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Treatment of COVID-19 Patients with Chloroquine, Hydroxychloroquine, and/or Azithromycin: A Systematic Review and Meta-Analysis

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Abstract

Background: Early in the pandemic, Chloroquine (CQ), Hydroxychloroquine (HCQ), and Azithromycin (AZ) were considered viable options due to promising results from preliminary studies.

Objective: To investigate the therapeutic efficacy of HCQ, CQ, and/or AZ in COVID-19 patients.

Data sources: PubMed, Scopus, and Web of Science were searched from inception to September 6, 2020. A retrospective chart review of patients treated at our institution between March 12, 2020 and June 1, 2020 was performed to identify additional subjects.

Study selection: Studies assessing outcomes associated with use of HCQ, CQ, and/or AZ in COVID-19 patients.

Data extraction/synthesis: Two reviewers independently extracted data and determined study quality.

Main outcomes/measures: Mortality, ICU admission, viral clearance

Results: Thirty-three studies containing 15,157 patients were included in this review. An additional 64 patients treated at our institution were pooled into the final analysis. Twenty-six studies were included in the meta-analysis. A significantly lower proportion of patients treated with combined HCQ and AZ died relative to control (p= 0.008). A higher proportion of patients receiving combined therapy (p<0.0001) or HCQ alone (p= 0.001**)** required intensive care compared to control. In terms of viral clearance, a greater

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proportion of subjects receiving HCQ and AZ concurrently ($p < 0.0001$) achieved this endpoint compared to control while treatment with HCQ alone ($p = 0.76$) conferred no observable benefit.

Conclusion: Although this review examined the largest cohort of COVID-19 patients treated with CQ, HCQ, and/or AZ to date, our findings must be interpreted with caution given the limitations.

Introduction

In December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus Disease 2019 (COVID-19), emerged from Wuhan, China and rapidly disseminated to other countries. As of December 9, effective therapy remains elusive as the number of cases soar over 68.8 million and deaths rise above 1.5 million worldwide [1]. The search for treatment options has resulted in the repurposing of known drugs. Among the plethora of experimental agents considered, the aminoquinolines Chloroquine (CQ) and its analogue Hydroxychloroquine (HCQ) had emerged as promising candidates owing to positive results derived from in vitro studies and ongoing clinical trials [2-4].

The anti-inflammatory and antiviral effects of these two aminoquinolines, which are widely used in the treatment of malaria and rheumatic diseases, made them attractive candidates for repurposing. HCQ has been shown to possess more potent antiviral properties and a better safety profile than CQ.[3] In addition, as an immunomodulatory agent, it decreases the production of cytokines, including IL-1 and IL-6, by interfering with toll-like receptor signaling [5]. When combined with Azithromycin (AZ), a macrolide antibiotic, a synergistic effect against SARS-CoV-2 was observed in an in vitro study [6].

The ongoing pandemic has made the acquisition of robust data demonstrating the therapeutic efficacy of HCQ, CQ, and/or AZ against the novel coronavirus difficult. Due to the dearth of well-designed clinical trials, the present study aimed to (1) review the existing scientific literature on treatment outcomes of COVID-19 patients using HCQ, CQ, and AZ, either alone or in combination, and (2) perform a meta-analysis on available data to ascertain any possible therapeutic advantage and associated risk of corrected QT (QTc) interval changes.

Materials and methods

Data sources and searches

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. To identify studies for inclusion in this review, detailed search strategies were developed for the following three databases: PubMed, Scopus, and Web of Science. Databases were searched from date of inception through September 6, 2020. The search strategies used a combination of subject headings (e.g., MeSH in PubMed) and keywords for the following three concepts: COVID-19, CQ/HCQ, and AZ. The PubMed search strategy was modified for the other two databases, replacing MeSH terms with appropriate subject headings, when available, and maintaining similar keywords. To identify additional articles, the reference lists of relevant articles were hand-searched, as well as citing articles. References were exported into the review management software, Covidence, for study selection.

Study selection

Only studies reporting on outcomes of patients with suspected or laboratory-confirmed COVID-19 treated with CQ, HCQ, and/or AZ were included. Studies were considered for inclusion if they were: (1) double- or single-blinded randomized controlled trials, (2) double- or single-blinded randomized comparison trials, (3) non-randomized controlled trials, and (4) prospective or retrospective observational studies. Abstracts were first independently assessed by two reviewers (E.Y. and Y.N.) to identify all articles that met the inclusion criteria. Conflicts were resolved by a third reviewer (S.A.N.). Non-English abstracts, non-human studies, review articles, pre-prints, case series (<20 patients), and case reports were excluded. Studies evaluating the prophylactic role of these medications were also excluded.

Data extraction and quality assessment

Data extraction was performed by two reviewers (E.Y. and Y.N.) independently. In instances of incomplete data, two attempts were made to contact the primary author via email for clarification or sharing of primary data. Included articles were critically appraised to assess level of evidence using the Oxford Center for Evidence-Based Medicine criteria [8]. The risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions version 6.0 [9]. Two authors (E.Y. and Y.N.) performed a pilot assessment on three studies to check for consistency of assessment. Both then performed independent risk assessments on the remaining studies. All disagreements were resolved by the way of discussion with a third author (S.A.N.).

