 (4.5)	1 (1.6)	.680
Corrected QT interval (Bazett formula) change from baseline, mean (SD), ms	9.21 (28.5)	16.0 (30.0)	2.10 (25.3)	**.029**
No follow-up EKG	48 (37.5)	26 (38.8)	22 (36.1)	.891
Safety laboratory changes on follow-up[f]				
Creatinine >1.5× baseline	7 (5.5)	5 (7.5)	2 (3.3)	.515
AST >3× ULN (if baseline normal) or 1.5× baseline	11 (9.6)	7 (10.4)	4 (6.6)	.639
ALT >3× ULN (if baseline normal) or 1.5× baseline	7 (5.5)	3 (4.5)	4 (6.6)	.898
Platelet count decrease to <75 K/µL	6 (4.7)	5 (7.5)	1 (1.6)	.255
Bilirubin >1.5× ULN (if baseline normal) or 1.5× baseline	2 (1.6)	1 (1.5)	1 (1.6)	1.000
Inflammatory laboratory changes on follow-up[f]				
Ferritin, mean (SD), ng/mL	−196 (1840)	9.56 (786)	−378 (2420)	.302
C-reactive protein, mean (SD), mg/L	−22.3 (96.3)	−19.9 (78.1)	−24.9 (114)	.792
LDH, mean (SD), U/L	−21.9 (158)	−2.65 (153)	−45.1 (162)	.194
D-dimer, mean (SD), ng/mL	301 (2870)	836 (3550)	−288 (1700)	**.047**
Interleukin-6, mean (SD), pg/nL	55.6 (195)	85.8 (245)	17.9 (98.7)	.251
SARS-CoV-2 follow-up RT-PCR				
Positive	49 (38.3)	29 (43.3)	20 (32.8)	.299

Table 2. Continued

	Overall (n = 128)	HCQ (n = 67)	Placebo (n = 61)	P
Interval between positive tests: median (IQR), d	6 (4)	6 (4)	6 (3)	.674
Negative	18 (14.1)	8 (11.9)	10 (16.4)	.639
Interval between tests if neg, median (IQR), d	6 (3.5)	8 (3)	6 (4)	.51
No follow-up PCR performed	61 (47.7)	30 (44.8)	31 (50.8)	.612

Abbreviations: AE, adverse event; ALT alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus 2019; EKG, electrocardiogram; HCQ, hydroxychloroquine; IQR, interquartile range; LDH, lactic acid dehydrogenase; O2, oxygen; PCR, polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T, temperature; U, units.

^aUnless otherwise specified, data are presented as number of subjects (%).

^bNumber of patients with composite end point is less than the sum of each category, as some subjects achieved multiple components of the composite end point.

^cPrimary safety composite: serious adverse event and/or grade 3 or 4 AE and/or discontinuation of therapy for any reason. Eight (4 placebo, 4 HCQ) of these end points were positive due to nursing error (medication not provided on discharge) or the subject was unable to confirm outpatient compliance.

^dWilcoxon rank-sum test was used for COVID-19 score.

^eFollow-up electrocardiogram performed at day 6 or, if discharged prior, on day of discharge.

^fDay 6 labs compared with baseline; if day 6 was not available, day 3 labs were used to calculate. The number of patients with missing data for all laboratory measures did not differ significantly between the HCQ and placebo arms.

Concomitant Medications

Data on concomitant antibacterial therapies, anticoagulation, off-label SARS-CoV-2 agents, and other COVID-19 clinical trials are shown in Table 3. Of the total study population, 30 (23.4%) subjects were taking azithromycin on admission or started azithromycin during the hospitalization. The majority (n = 115, 89.8%) were on either prophylactic or therapeutic anticoagulation, with no difference between arms. Other off-label SARS-CoV-2 therapies were administered to 44 (34.4%) participants, most commonly zinc (n = 17, 13.3%). Importantly, there were no statistically significant differences in the individual concomitant off-label SARS-CoV-2 therapies between the HCQ and placebo groups. One in 5 subjects was co-enrolled in another COVID-19 clinical trial during the study period, with comparable numbers in the HCQ (n = 13, 19.5%) and placebo (n = 13, 21.3%) arms (P = .962).

