MINI-REVIEW

Hydroxychloroquine is effective, and consistently so when provided early, for COVID-19: a systematic review

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Abstract

Hydroxychloroquine (HCQ) has shown efficacy against coronavirus disease 2019 (COVID-19) in some but not all studies. We hypothesized that a systematic review would show HCQ to be effective against COVID-19, more effective when provided earlier, not associated with worsening disease and safe. We searched PubMed, Cochrane, Embase, Google Scholar and Google for all reports on HCQ as a treatment for COVID-19 patients. This included preprints and preliminary reports on larger COVID-19 studies. We examined the studies for efficacy, time of administration and safety. HCQ was found to be consistently effective against COVID-19 when provided early in the outpatient setting. It was also found to be overall effective in inpatient studies. No unbiased study found worse outcomes with HCQ use. No mortality or serious safety adverse events were found. HCQ is consistently effective against COVID-19 when provided early in the outpatient setting, it is overall effective against COVID-19, it has not produced worsening of disease and it is safe.

Keywords: Azithromycin, COVID-19, hydroxychloroquine, outpatient, SARS-CoV-2
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Introduction

There is a need for effective treatment for coronavirus disease 2019 (COVID-19) infection. Hydroxychloroquine (HCQ), with or without azithromycin (AZ), has been found to have efficacy as a treatment for COVID-19 in some studies [1,2], while other studies have not shown efficacy [3,4]. While we do not prescribe HCQ to typical patients, we do treat various forms of inflammatory arthritis in patients prescribed HCQ by outside providers. Some physicians have stated that HCQ has greater efficacy if provided earlier in the course of the disease [5,6]. Several studies showing negative efficacy have been withdrawn as a result of methodologic problems [7].

We hypothesized that HCQ clinical studies would show the agent to have significant efficacy more often than not for COVID-19, and that efficacy would be greater if HCQ was provided earlier in the disease course. We also hypothesized that some studies that failed to show efficacy would be biased against positive efficacy and that no unbiased studies would show worsening. Finally, we hypothesized that HCQ would be found to be safe.

Methods

We searched PubMed, Cochrane, Embase, Google Scholar and Google for all reports on HCQ as a treatment for COVID-19 patients. This included preprints and preliminary reports on larger COVID-19 studies. We included reports with HCQ alone as well as in combination with AZ and/or zinc. We excluded reports that studied chloroquine. While chloroquine has shown efficacy, it has a worse adverse effects profile than HCQ. For this reason, and because HCQ is inexpensive and widely available, we believe that future treatment will and should focus on HCQ. It was thus our priority to examine HCQ as fully as possible. We excluded reports that only examined HCQ as a means to decrease transmission of

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coronavirus because our focus was on demonstrated clinical efficacy. Reports were analysed for efficacy, type of study, time of intervention with HCQ during the COVID-19 disease course and adverse events. Our final search was performed 3 August 2020.

Results

A total of 43 reports were found that examined HCQ treatment for COVID-19 patients. Twenty-five reported positive clinical efficacy from providing HCQ to for COVID-19 patients; 15 showed no improvement with HCQ and three showed worse clinical results in patients who received HCQ.

Eleven studies in our review examined HCQ efficacy in patients in the outpatient or 'day hospital' setting; all reported positive results [8]. However, in two of the studies [9,10], the positive results, while clinically important (decreased risk of hospitalization and improvement in symptom resolution), were not statistically significant.

We found 32 reports of HCQ treatment in hospitalized patients with COVID-19. Of these 32 reports of hospitalized patients, 14 reported good results, 15 reported no improvement and three reported worse results. Fourteen studies reported the time during treatment during which HCQ was initiated. In nine studies, HCQ was administered within 48 hours of admission. In six [11–16] of these nine, improvement was noted. In three, no improvement was noted [3,17,18]. In five studies, HCQ was administered more than 48 hours after admission or in the intensive care unit (ICU). In two [19,20] of these five improvement was noted. In three it was not [21–23]. In 18 studies, the time of administration was not specified.

Seven of the 43 total studies [12,17,20,24–27] were chartless retrospective studies that used only billing codes. These studies all allowed initiation of HCQ treatment at times that differed with initiation of the control treatment, with HCQ presumably being chosen at the physician's discretion in worsening patients who were more in need of treatment. All such studies were thought to exhibit selection bias against a positive result. Four additional studies [9,10,15,16] had positive trends towards efficacy that did not reach statistical significance. In one study [22], 8% of the treatment group was untreated but not excluded from the treatment group calculations. In addition, the median level of treatment was only 67% of the specified treatment. Nineteen of the 43 reports were preprints or otherwise not peer reviewed. Twenty-four of the articles were from peer-reviewed journals. Of the 11 outpatient reports, all of which reported positive results, seven were peer reviewed and four were not. Of the 32 hospitalization reports, 17 were peer reviewed and 15 were not.