Data synthesis and analysis

Meta-analysis and Risk Assessment of selected studies with continuous variables (comparison of means and standard deviations between pre-treatment and post-treatment groups) was performed with Cochrane Review Manager (RevMan) version 5.4 (Nordic Cochrane Center, Cochrane Collaboration, 2011, Copenhagen, Denmark). In addition, a meta-analysis of proportions was performed using MedCalc 19.4.1 (MedCalc Softwarebvba, Belgium). Primary outcomes (Mortality, ICU admission, Negative PCR conversion, and QTc prolongation) were expressed as pooled proportion with 95% CI given both for the fixed effects model and the random effects model. Each technique was weighted according to the number of patients treated. MedCalc used a Freeman-Tukey transformation [10] to calculate the weighted summary proportion under the fixed and random effects model [11]. Both the fixed effects model and the random effects model were used in this study for continuous and nominal variables. If there is high heterogeneity (I^2>50 %), then a random effects model is used; if low heterogeneity, then a fixed effects model is allowable. Using random effect modeling is more conservative, thus, it is preferable to assume random effects modeling unless I^2 is small. A p-value of <0.05 was considered to indicate a statistically significant difference for all statistical tests.

Results

The literature search yielded a total of 919 unique articles after de-duplication. Screening by title and abstract excluded 853 articles. A full-text review of remaining studies further eliminated 35 articles. Two articles were identified by hand-searching the reference lists of relevant articles, leaving a total of 33 articles for inclusion in the final analysis. A diagram outlining the summary of the search process is shown in (Figure 1). Assess-

ment of risk of bias is shown in (Appendix Figure 1) .

The 33 included studies [12-44] originated from 10 different countries. The majority of studies were retrospective (n= 18), followed by prospective observational (n= 6), randomized (n= 8) and non-randomized (n= 1) controlled trials. A total of 15,157 patients with an age range of 14 to 99 were identified through this review. There were 8,043 males and 6,807 females. The age and gender of the subjects were not routinely extractable for all studies. The treatment regimens consisted of combined therapy with HCQ and AZ (n= 6,742), HCQ monotherapy (n= 3,609), CQ monotherapy (n= 383), and AZ monotherapy (n= 385). A total of 3,837 patients received other treatments, including standard of care, and served as the control group. An additional 119 patients received HCQ or CQ in combination with AZ while 82 received HCQ or CQ alone. The frequency of patients treated with either aminoquinoline, however, was not specified in that study. Descriptive features and reported results of included studies are summarized in (Tables 1 & 2).

In addition, data from a retrospective study from the Medical University of South Carolina was also included for this systematic review and meta-analysis study. Patients undergoing treatment for COVID-19 with the senior author (C.D.S) between March 12, 2020 and June 1, 2020 were enrolled in a database. The study was approved by the MUSC Institutional Review Board (Pro00099838).

The therapeutic efficacy of CQ could not be further analyzed as insufficient data was reported. The present study pooled data from 26 articles to examine five outcomes associated with the remaining treatment arms: (1) mortality, (2) ICU admission, (3) negative PCR conversion, (4) QTc prolongation (≥500 milliseconds (ms)), and (5) ΔQTc (i.e. pre- versus post-treatment QTc).

Summary of findings

Mortality

Fifteen studies reported data on mortality for 12,657 patients treated with HCQ and AZ (11 studies, n= 6,467), HCQ alone (10 studies, n= 3,047), AZ alone (3 studies, n= 495), or neither (10 studies, n= 2,648). An additional 54 and 10 patients treated with combined therapy and HCQ alone, respectively, at MUSC were included in the meta-analysis (Figure 2, Appendix Figures 2-4). The weighted proportion of patients who died in each intervention arm is as follows: 10.64% (95% CI, 4.07-19.81 %) with combined therapy, 11.52% (95% CI, 7.72-15.97 %) with HCQ monotherapy, 11.15% (95% CI, 3.30-22.83 %) with AZ monotherapy, and 12.56% (95% CI, 5.30%-22.35%) with neither treatment. Comparison of weighted proportions revealed a statistically significant difference between the control and combined treatment arms (p= 0.008). All other comparisons did not meet statistical significance (Appendix Table 1).