Adverse Events

Adverse events did not differ significantly between the HCQ and placebo arms (Table 4). There were 122 separate AEs captured in 74 (58.7%) subjects during the study period, the majority of which (n = 94, 77.0%) were mild to moderate in severity. Seven (10.4%) participants assigned to HCQ and 4 (6.6%) participants assigned to placebo had AEs deemed "possibly related" (P = .639) to study medication, and no AEs were reported as "definitely related" to study medication. The most common AE of interest was gastrointestinal complaints, with no significant difference between the number of HCQ (n = 17, 25.4%) and placebo (n = 10, 16.4%) subjects affected (P = .305). There were no arrhythmias or cardiac arrests in either treatment group.

DISCUSSION

In this multicenter, double-blind randomized controlled trial of non-ICU patients hospitalized with COVID-19, a 5-day course of HCQ did not suggest improved outcomes or clinical scores at day 14 compared with placebo. There was a slightly increased QTc interval, an increased D-dimer, and an indication of an increased LOS for participants treated with HCQ compared with those treated with placebo. Adverse events were similar between the HCQ and placebo groups. However, our findings are limited by a relatively small sample size due to a decrease in COVID-19 cases across the New York area.

Our results are concordant with recent large randomized clinical trials examining the effect of HCQ in hospitalized COVID-19 patients. The RECOVERY trial randomized 1561 patients to HCQ and found no difference in mortality but an increased LOS and risk of disease progression, when compared with 3155 patients assigned usual care [29]. Despite our smaller sample size, our findings also suggest a 3-day increase in LOS, on average, in the HCQ arm compared with placebo (P = .053). Additionally, our results are compatible with the World Health Organization (WHO) international COVID-19 therapeutic trial SOLIDARITY [30] and a recently published Brazilian multisite, open-label RCT (n = 504) that failed to show any benefit of HCQ compared with standard care for inpatients with COVID-19 [31]. Finally, our results are consistent with ORCHID, a US multisite trial (n = 479) of COVID-19 hospitalized patients that stopped enrollment due to a lack of observed benefit of HCQ compared with placebo [32]. Our trial, in concordance with these RCTs, supports the bedrock medical research principle that RCTs are needed to determine whether therapies are effective or—just as importantly—not beneficial, even in the midst of a pandemic. Despite in vitro activity, anecdotal success, and observational data suggesting benefit, data from well-designed RCTs are mounting that HCQ does not benefit patients hospitalized with COVID-19.

Patients assigned to HCQ in this study had a slight increase in QTc interval compared with placebo. This is consistent with observational studies showing that QT prolongation is associated with HCQ use in COVID-19 [19]. However, the number
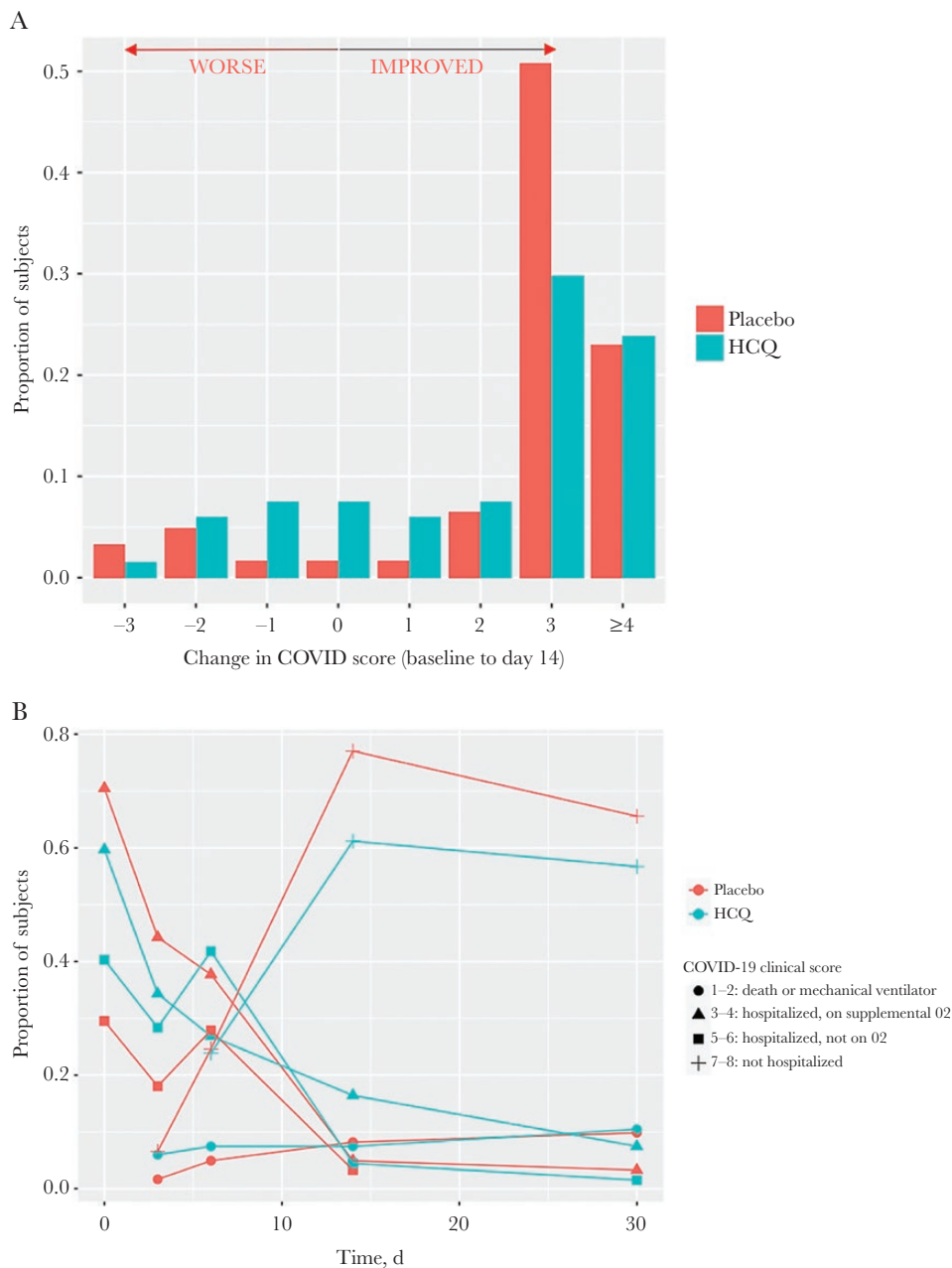
Figure 2. Changes in COVID-19 ordinal severity scores by treatment group. A, Change in clinical score at day 14 by treatment assignment. No difference between HCQ and placebo by Wilcoxon rank-sum test (*P* = .274). B, Proportion of subjects with COVID-19 ordinal clinical scores measured at baseline, day 3, day 6, day 14, and day 30. Abbreviations: COVID-19, coronavirus 2019; HCQ, hydroxychloroquine; O2, oxygen.