TABLE 1. Study results by time of treatment initiation

Time of treatment initiation	No. of studies showing clinical improvement	No. showing no improvement	% improved vs. total studies
Outpatient[a]	11	0	100
Within 48 hours after hospitalization[a]	6	3	67
After 48 hours of hospitalization; or in ICU	2	3	40
Nonspecified inpatient studies	8	10	44
Total	27	16	63

ICU, intensive care unit.
[a]Both outpatient and hospitalization within 48 hours groups each had two studies that trended towards positive results but without statistical significance. Here studies with good results are grouped.

Overall, 12 (50%) of the 24 peer-reviewed reports and 11 (58%) of 19 non–peer reviewed reports showed positive efficacy.

Some studies provided HCQ alone; some included the addition of AZ and/or zinc. No difference in outcome was observed with the addition of AZ (Table 1), although all of the outpatient studies that provided AZ had positive results. There were no deaths reported as a result of HCQ, AZ or zinc treatment. Increased QTc was seen but not torsades de pointes (TDP). Adverse events that were thought to be likely due to HCQ treatment were not life threatening. No permanent sequelae were described. Adverse events are listed in Tables 2–4. Table 5 provides a comparison of study treatments, settings and results.

Discussion

This review found four important results. The first is that HCQ appears to be consistently effective for the treatment of COVID-19 when provided early in the course of disease in the outpatient setting, and it is generally more effective the earlier it is provided. The second is that overall, in most studies, HCQ exhibits efficacy against COVID-19. The third is that there are no unbiased studies showing a negative effect of HCQ treatment of COVID-19. The fourth is that HCQ appears to be safe for the treatment of COVID-19 when used responsibly.

Timing of HCQ provision

It was striking that 100% of the 11 studies which provided HCQ early in the disease on an outpatient basis showed positive results. In two of the studies [9,10], the benefit was only a trend. However, the effects were clinically important. In the study of Mitjà et al. [9], resolution of symptoms was decreased from 12 to 10 days; in that of Skipper et al. [10], the rate of hospitalization was decreased by 60%. It is likely that if the