ICU admission

Six studies provided data on ICU admission rates for 7,351 patients treated with HCQ and AZ (5 studies, n = 5,109), HCQ alone (3 studies, n = 1,341), AZ alone (2 studies, n = 284), or neither (3 studies, n = 617). An additional 54 and 10 patients treated with combined therapy and HCQ alone, respectively, at MUSC were pooled into the analysis (Appendix Figures 5-8). The weighted proportion of patients who required ICU admission was significantly higher among subjects receiving combined therapy (18.49%, 95% CI, 4.19-39.80 %) relative to those treated with any of the other three interventions: HCQ alone (15.73%, 95% CI, 4.70-31.62 %), AZ alone (9.40%, 95% CI, 3.69-17.37 %), and control (10.21%, 95% CI, 0.89-27.83 %). The weighted proportion was also significantly higher among those receiving HCQ monotherapy in comparison to the two remaining interventions: AZ alone (p= 0.006) and control (p= 0.001). The difference in proportions between the AZ treatment arm and control (0.81%, 95% CI, -3.69-4.71 %) did not meet statistical significance (Appendix Table 2).

Negative PCR conversion

Eight studies with 4,531 total patients contributed data on this outcome (Appendix Figures 9-11). Treatment consisted of combined therapy (5 studies, n = 4,279), HCQ alone (5 studies, n = 146), or neither (3 studies, n= 106). A significantly higher proportion of patients in the combined treatment arm (77.22%, 95% CI, 64.41-87.86 %) achieved viral clearance in comparison to those in the HCQ (46.20%, 95% CI, 21.85-71.57 %) and control (44.29%, 95% CI, 7.66-85.21 %) arms. Treatment with HCQ alone did not confer a significant advantage in meeting this endpoint when compared to control (p= 0.76) (Appendix Table 3).

QTc prolongation

Twelve studies reported data on QTc prolongation events for 6,570 patients treated with HCQ and AZ (11 studies, n= 5,478), HCQ alone (5 studies, n= 496), AZ alone (3 studies, n= 375), or neither (1 study, n= 221). An additional 44 and 5 patients treated with combined therapy and HCQ alone, respectively, at MUSC were included in the meta-analysis (Appendix Figures 12-14). Using QTc interval ≥500 ms as the outcome of interest, a significantly higher weighted proportion of patients treated with combined therapy (10.80%, 95% CI, 4.90-18.64 %) or HCQ alone (10.70%, 95% CI, 4.65-18.87 %) experienced QTc prolongation when compared to control (5.88%). The difference in proportions between the combined treatment and AZ arms (3.78%, 95% CI, 0.64-6.11 %) also met statistical significance while all other comparisons did not (Appendix Table 4).

ΔQTc

Three studies provided sufficient data to assess the change in QTc interval following intervention with HCQ and AZ (3 studies, n = 231), HCQ alone (2 studies, n = 148), or AZ alone (1 study, n= 27). An additional 44 and 5 patients treated with combined therapy and HCQ alone, respectively, at MUSC were included in the analysis. The weighted mean change in QTc interval for each intervention arm is as follows: 21.65 (95% CI, 17.1-26.2) with combination therapy, 10.03 (95% CI, 6.07-14) with HCQ monotherapy, and 0.5 (95% CI, -14.7-15.7) with AZ monotherapy. Comparison of weighted means revealed that the difference between the combined treatment and HCQ monotherapy arms (mean difference (MD) 11.62, 95% CI, 4.86-18.38) and that between the combined treatment and AZ monotherapy arms (MD 21.15, 95% CI, 5.91-36.39) were significant. The weighted mean change in QTc interval was not significantly different when comparing treatment with HCQ alone and AZ alone (MD 9.53, 95% CI, -1.91-20.97) (Appendix Table 5).

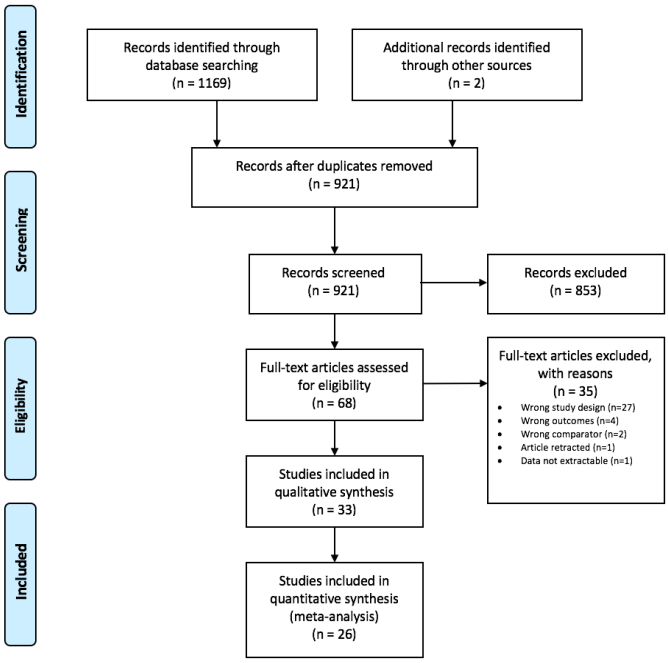

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Diagram.