of subjects (n = 4, 3.1%) with QTc intervals that increased to a generally accepted clinically significant level (>500 ms) was not large enough to show any treatment-related differences. Interestingly, subjects on HCQ had a mean increase in D-dimer, while those assigned to placebo had a decreased D-dimer. The mechanism behind this finding is unclear, but D-dimer levels correlate with COVID-19 severity [33] and thrombosis in COVID-19 [34]. Although our sample size is limited with respect to the primary composite outcome, the increases in QTc interval and D-dimer and the trend toward increased LOS may

be subtle indicators that HCQ worsens disease in hospitalized COVID-19 patients.

Our trial had several limitations. First, the primary outcome rate was initially estimated at 30%, but likely as a result of improved COVID-19 care, the primary outcome occurred in only 13.3% of subjects at 14 days and 14.8% at 30 days. Second, the sample size did not meet enrollment targets due to the waning COVID-19 case numbers across the region. The number of COVID-19 hospitalizations in New York City peaked on April 6, 2020, at 1724 daily admissions, but by the first enrollment

Table 3. Concomitant Medications and Clinical Trial Co-enrollment by Treatment Group[a]

	Overall (n = 128)	HCQ (n = 67)	Placebo (n = 61)	P
Antibacterial agents				
Azithromycin	30 (23.4)	13 (19.4)	17 (27.9)	.357
Ceftriaxone	31 (24.2)	19 (28.4)	12 (19.7)	.348
Anticoagulation				
VTE prophylaxis[b]	69 (53.9)	39 (58.2)	30 (49.2)	.463
Therapeutic anticoagulation[c]	46 (35.9)	22 (32.8)	24 (39.3)	.535
Antiplatelet agents[d]	38 (29.7)	25 (37.3)	13 (21.3)	.096
Off-label COVID-19 therapies	41 (32.0)	27 (40.3)	14 (23.0)	.056
Zinc	18 (14.1)	13 (19.4)	5 (8.2)	.117
Corticosteroids	13 (10.2)	7 (10.4)	6 (9.8)	1.000
Tocilizumab	5 (3.9)	3 (4.5)	2 (3.3)	1.000
Lopinavir-ritonavir	1 (0.8)	1 (1.5)	0 (0)	1.000
Remdesivir	1 (0.8)	1 (1.5)	0 (0)	1.000
Co-enrollment in other trials	26 (20.3)	13 (19.4)	13 (21.3)	.962
Convalescent plasma	17 (13.3)	7 (10.4)	10 (16.4)	.466
Clazakizumab	4 (3.1)	4 (6.0)	0 (0)	.153
Remdesivir (ACTT-2)	1 (0.8)	0 (0)	1 (1.6)	.962
Anticoagulation (PROTECT study)[e]	3 (2.3)	2 (3.0)	1 (1.6)	1.000