TABLE 2. Studies showing positive results with HCQ used to treat COVID-19

Study	No. of patients and treatments	Total HCQ dose	Peer reviewed	Study type	Case severity	Treatment initiation	AEs	Results
Ahmad 2020 [28]	54 total patients; all receiving HCQ + AZ	Average 3700 mg	No	Retrospective case series	High-risk long-term care facility patients	NA	1 seizure; HCQ discontinued, with no report regarding HCQ was likely cause	44% reduction in hospitalization in study patients compared to similar patient population
Arshad 2020 [12]	2541 total patients: 1202 receiving HCQ, 783 receiving HCQ + AZ, 1202 receiving AZ = 1202; usual care = 409	2800 mg	Yes	Retrospective observational study (chartless)	Hospitalized patients	Average 1 day after hospitalization, with 91% receiving treatment within 48 hours	1 prolonged QT interval on ECG	8.1% mortality for entire cohort, with 13.5% mortality for HCQ alone vs. 20.1% HCQ + AZ vs. 22.4% just AZ vs. 26% mortality for usual care
Ashraf 2020 [29]	100 total patients, all receiving oseltamivir, 94 receiving HCQ, 60 receiving LPV/r, 12 receiving ribavirin	400 mg/d for 5–14 days	No	'Comprehensive report' (retrospective observational study)	Hospitalized patients, 15 critically ill, 85 non–critically ill	NA	None reported	HCQ associated with better clinical outcomes
Bernaola 2020 [30]	1645 total patients, 1498 receiving HCQ ± AZ	NA	No	Retrospective observational study	Hospitalized patients	NA	None reported	Only prednisone or HCQ associated with decrease in mortality after propensity score matching; only HCQ was associated with improvement in mortality before propensity matching
Carlucci 2020 [31]	932 total patients, 411 received HCQ + AZ + Zn, 521 receiving HCQ + AZ	2400 mg	No	Retrospective observational study	Hospitalized patients	NA	None reported	Addition of Zn to regimen was associated with decreased mortality, hospice or ventilator rates; effect driven by noncritical patients
Chen 2020 [11]	62 total patients, 31 receiving HCQ, 31 receiving usual care	2000 mg	No	Prospective randomized clinical trail	Hospitalized patients, severe and critical infections excluded	1 day after hospitalization	1 rash, 1 headache; no severe AEs reported	Time to clinical recovery, body temperature recovery and cough remission time was significantly shorter in HCQ group; 4 patients whose disease progressed to severe illness were all in usual care group
Davido 2020 [13]	132 total patients, 52 receiving HCQ + AZ	5800 mg average	Yes	Retrospective observational study	Hospitalized patients	Average 0.7 days after hospitalization	1 prolonged QT interval on ECG	Reduction in unfavourable outcome in patients receiving HCQ + AZ, especially patients with elevated lymphocyte or CRP levels
de Novales 2020 [32]	164 total patients, 123 receiving HCQ, 34 receiving usual care	Average total 3600 mg	No	Retrospective cohort study	Hospitalized patients, 83 mild cases, 38 moderate, 35 severe	NA	None reported	22.2% death rate in HCQ group vs. 48.8% in usual treatment group; 1.8 × high mean cumulative survival in mild group vs. 1.4 × in moderate vs. 1.6 × in severe (statistically significant in mild group)
Esper 2020 [8]	636 total patients, 412 receiving HCQ + AZ, 224 receiving usual care	3200 mg	No	Prospective observational study	Outpatient telemedicine visits	Average 5.2 days since symptom onset	2 serious: maculopapular rash, severe pruritus	Hospitalization rate of 1.9% in treatment group and 5.4% in control group; lower hospitalization rates (1.17% vs. 3.2%) for patients who began treatment before day 7 of symptoms vs. after day 7 of symptoms
Gautret 1 2020 [33]	36 total patients, 20 receiving HCQ, 16 receiving usual care	6000 mg	Yes	Prospective open-label nonrandomized clinical trial	'Day hospital' patients; included 8 asymptomatic cases	NA	None reported	70% of HCQ patients had virus clearance after 6 days via nasal swab PCR vs. 12.5% in control group
Gautret 2 2020 [34]	80 total patients, all receiving HCQ	6000 mg	Yes	Prospective uncontrolled observational study	'Day hospital' patients with mild infections	NA	2 nausea/vomiting, 4 diarrhoea, 1 blurred vision after 5 days' treatment; none required treatment discontinuation	65 had favourable outcome, 15% required oxygen therapy, 1 ICU admission, 1 death; positive PCR test results for 83% on day 7, 93% on day 8, 100% by day 12