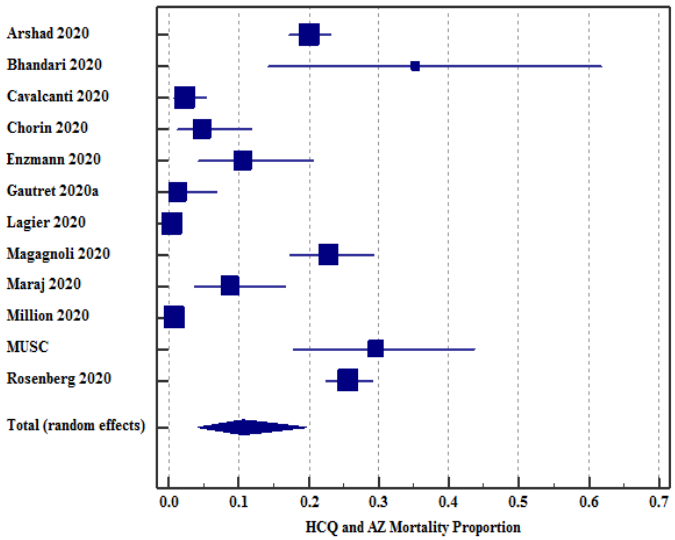

Figure 2: Mortality: Forest plot for HCQ + AZ treatment.

Table 1: Descriptive Features of Included Studies.

Author	LOE	Country	Study Design	Comparison	Total Patients (n)	Cases (n)	Control (n)	Mean Age (range), y	Male (n)
Arshad	4	USA	Retrospective	HCQ alone vs. AZ alone vs. HCQ + AZ vs. neither	2541	HCQ alone (n=1202), AZ alone (n=147), HCQ + AZ (n=783)	Neither (n=409)	63.7 ± 16.5	1298
Bessiere	4	France	Retrospective	HCQ alone vs. HCQ + AZ	40	18	22	Median: 68 (58-74)	32
Bhandari	4	India	Retrospective	HCQ ± AZ vs. NHCQ	122†	HCQ alone (n=73), HCQ + AZ (n=17)	32	NE	NE
Borba	2	Brazil	Double-blinded, randomized, phase IIb trial	High vs. low dose of CQ	81	41	40	51.1 ± 13.9	61
Bun	3	France	Prospective observational	HCQ + AZ	73	73	NA	62 ± 14 (29-92)	49
Cavalcanti	3	Brazil	Multicenter RCT	HCQ ± AZ vs. SOC	665	HCQ alone (n=221), HCQ + AZ (n=217)	227	50.3 ± 14.6	388
Chang	3	USA	Prospective observational	HCQ + AZ vs. HCQ alone	117	51	66	60.2 ± 14.9 (27-93)	70
Chen 2000	2	China	RCT	HCQ vs. NHCQ	30	15	15	NE	NE
Chorin	3	USA	Non-comparative retrospective	HCQ + AZ	84	84	NA	NR	NR
Davoodi	2	Iran	Double-blinded RCT	HCQ vs. NHCQ	54	25	29	57.7±8.4	32
Enzmann	3	USA	Non-comparative retrospective	HCQ + AZ	66	66	NA	NE	NE
Gautret 2020a	3	France	Prospective, non-comparative observational	HCQ + AZ	80	80	0	Median: 52.5 (20–88)	43
Gautret 2020b	3	France	Open-label non-randomized trial	HCQ ± AZ vs. NHCQ	36	HCQ alone (n=14), HCQ + AZ (n=6)	16	45.1 ± 22.0	15

Geleris	3	USA	Prospective observational	HCQ vs. NHCQ	1376	811	565	NE	781
Huang 2000a	2	China	RCT	CQ vs. L/R	22	10	12	Median: 44	13
Huang 2000b	3	China	Multicenter prospective observational	CQ vs. NCQ	373	197	176	Mean: CQ: 43.8±13.1; NCQ: 45.6 ± 13.5	175
Kim	4	Korea	Retrospective	HCQ vs. NHCQ	65	34	31	64.3 ± 15.4	25
Lagier	4	France	Retrospective	HCQ + AZ vs. Other	3737	3119	618	45.3 ± 16.8	1704
Magagnoli	4	USA	Retrospective	HCQ ± AZ vs. NHCQ	807	HCQ alone (n=198), HCQ + AZ (n=214)	395	Median: HCQ: 71 (27-99); HCQ + AZ: 68 (28-95); NHCQ: 70 (22-99)	772
Mahevas	4	France	Retrospective	HCQ vs. NHCQ	181	84	89	Median: 60 (18-80)	125
Maraj	3	USA	Non-comparative retrospective	HCQ + AZ	91	91	NA	62.7 ± 15.1 (29-93)	51
Mercuro	4	USA	Retrospective	HCQ + AZ vs. HCQ alone	90	53	37	60.1 ± 16.7	46
Million	3	France	Non-comparative retrospective	HCQ + AZ	1061	1061	NA	43.6 ± 15.6 (14-95)	492
Mitja	2	Spain	Multicenter RCT	HCQ vs. NHCQ	293	136	157	41.6 ± 12.6	92
Paccoud	4	France	Retrospective cohort	HCQ vs. NHCQ	89	38 + 5 excluded from primary analysis	46	65.5 ± 16.0	52
Ramireddy	4	USA	Retrospective	AZ alone vs. HCQ + AZ	98*	61	27	62.3 ± 17	60
Rosenberg	4	USA	Retrospective multicenter cohort	HCQ alone vs. AZ alone vs. HCQ + AZ vs. neither	1438	HCQ alone (n=271), AZ alone (n=211), HCQ + AZ (n=735)	Neither (n=221)	Median: 63	858
Saleh	3	USA	Prospective observational	HCQ/CQ vs. HCQ/CQ + AZ	201	119 (HCQ/CQ + AZ)	82 (HCQ/CQ)	58.5 ± 9.1	115
Samuel	4	USA	Single center retrospective	HCQ ± AZ vs. Neither	36	HCQ alone: 16; HCQ + AZ: 9	11	12.6 ± 6	20
Skipper	2	USA, Canada	Double-blinded, placebo-controlled RCT	HCQ vs. Placebo	423	212	211	Median: 40 [32-50]	185
Tang	2	China	Multicenter, open-label RCT	HCQ vs. NHCQ	150	75	75	46.1 ± 14.7	82
van den Broek	3	Netherlands	Non-comparative retrospective	CQ	95	95	NA	Median: 65 (18-91)	63
Yu	4	China	Retrospective	HCQ vs. NHCQ	550	48	502	Median: 68 (59-77)	344