Abbreviations: ACTT-2, Adaptive COVID-19 Treatment Trial 2; COVID-19, coronavirus 2019; HCQ, hydroxychloroquine; VTE, venous thromboembolism.

[a]Unless otherwise specified, data are presented as number of subjects (%).

[b]Subcutaneous heparin 2 or 3 times per day or enoxaparin once per day.

[c]Intravenous heparin, subcutaneous enoxaparin twice daily, apixaban or rivaroxaban.

[d]Aspirin and/or clopidogrel.

[e]The PROTECT trial randomized patients to prophylactic or therapeutic anticoagulation.

Table 4. Adverse Events by Treatment Group[a]

	Overall (n = 128)	HCQ (n = 67)	Placebo (n = 61)	P[b]
Total No. of patients with AE	74 (58.7)	38 (56.7)	36 (59.0)	.933
Total No. of events	122	63	59	
AE severity				
Mild	49 (38.3)	22 (32.8)	27 (44.3)	.252
Mild, No. of events	68	30	38	
Moderate	21 (16.4)	14 (20.9)	7 (11.5)	.231
Moderate, No. of events	26	18	8	
Severe	17 (13.3)	9 (13.4)	8 (13.1)	1.000
Severe, No. of events	27	14	13	
Relatedness to study treatment				
Possibly related	11 (8.6)	7 (10.4)	4 (6.6)	.639
Possibly related, No. of events	16	9	7	
AEs of interest				
GI symptoms[c]	27 (21.1)	17 (25.4)	10 (16.4)	.305
GI symptoms,[c] No. of events	29	18	11	
Rash	5 (3.9)	1 (1.5)	4 (6.6)	.308
Rash, No. of events	7	2	5	
Headaches	3 (2.3)	1 (1.5)	2 (3.3)	.934
Headaches, No. of events	4	1	3	
Vision changes[d]	0	0	0	
Arrhythmia	0	0	0	
Cardiac arrest	0	0	0	

Abbreviations: AE, adverse event; GI, gastrointestinal; HCQ, hydroxychloroquine.

[a]Unless otherwise specified, data are presented as number of subjects (%).

[b]P values were calculated for the proportion of patients with AEs, not number of events.

[c]Nausea, vomiting, diarrhea, and/or constipation.

[d]Subjective complaint (vision was not objectively assessed as part of the study).

in this trial (April 17, 2020), COVID-19 admissions had nearly halved to 902 per day and continued rapidly falling during the study period [35]. Our difficulty enrolling during a declining epidemic was similar to trials during the Ebola [36] and Zika [37] outbreaks and poses the risk of overinterpreting the data. However, our negative findings are concordant with larger trials examining HCQ as therapy for COVID-19 [29–32], and our significant findings of a prolonged QTc, increased D-dimer, and a trend toward increased LOS with HCQ treatment remain notable. Additionally, data pooling efforts are ongoing as part of the COVID-19 Collaborative Platform [38] and other established methods [39] to combine our data with other RCTs to increase statistical power. A third limitation was the use of calcium citrate as a placebo agent, which raises concerns of participant unblinding and unforeseen COVID-19 therapeutic effects. To mitigate these concerns, we selected a formulation of calcium citrate that closely mimicked the size, color, and characteristics of HCQ, and the dose remained within the daily recommended dietary allowance [40]. Finally, our study did not enroll children or pregnant women. Therefore, our trial results are only relevant to the adult nonpregnant population hospitalized with COVID-19.

CONCLUSIONS

Therapies against SARS-CoV-2 are urgently needed to improve COVID-19 morbidity and mortality. This double blind, placebo-controlled randomized trial did not suggest that HCQ is beneficial in preventing severe outcomes or improving clinical scores among non-ICU hospitalized patients with COVID-19. Treatment with HCQ was associated with a slight QTc interval prolongation, increased D-dimer, and a trend toward increased length of stay. However, our findings are limited due to a relatively small sample size, and larger randomized trials are needed.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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