Continued

TABLE 2. Continued

Study	No. of patients and treatments	Total HCQ dose	Peer reviewed	Study type	Case severity	Treatment initiation	AEs	Results
Guerin 2020 [2]	88 total patients, 34 receiving usual care, 34 receiving AZ, 20 receiving HCQ + AZ	Average total 5100 mg	Yes	Retrospective cohort analysis	Outpatients with mild/moderate COVID-19	Day after symptoms for 36 patients, within 15 days for the rest	No serious AEs; 5 minor events including urticaria, headache, nausea, vomiting	AZ alone and HCQ + AZ both associated with significant improvement in recovery time compared to usual care (9.2, 12.9 and 25.8 days respectively)
Kim, JW 2020 [35]	65 total patients, 31 receiving LPV/r, 24 receiving HCQ; 26.5% of HCQ patients also receiving AZ	Minimum 2800 mg	Yes	Retrospective cohort study	Hospitalized patients	Average 7 days before initiation of therapy	1 respiratory failure, 1 shock in HCQ group (likely from COVID-19, not treatment)	Slower virus clearance in HCQ group compared to LPV/r group but equivalent time to symptom remission
Kim, MS 2020 [36]	97 total patients, 22 receiving HCQ ± AZ, 35 receiving LPV/r, 40 receiving usual care	200 mg twice daily, duration not reported	No	Retrospective cohort study	Moderate hospitalized patients	NA	No serious AEs reported; 20 abdominal/GI	HCQ treatment associated with improved virus clearance, shorter hospital stays and quicker resolution of cough
Lagier 2020 [37]	3737 total patients, 3119 receiving HCQ + AZ, 618 receiving usual care	6000 mg	Yes	Retrospective observational study	Hospitalized patients and patients seen at 'day-care hospital'	1 day after testing positive	12 QT prolongation on ECG requiring discontinuation of HCQ; 3 QTc > 500 ms; no torsades de pointes or sudden deaths	HCQ + AZ associated with decreased risks of ICU transfer, extended hospitalization and risk of death
Million 2020 [6]	1061 patients, all receiving HCQ + AZ	6000 mg	Yes	Retrospective observational study	Hospitalized patients and patients seen at 'day-care hospital'	Within 2 days after testing positive	25 mild and 0 serious AEs reported	4.6% poor clinical outcome (death, transfer to ICU, hospitalization for ≥10 days); 20 of 21 repeat nasal swabs were negative by day 15 after treatment
Monforte 2020 [1]	539 total patients, 197 receiving HCQ, 94 receiving HCQ + AZ, 92 receiving usual care	NA	Yes	Retrospective study, not randomized	Hospitalized patients	NA	None reported	27% mortality rates with HCQ, 23% with HCQ + AZ and 51% with usual care; mechanical ventilation rates of 4.3% in HCQ, 14.2% in HCQ + AZ and 26.1% with usual care. After adjusting for confounders, HCQ + AZ associated with 66% reduction in risk of death compared to usual care
Sbidian 2020 [38]	4642 total patients, 623 receiving HCQ, 227 receiving HCQ + AZ	NA	No	Retrospective cohort study (chartless)	Hospitalized patients	NA	None reported	No difference in mortality rate found in HCQ vs. usual care after regression analysis; discharge rates significantly higher in HCQ group
Scholz 2020 [39]	141 total patients, all receiving HCQ, AZ, Zn	2000 mg	No	Retrospective case series	Outpatient cases	Average 4.8 days after symptom onset	No serious AEs reported	Hospitalization rates in treated patients 84% less than community control; decreased risk of mortality
Xue 2020 [14]	30 total patients, 15 receiving HCQ within 7 days of hospitalization, 15 after 7 days	Minimum 2000 mg	Yes	Retrospective cohort study	Hospitalized patients	Either before 7 days or after 7 days of hospitalization	None reported	Earlier treatment with HCQ resulted in faster recovery than later; and lower rates of mechanical ventilation and ICU transfer
Yu 2020 [20]	568 total critically ill (ventilated, septic shock, ICU/organ failure) COVID-19 patients, 48 patients receiving HCQ, 520 usual care	Average total 3400 mg	Yes	Retrospective cohort study	Hospitalized patients, all critically ill (including ICU patients, ventilated or in septic shock)	NA	None reported	18.8% death rate in HCQ group vs. 45.8% in usual care group; Cox regression analysis showed significantly decreased mortality risk in HCQ group; showed significant decrease in IL-6 after HCQ application; no change in control group
Yu 2020 letter to editor [19]	2882 total patients, 278 receiving HCQ	Average total 3400 mg	Yes	Retrospective cohort study (chartless)	Hospitalized patients	Median 10 days after hospitalization	None reported	HCQ group associated with reduced levels of IL-6 as well as with

TABLE 2. Continued

Study	No. of patients and treatments	Total HCQ dose	Peer reviewed	Study type	Case severity	Treatment initiation	AEs	Results
								improvement in albumin, troponin I, BNP; reduction in mortality rates in COVID-19 patients with cardiac injury treated with HCQ
Zelenko 2020 [5]	1450 total patients, all receiving HCQ, AZ, Zn	2000 mg	No	Retrospective report	Outpatient treatment	NA	Nausea or diarrhoea in 10%; no serious AEs	No comparison to control group; 2 deaths, 6 hospitalizations, 4 intubations

AZ, azithromycin; BNP, B-type natriuretic peptide; AE, adverse event; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ECG, electrocardiogram; HCQ, hydroxychloroquine; ICU, intensive care unit; IL-6, interleukin 6; LPV/r, lopinavir/ritonavir; NA, not applicable; Zn, zinc.