AZ: Azithromycin; CQ: Chloroquine; D1-D5: Days 1-5, D: Day; FBX: Febuxostat; HCQ: Hydroxychloroquine; HD: High Dose; LD: Low Dose; LOE: Level of Evidence; L/R: Lopinavir/Ritonavir; Mg: Milligrams; NA: Not Available; NCQ: Non-Chloroquine; NE: Not Extractable; NHCQ: Non-Hydroxychloroquine; NR: Not Reported; RCT: Randomized Controlled Trial; SOC: Standard of Care; Y: Year.
†Only data on 131 patients was available. Nine in this sample population received L/R and were excluded.

Table 2: Reported Results of Included Studies.

Author	Study endpoint(s)	Outcome(s)	Conclusion
Arshad	(1) In-hospital mortality	HCQ and HCQ + AZ provided a 66% and 71% mortality reduction, respectively, compared to neither treatment.	Treatment with HCQ alone and in combination with AZ was associated with reduction in COVID-19 associated mortality.
Bessiere	(1) QTc prolongation (ΔQTc >60 ms or QTc ≥500 ms)	Prolonged QTc was observed in 14 patients (36%) (10 with ΔQTc >60 ms and 7 with QTc ≥500 ms) after treatment duration of 2 to 5 d. Combined therapy resulted in QTc ≥500 ms in 33% of patients vs. 5% of those treated with HCQ alone.	QTc intervals increased in more than 90% of patients, raising concerns about the widespread use of HCQ, with or without AZ, to treat COVID-19 in settings where patients cannot be adequately monitored.