TABLE 3. Studies showing no improvement with HCQ used to treat COVID-19

Study	No. of patients and treatments	Total HCQ dose	Peer reviewed	Study type	Case severity	Treatment initiation	AEs	Results
An 2020 [21]	226 total patients, 31 receiving HCQ, ± AZ at physician discretion	Average 3400 mg	No	Retrospective nonrandomized cohort study	Hospitalized patients; targeting 'mild to moderate cases'	Average 6.7 days after diagnosis	No SAEs reported	After propensity score matching and Cox regression, analysis found that HCQ was not associated with better clinical outcomes like virus clearance, length of hospital stay or duration of symptoms
Cavalcanti 2020 [4]	667 total patients, 217 receiving HCQ + AZ, 221 receiving HCQ, 229 receiving standard care	5600 mg twice daily	Yes	Prospective randomized controlled trial	Hospitalized with mild/moderate cases	NA (provides time to group assignment, not time to treatment initiation)	30 reports of increased QTc, 6 reports of arrhythmia	No significant difference in 15-day outcome between HCQ, HCQ + AZ, usual care
Geleris 2020 [17]	1446 total patients, 70 intubated initially, 811 receiving HCQ,	Average 3200 mg	Yes	Retrospective cohort (chartless)	Hospitalized patients	Within 24 hours after hospitalization	None reported	No significant difference between HCQ receipt and intubation or death, ± AZ also no change
Giacomelli 2020 [40]	172 patients, 43 receiving HCQ + LPV/r within 5 days of symptoms and 129 after 5 days of symptoms	2000–8000 mg (200 mg twice daily for 5–20 days)	No	Retrospective nonrandomized cohort study	Hospitalized patients	Either before or after 5 days of symptoms	Increase in hepatic enzymes, nausea and diarrhoea reported, attributed to LPV/r	No difference between groups in mortality rates after adjusting for comorbidities
Ip 2020 [24]	2512 total patients, 1914 receiving HCQ, 59% of HCQ patients receiving AZ	2600 mg	No	Retrospective cohort study (chartless)	Hospitalized patients not discharged home within 24 hours	NA	Prolonged QTc or arrhythmia reported in 134 patients, cardiomyopathy in 20 patients; does not comment on whether these were treatment-related AEs	No significant difference between HCQ and standard care group; 30-day mortality for standard care was 0.2, vs. any HCQ 0.2, vs. HCQ + AZ 0.18
Kalligeros 2020 [41]	108 total patients, 36 receiving HCQ ± AZ, 72 receiving usual care	NA; 5 days' treatment with HCQ but dosage not provided	Yes	Retrospective cohort study	Hospitalized patients	NA	2 QTc prolongation, 1 altered mental status, 0 torsades de pointes	After regression analysis, no significant improvement in mortality rates, hospitalization duration or time to clinical improvement
Lopez 2020 [23]	29 total patients, all receiving HCQ + AZ, 17 patients with on-target HCQ levels, 12 patients with HCQ below target levels	4400 mg	Yes	Retrospective cohort study	ICU patients	NA	7 abnormal ECG; all discontinued treatment	No significant difference in 15-day mortality rate or discharge from ICU for patients reaching HCQ level goals and not
Mahevas 2020 [16]	29 total patients (all receiving HCQ + AZ), 17 patients with on-target HCQ levels, 12 patients with	600 mg/d, duration not provided	No	Retrospective cohort study	Hospitalized patients requiring oxygen therapy	Within 48 hours after hospitalization	8 patients discontinued HCQ due to ECG changes; 1 QTc > 500 ms	No statistically significant difference in poor clinical outcomes; 20.5% of patients who received HCQ transferred to

Continued

TABLE 3. Continued

Study	No. of patients and treatments	Total HCQ dose	Peer reviewed	Study type	Case severity	Treatment initiation	AEs	Results
	HCQ below target levels							ICU or died within 7 days, 22.1% for control; 2.8% of patients in HCQ group died within 7 days vs. 4.6% control; ARDS in 27.7% of HCQ group vs. 24.1% control
Mallat 2020 [3]	34 total patients, 21 receiving HCQ	4800 mg	No	Retrospective observational study	Hospitalized patients, with ICU and ventilator patients excluded	Within 2 days after hospitalization; median administration of HCQ at 0 days from hospitalization	None reported	Hospital stay longer for HCQ group vs. standard care but NS. Main outcome: time to negativity longer for HCQ patients 17 days vs. 10 days for non-HCQ patients. Also showed no improvement in inflammatory markers/ lymphopenia in HCQ group
Mitja 2020 [9]	353 total patients, 169 receiving HCQ, 184 receiving usual care	3200 mg	Yes	Prospective randomized controlled trial	Outpatients	Average 3 days from symptom onset to treatment initiation	No treatment-related SAEs; multiple reports of nausea vomiting, headache	No difference in virus clearance, no improvement in risk of hospitalization compared to control group
Molina 2020 [42]	11 total patients, all receiving HCQ + AZ	6000 mg	Yes	Prospective noncontrolled trial	Hospitalized patients with moderate to severe infections	NA	1 QT prolongation; HCQ discontinued	Nasopharyngeal swabs still positive in 8/10 after treatment 5–6 days after treatment. Clinical results: 1 death, 2 ICU admissions
ORCHID trial [43]	470 total patients	2400 mg	No	Prospective randomized controlled blinded study	Hospitalized patients	NA	None reported	No data yet released; trial arm stopped for 'lack of efficacy'
Paccoud 2020 [15]	89 total patients, 38 patients receiving HCQ, 46 receiving with standard care	6000 mg	Yes	Retrospective cohort study	Hospitalized patients	Within 2 days after hospitalization	6 AEs reported: 2 QTc prolongation, 1 each cytopenia, paresthesia, headache diarrhoea	No significant difference in risk for long hospital admission, ICU admission or death between HCQ group and standard of care group
Rosenberg 2020 [18]	1438 total patients, 735 receiving HCQ + AZ, 271 receiving HCQ alone, 211 receiving AZ alone, 221 receiving usual care	NA	Yes	Retrospective cohort study	Hospitalized patients	Median 1 day after admission for HCQ; median 0 days after admission for AZ	194 arrhythmia in patients receiving HCQ; 120 QT prolongations. No effort to determine if AEs were treatment related	Mortality 22.5% for HCQ + AZ, 18.9% HCQ alone, 10.9% for AZ alone, 17.8% for neither drug. Differences between groups NS
Singh 2020 [25]	3372 total patients, 1125 receiving HCQ, 799 HCQ + AZ, 2247 receiving usual care	NA	No	Retrospective cohort study (chartless)	Hospitalized patients	NA	None reported	After propensity score matching, no significant difference in mortality rates between patients treated with HCQ and usual care
Skipper 2020 [10]	423 total patients, 212 receiving HCQ, 211 receiving placebo	3800 mg	Yes	Prospective randomized controlled trial	Outpatients	Within 4 days of symptoms	Multiple reports of abdominal pain, nausea, diarrhoea; no SAEs related to treatment reported.	No statistically significant improvement of symptom severity between HCQ and placebo group; no statistically significant difference in hospitalization/ mortality between the two groups
Tang 2020 [44]	150 total patients, 75 receiving HCQ, 75 receiving usual care	12 400 or 18 000 mg (average 15 200)	Yes	Prospective open-label randomized, controlled trial	Hospitalized patients, 148 patients with mild to moderate infections, 2 with severe infections	NA	2 serious AEs reported: 1 report of blurred vision, 1 report of thirst. Both transient and self limited	Only results on 'negative conversion' presented: 2 negative results 24 hours apart. Conversion rate in 28-day experimental group 85.4%, control group 81.3% (NS)

AE, adverse event; ARDS, acute respiratory distress syndrome; AZ, azithromycin; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; HCQ, hydroxychloroquine; ICU, intensive care unit; LPV/r, lopinavir/ritonavir; NS, not statistically significant; SAE, severe adverse event.

TABLE 4. Studies that showed worse results with HCQ used to treat COVID-19

Study	No. of patients and treatments	Total HCQ dose	Peer reviewed	Study type	Case severity	Treatment initiation	AEs	Results
Horby 2020 [22]	4686 total patients, 1561 receiving HCQ, 3155 receiving usual care, 17% receiving HCQ + AZ	8800 mg	No	Prospective randomized controlled trial	Hospitalized patients	Average 3 days after hospitalization	1 torsades de pointes (patient recovered without need for intervention)	No significant difference in 28-day mortality (25.7% HCQ, 23.5% usual care). HCQ group had worse discharge and ventilation rates compared to usual care. No difference in arrhythmia rates
Magagnoli 2020 [26]	807 total patients, 198 receiving HCQ, 214 received HCQ + AZ	Median 2000 mg	Yes	Retrospective cohort study (chartless)	Hospitalized patients	NA	None reported	Mortality risk higher in HCQ group, no significant difference in chance of mechanical ventilation between groups
Rivera 2020 [27]	2186 total patients, 538 receiving HCQ ± AZ, 1321 receiving usual care, 327 receiving other medications	NA	Yes	Retrospective observational study (chartless)	Hospitalized patients	NA	None reported	After multivariable logistic regression, HCQ alone was associated with no improvement in mortality vs. usual care; HCQ in combination with other medication was associated with increase in mortality

AZ, azithromycin; COVID-19, coronavirus disease 2019; HCQ, hydroxychloroquine; NA, not applicable.

studies had higher power, statistical significance would have been reached. In the 32 other studies, HCQ was provided on an inpatient basis in patients with more advanced disease. The studies were divided into early, late and ICU administration. Early provision—within 48 hours of admission—showed 67% (6/9) of the studies to have positive efficacy. Later provision—after 48 hours' admission or in the ICU—found positive efficacy in 40% (2/5). Thus, from 100% for early outpatient, to 67% for early hospital to 40% for later hospital provision, there appears to be a relationship with time of initiation of treatment, with better results observed the earlier HCQ is provided.