Bhandari	(1) Mortality, (2) recovery time	Mortality for each subset of patients is as follows: HCQ + AZ (35.3%), HCQ (mild disease, 6.07%), HCQ (asymptomatic, 2.5%), and NHCQ (3.15%); average recovery times were 12.6 d, 10 d, 5 d, and 7.5 d, respectively	Asymptomatic patients treated with HCQ recovered early compared to that observed in control without influencing mortality overall. The difference in percentage of recovered patients in the two groups was not statistically significant.
Borba	(1) Reduction in lethality by at least 50% in HD *vs*. LD group on D13, (2) EKG results, (3) viral respiratory secretion RNA detection	(1) Lethality until D13 was 39% (HD) vs 15% (LD), (2) HD group had more instances of QTc >500 ms (18.9%) vs. LD group (11.1%), (3) viral RNA was detected in 75.6% (HD) vs. 77.5% (LD) of patients.	Higher CQ dosage should not be recommended for critically-ill patients with COVID-19 because of its potential safety hazards.
Bun	(1) Change in QTc interval 48 hours after receiving HCQ + AZ	After 2 d of combined therapy, average QTc values were prolonged.	HCQ + AZ could be administered in more than 94% of inpatients who presented with LRTI with EKG monitoring.
Cavalcanti	(1) Clinical status at 15 d†	(1) No significant differences in odds of having a worse clinical status among the three treatment groups	HCQ, alone or with AZ, did not improve clinical status at 15 d as compared with SOC.
Chang	(1) Change in QTc interval after receiving HCQ ± AZ, (2) adverse events	(1) The maximum QTc and its change from baseline were similar in patients treated with HCQ vs. HCQ + AZ, (2) total of 28 urgent alerts were recorded, of which 16 required management changes.	There was no significant difference in QTc interval following treatment initiation with HCQ alone vs. HCQ + AZ or change in maximum QTc from baseline.
Chen	(1) Negative conversion rate of SARS-CoV-2 nucleic acid on D7	No difference in negative conversion rate on D7 or median duration from hospitalization to negative conversion.	Larger sample size studies are needed to investigate the effects of HCQ in the treatment of COVID-19.
Chorin	(1) Change in QTc interval after receiving HCQ + AZ	Combined treatment resulted in significantly prolonged QTc interval from baseline average. QTc prolongation to >500 ms was observed in 9 (11%) patients.	QTc should be followed repeatedly in patients treated with HCQ + AZ, particularly in those with co-morbidities and in those who are treated with other QT-prolonging medications.
Davoodi	(1) Rate of hospitalization, (2) resolution of clinical manifestations, and (3) lung CT findings	(1) 3 patients in each group were hospitalized due to progression of symptoms, (2) fever, cough, and tachypnea were significantly mitigated after 5 d of treatment in both groups, and (3) reduction of lung involvement on CT was significant for both groups on D14	In adult outpatients with moderate COVID-19 infection, the effectiveness of FBX and HCQ was not different.
Enzmann	(1) In-hospital mortality, (2) adverse effects	(1) 7 patients (10.6%) treated with HCQ + AZ died. (2) 14 (21.2%) and 15 (22.7%) patients developed an arrhythmia and a QTc ≥500 ms, respectively, following treatment initiation.	The efficacy of HCQ + AZ use is unclear but was not without risks of corrected QT interval prolongation and arrhythmias in the cohort.
Gautret 2020a	(1) Need for O_2 therapy or ICU transfer after at least 3 d of treatment, (2) contagiousness (PCR and culture), and (3) LOS in unit	(1) 15 (18.8%) required O_2 therapy or ICU transfer, (2) none were contagious by D9 (culture) or D12 (PCR), (3) mean LOS in unit was 4.6 d	There is evidence of a beneficial effect of co-administration of HCQ + AZ and its potential effectiveness in the early reduction of contagiousness.
Gautret 2020b	(1) Viral clearance at D6 post-inclusion	(1) Viral clearance at D6 was achieved in 8/14 (HCQ alone), 6/6 (HCQ + AZ), and 2/16 (NHCQ) of patients.	HCQ treatment is significantly associated with viral load reduction/disappearance and its effect is reinforced by AZ.
Geleris	(1) Intubation or death	262 (32.3%) were intubated or died in the HCQ group vs. 84 (14.9%) in the NHCQ group.	No significant association between HCQ use and intubation or death.
Huang 2000a	(1) Negative viral RNA conversion, (2) improvement in lung CT, (3) hospital LOS	(1) Compared to L/R group, percentage of patients who became negative in CQ group were slightly higher at D7, D10, and D14. (2) By D14, incidence rate of lung improvement from CQ group was more than doubled to that of L/R group. (3) By D14, all 10 patients (100%) from CQ group were discharged compared to 6 patients (50%) from L/R group.	Preliminary results suggest that CQ could be an effective and inexpensive option among many proposed therapies.
Huang 2000b	(1) Time to undetectable RNA, (2) proportion of patients with undetectable RNA at D10 and D14, (3) hospitalization time, (4) duration of fever, (5) adverse events	CQ group experienced significantly faster and higher rate of viral suppression even when dose reduced to half. The duration of fever was also shorter in CQ group but there was no difference in hospital LOS.	This study provides evidence for safety and efficacy of CQ in COVID-19 and suggests that it can be a cost-effective therapy for combating the COVID-19 pandemic.
Kim	(1) Negative conversion of viral RNA, (2) clinical improvement‡, (3) safety outcomes	At 6-week follow-up, 21 (61.8%) vs. 27 (87.1%), 29 (90.6%) vs. 30 (96.8%), and 2 (5.8%) vs. 1 (3.2%) patients in the HCQ vs. L/R groups, respectively, had negative conversion of viral RNA, clinical improvement, and serious adverse events.	Patients receiving L/R had more rapid viral clearance than those receiving HCQ, but there was no significant benefit in terms of clinical responses.