Overall efficacy

Twenty-three (53%) of the 43 studies showed a definite positive effect of HCQ vs. COVID-19. However, if negatively biased studies are removed and the clinically important positive trends from underpowered studies are moved to the positive efficacy group, then the ratio changes to 28 positive vs. nine with no effect, resulting in a 75% ratio of positive to nonpositive HCQ studies. Interestingly, none of the no-effect studies showed a clear trend towards worsening.

Randomized controlled trials

Of the seven randomized controlled trials (RCTs), two [9,10] were in the outpatient early treated group. As described above, both these studies had clinically important trends towards positive results, although results were underpowered and did not reach statistical significance. The other five RCTs were performed in hospitalized patients later in the disease course, where the efficacy of HCQ seems to be less. There was one positive [11], three no-effect [4,43,44] and one negative effect [22] studies. The negative effect study, however, was biased, as described below, such that any negative or no-effect result would not be valid. Thus, both RCTs with early treatment showed positive results; one of three hospitalized patients had a positive result, consistent with the general finding of better results with earlier HCQ provision.

Negative effect studies

Three studies had data that seemed to show worse outcomes with HCQ. However, all had significant biases. Further, all were reported in hospitalized patients, when results with HCQ are less good. Two [3,16] of the three studies were well-done studies that were nonetheless constrained by being chartless hospitalization studies that only used billing codes at particular time points to evaluate patients but had no information regarding events between these time points within their hospital course which led to initiation of treatment. Both studies were retrospective. Patients were not randomized to treatment with HCQ vs. other care. Rather patients apparently

TABLE 5. Comparison of treatments, settings and results

Characteristic	Positive results		No change		Negative results	
Outpatient	9	Treatments: HCQ: 2 HCQ + AZ: 7 HCQ ± AZ: HCQ + antivirals:	2	Treatments: HCQ: 2 HCQ + AZ: HCQ ± AZ: HCQ + antivirals:	0	Treatments: HCQ: HCQ + AZ: HCQ ± AZ: HCQ + antivirals:
Hospitalized, treated within 48 hours	4	Treatments: HCQ: 2 HCQ + AZ: 1 HCQ ± AZ: 1 HCQ + antivirals:	5	Treatments: HCQ: 3 HCQ + AZ: HCQ ± AZ: 2 HCQ + antivirals:	0	Treatments: HCQ: HCQ + AZ: HCQ ± AZ: HCQ + antivirals:
Hospitalized, treated after 48 hours; or in ICU	2	Treatments: HCQ: 2 HCQ + AZ: HCQ ± AZ: HCQ + antivirals:	2	Treatments: HCQ: HCQ + AZ: 1 HCQ ± AZ: 1 HCQ + antivirals:	1	Treatments: HCQ: HCQ + AZ: HCQ ± AZ: 1 HCQ + antivirals:
Administration time not reported in relation to hospitalization	8	Treatments: HCQ: 1 HCQ + AZ: 1 HCQ ± AZ: 5 HCQ + antivirals: 1	8	Treatments: HCQ: 2 HCQ + AZ: 1 HCQ ± AZ: 4 HCQ + antivirals: 1	2	Treatments: HCQ: HCQ + AZ: HCQ ± AZ: 2 HCQ + antivirals:

Values recorded in this table are the number of studies that achieved the designated result.
AZ, azithromycin; HCQ, hydroxychloroquine; ICU, intensive care unit.

received HCQ at the discretion of the physician. The time of administration of HCQ to the patients who received it was not specified during hospitalization. This introduces selection bias in both studies regarding treatment with HCQ for sicker patients who were faring worse after admission, and who presumably would be more likely to have treatment vs. no treatment selected by their physician. Attempting to normalize comorbidities did not correct this bias because the clinical progress of COVID-19 infection is not well predicted by preexisting comorbidities. This selection bias means that patients whose condition worsened after admission, and who are thereby more likely to have worse outcomes, would be overrepresented in the HCQ treatment group. For this reason, negative results from the treatment arm of these studies are not valid because outcomes are moved negatively. A positive effect, however, would have validity because it could only occur despite the negative selection bias, not because of it.

The third study showing worse results with HCQ was a highly powered non–peer reviewed study whose primary outcome of 28-day mortality actually showed no difference between the HCQ-treated group and the usual treatment group. Two of the secondary results did just barely reach significance regarding the negative results [22]. However, the reporting of results was flawed: 8% of the patients in the treatment group did not receive HCQ at all, and the median number of days of treatment for all treated patients was only 6 out of a prescribed 9. These facts mean that less than half of patients received the full treatment regimen, or even two thirds of the full treatment regimen, with one in 12 receiving no treatment at all. However, these outcomes in untreated and undertreated patients were grouped with the fully treated patient outcomes. If HCQ has any positive effect, which we believe is well established, then this undertreatment would invalidate their borderline negative secondary results. In addition, treatment was initiated more than 48 hours after admission—a time point that our aggregate data has shown to have a high incidence of no-effect results. The study was not blinded, introducing a potential undertreatment bias towards patients who were known by the staff to be treated with HCQ. This study most reasonably is actually a no-effects study, which is common in already hospitalized patients (such as these) treated more than 48 hours after admission.

Adverse events

Some clinicians fear that the increased QTc observed in the electrocardiogram results of some patients treated with HCQ or AZ indicates a predisposition to TDP and then death from ventricular fibrillation. We found no such deaths; nor did we find death from any cause related to HCQ treatment. Indeed, we found only one case of TDP at all, which resolved spontaneously without treatment and without sequelae. This is consistent with our prior study showing an absence of TDP mortality with HCQ treatment [45]. All of the adverse events which seemed attributable to HCQ treatment in the 43 studies were side effects known to occur with HCQ. These included nausea, vomiting, diarrhoea, stomach pain, headache, rash, dizziness, itching and blurred vision. In all cases, there was no indication of persistence of symptoms after discontinuing HCQ therapy. HCQ has been used with good safety for more than 50 years; the relatively minor adverse events seen in these studies is consistent with this good safety profile.

Strengths and weaknesses

A strength of this study is the large number of cohorts. A further strength is the critical methodologic study analysis, which to our knowledge has not heretofore been attempted for

COVID-19. One weakness is the heterogeneity of study designs, which made it hard to compare results across studies. A perceived weakness of the study could be that our review includes reports made outside the peer-reviewed literature. Several studies, reporting both improvement and no efficacy with the provision of HCQ, included in our review are either preprints or preliminary results of larger trials. Because of the unprecedented and time-sensitive nature of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic, the scientific community has shared data and studies on a level unseen before this emergency. We believe that these reports hold valuable information and decided to include them, regardless of their publication venue. In addition, we found that both the peer-reviewed and non–peer-reviewed reports showed a similar breakdown between studies showing efficacy vs. not, so bias was therefore not introduced.

Significance

Our findings have substantial societal global importance because there have been numerous edicts either preventing HCQ provision for the treatment of COVID-19 or limiting it to the inpatient setting, which we believe have unintentionally resulted in many unnecessary deaths. Our findings showing efficacy and safety of HCQ against COVID-19 indicate that HCQ should be freely available to patients and physicians who choose to use it. It should especially be freely available to be provided on an outpatient basis before hospitalization, where it appears to be more effective and where early fears of fatal heart arrhythmias have been shown to be unfounded [45]. This is particularly important because of the other drugs to have demonstrated efficacy, remdesivir has shown no significant benefit in a recent study [46]. Remdesivir is also expensive and not widely available. Dexamethasone has only been shown to be effective in critically ill hospitalized patients [47]. Convalescent plasma has shown benefit [48], but even this is not well validated, and plasma is not available in large numbers of doses. Thus, HCQ, with proven efficacy and safety, a cost of 37 cents per pill and thus a total treatment cost of under $20 [49], vs. $3100 for remdesivir [50], as well as wide supply-chain availability, would appear to be the best COVID-19 treatment option available, and it needs to be widely promoted as such. Unfortunately, the controversies surrounding HCQ have resulted in physicians being afraid to prescribe it for reasons which have nothing to do with medicine and in patients being afraid to take it as a result of spurious reports of danger or fears that it is not effective. We hope that our study findings will disabuse the medical community of these misapprehensions about efficacy and validate that it is both efficacious and safe—and needs to be freely prescribable.

We do not believe that randomized controlled studies are necessary before HCQ is authorized for general use because the efficacy seen in studies already performed indicates that control patients in such studies might die unnecessarily, and because the time delay to perform any such study would cause yet more deaths by preventing HCQ use when it is most needed: immediately! Our study has shown that good evidence of efficacy exists and that there is no safety, cost or supply reason to not treat now. Unnecessary death from delayed treatment is too high a price to pay for greater certainty of knowledge. Many may have already died unnecessarily as a result of inaccurate HCQ information. It is imperative that we do not further add to the COVID-19 death toll by refusing to prescribe HCQ.

Conclusions

HCQ has been shown to have consistent clinical efficacy for COVID-19 when it is provided early in the outpatient setting; in general, it appears to work better the earlier it is provided. Overall, HCQ is effective against COVID-19. There is no credible evidence that HCQ results in worsening of COVID-19. HCQ has also been shown to be safe for the treatment of COVID-19 when responsibly used.

Conflict of interest

None declared.

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