Lagier	(1) Death, (2) ICU transfer, (3) ≥10 d of hospitalization, (4) persistence of viral shedding ≥10 d	Treatment with HCQ + AZ was associated with a decreased risk of transfer to ICU or death, decreased risk of hospitalization ≥10 d, and shorter duration of viral shedding	Early diagnosis, isolation, and treatment with at least 3 d of HCQ-AZ led to a significantly better clinical outcome and a faster viral load reduction than other treatments.
Magagnoli	(1) Mortality, (2) use of mechanical ventilation	(1) Risk of death from any cause was higher in the HCQ group but not in the HCQ + AZ group compared to no HCQ group. (2) risk of mechanical ventilation was not significantly different in both intervention groups compared to no HCQ group.	No significant reduction in mortality or need for mechanical ventilation with HCQ treatment with or without AZ was identified.
Mahevas	(1) Survival without ICU transfer, (2) overall survival, (3) survival without ARDS, (4) weaning from O_2, and (5) hospital discharge, all at D21	Differences in all outcome measures between the two groups were not significant.	The results of this study do not support its use in patients admitted to hospital with COVID-19 who require O_2.
Maraj	(1) Development of significant QTc prolongation§, (2) development of ventricular tachyarrythmias	QTc prolongation and ventricular arrhythmias occurred in 21 (23%) and 2 (2%) patients (1 TdP, 1 VF), respectively.	Combined HCQ + AZ resulted in significant QTc prolongation in one in four hospitalized patients.
Mercuro	(1) Change in QTc interval after receiving HCQ ± AZ	Treatment with HCQ and AZ was associated with a greater change in QTc compared with HCQ alone.	Patients who received HCQ were at high risk of QTc prolongation, and concurrent treatment with AZ was associated with greater QTc prolongation changes.
Million	(1) Death, (2) clinical worsening (ICU transfer, >10 d hospitalization), (3) viral shedding persistence (>10 d)	There were: (1) 8 deaths (0.75%), (2) 10 (0.9%) ICU transfers, 30 (2.8%) hospitalized for >10 d, (3) 47 (4.4%) who exhibited persistent viral carriage.	Administration of the HCQ+AZ combination before COVID-19 complications occur is safe and associated with a very low fatality rate in patients.
Mitja	(1) Reduction in viral RNA load, (2) disease progression (WHO scale), (3) time to symptom resolution	No significant differences in (1) reduction of viral load at D3 or D7, (2) risk of hospitalization, and (3) time to symptom resolution between both groups.	In patients with mild COVID-19, no benefit was observed with HCQ beyond usual care.
Paccoud	(1) Time to unfavorable outcome¶	Treatment with HCQ was not associated with a significantly reduced risk of unfavorable outcome. Overall survival was not significantly different between the two groups.	In hospitalized adults with COVID-19, no significant risk reduction of unfavorable outcomes was observed with HCQ in comparison to SOC.
Ramireddy	(1) Post-medication critical QTc prolongation£	Twelve patients (12%) reached critical QTc prolongation. Changes in QTc were highest with combined therapy compared with either drug, with significantly greater prolongation with combination vs AZ alone.	Among patients prescribed AZ, HCQ, or a combination of both, 12% achieved a critical level of QTc prolongation, which was many folds higher in the combination group than with AZ alone.
Rosenberg	(1) In-hospital mortality, (2) cardiac arrest, (3) abnormal EKG findings (arrhythmia or QTc prolongation)	(1) Compared to patients receiving neither drug, there was no significant difference in mortality for those receiving any of the 3 interventions, (2) cardiac arrest was only more likely in the HCQ + AZ group, (3) no significant differences in likelihood of abnormal EKG findings between groups.	Treatment with HCQ, AZ, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality.
Saleh	(1) QTc prolongation resulting in TdP, (2) QTc prolongation, (3) premature discontinuation of any medication due to QTc prolongation, (4) arrhythmogenic death	TdP and arrhythmogenic deaths were not reported. Eighteen patients experienced QT prolongation, of which 7 (3.5%) required discontinuation of medications.	In hospitalized COVID-19 patients, the use of CQ/HCQ + AZ resulted in a significantly greater increase in QTc interval when compared with monotherapy with either CQ or HCQ.
Samuel	(1) Electrophysiologic findings after receiving HCQ ± AZ	QTc was significantly prolonged (but still clinically normal) with HCQ treatment alone but not with both drugs. Longest daily measured QTc after starting therapy was not different in patients who received HCQ ± AZ compared to those who received neither drug.	Treatment using HCQ is associated with QTc prolongation, but was not associated with arrhythmias in pediatric patients.
Skipper	(1) Change in overall symptom severity over 14 d¤, (2) hospitalization or death	(1) Change in symptom severity over 14 d and (2) incidence of hospitalization or death did not significantly differ	HCQ did not substantially reduce symptom severity in outpatients with early, mild COVID-19.
Tang	(1) Negative conversion, (2) alleviation of symptoms by 28 d«	(1) 53 (70.7%) receiving HCQ + SOC and 56 (74.7%) receiving SOC alone had negative conversion before 28 d. (2) probability of alleviation of symptoms by 28 d was similar in patients treated with HCQ + SOC (59.9%) vs. SOC (66.6%).	Administration of HCQ did not result in a significantly higher probability of negative conversion than SOC alone.

van den Broek	(1) Change in QTc interval after receiving CQ	CQ treatment resulted in a mean QTc prolongation of 35 ms using computerized interpretation and 34 ms on manual interpretation.	CQ significantly prolonged the QTc interval in a clinically relevant matter.
Yu	(1) Fatality of patients, (2) inflammatory cytokine levels	(1) Fatality was significantly lower in the HCQ (18.8%) vs. NHCQ group (47.4%), (2) cytokine levels were significantly reduced in the HCQ group but no change in NHCQ group.	The addition of HCQ on top of the basic treatments is highly effective in reducing the fatality of critically ill patients of COVID-19.

ARDS: Acute Respiratory Distress Syndrome; AZ: Azithromycin, CI: Confidence Interval, CQ: Chloroquine, D6-D21: Days 6-21, D: Day, FBX: Febuxostat, HCQ: Hydroxychloroquine, HD: High Dose, HR: Hazard Ratio, LD: Low Dose, LOE: Level of Evidence, LOS: Length of Stay, L/R: Lopinavir/Ritonavir, LRTI: Lower Respiratory Tract Infection, Mg: Milligrams, Ms: Milliseconds, NA: Not Available, NCQ: Non-Chloroquine, NE: Not Extractable, NHCQ: Non-Hydroxychloroquine, PCR: Polymerase Chain Reaction, SOC: Standard of Care, Tdp: Torsades De Pointes, VF: Ventricular Fibrillation, Y: Year

[†]Assessed using seven-level ordinal scale

[‡]Cessation of oxygen support or resolution of respiratory symptoms such as cough and/or sputum and normalization of body temperature below 37.5ºC

[§]Increase in baseline QTc ≥60 ms and/or absolute QTc >500 ms

[¶]Death, ICU admission, or decision to withdraw/withhold life-sustaining treatments

[£]Maximum post-medication QTc ≥500 ms (if QRS <120 ms) or QTc ≥550 ms (if QRS ≥120 ms or QTc increase of ≥60 ms)

[¤]Measured by 10-point visual analogue scale

[«]Resolving from fever to an axillary temperature of 36.6°C or below, normalization of SpO2 (>94% on room air), and disappearance of respiratory symptoms including nasal congestion, cough, sore throat, sputum production, and shortness of breath.

Discussion

The purpose of this meta-analysis was to compare the efficacy of HCQ and AZ, used alone or in combination, in COVID-19 patients as measured by five clinical outcomes and to ascertain any possible therapeutic advantage. Although similar studies [45,46] have been undertaken, the present review examined a different set of clinical outcomes and included data from more recent publications. In a meta-analysis of three studies (n= 474), Singh et al., [46]. found that treatment with HCQ compared to control resulted in a significant increase in mortality. In contrast, the present meta-analysis of 11 studies (n= 5,705) observed that the difference in weighted proportion of patients who died was not significant between the two groups. A difference was only demonstrated between the combined treatment arm and control (p= 0.008), with mortality favoring the latter. Among the individual studies examining the mortality benefit of combination therapy, two of the larger ones [20,22] observed a survival advantage while a third [21] did not when compared to control. The conflicting findings may be attributed to variations in time to treatment between the studies, as delayed therapy is hypothesized to confer little benefit once the hyperimmune response has commenced. Arshad et al., [20], who initiated treatment within 48 hours of admission for 91% of their patients, reported a significant reduction in mortality among patients treated with combined therapy. In contrast, Rosenberg et al., [21], who reported data on those receiving therapy at any time during their hospitalization, found no such benefit. Comparison of weighted proportions also revealed that a higher proportion of patients receiving combined therapy (p<0.0001) or HCQ alone (p= 0.001**)** required intensive care relative to those receiving neither treatment.

Among survivors hospitalized in China, the duration of viral shedding reportedly ranged from 8-37 days, with a median of 20 days [47]. In one study, Liu et al., [48] found that viral load may be a useful marker of disease severity and prognosis. Therefore, multiple studies have used viral clearance, confirmed by a negative PCR result, to assess the efficacy of these experimental drugs. Many of them, however, were non-comparative studies utilizing a single treatment arm [13,16,22], with only a small number including a control arm [14,17,27]. In one such study, Gautret et al., [17] reported that HCQ was effective in clearing viral nasopharyngeal carriage in most COVID-19 patients in only three to six days. In contrast, two studies comparing HCQ monotherapy to control found no difference in the negative PCR conversion rate by 7 and 28 days [14,27]. In the present study, meta-analysis of proportions showed that 77.2% of patients treated with combined therapy achieved viral clearance while 46.2% and 44.3% in the HCQ monotherapy and control groups, respectively, reached this endpoint. The difference in weighted proportions was significant in both comparisons (p<0.0001). In agreement with prior meta-analyses [45,46], no difference in virological cure was observed when comparing intervention with HCQ alone versus control (p= 0.76).

The cardiotoxicity profiles of HCQ, CQ, and AZ are well-documented, with two notable side effects of QT prolongation and Torsade de pointes (TdP) [32,33]. The risk of TdP is increased by two to three folds when the QTc interval exceeds 500 ms [33]. Although studies consistently demonstrated a significant increase in the QTc interval following treatment in patients with COVID-19, occurring in 9-36% [33,40] of the study population and more frequently when combination therapy was employed, most did not observe any instance of TdP in their cohort [15,33-35,38,40,42]. Even when cases of QTc prolongation were documented, the intervention only had to be discontinued in 2.8-3.5 % of patients [32,33]. In critically-ill patients simultaneously receiving other QT prolonging agents, a higher proportion (11-17.5 %) required treatment discontinuation [31,40]. Of note, the relationship between QTc prolongation and TdP is not linear; although the former is sensitive for predicting the latter, it is not specific [32,33]. As anticipated, our analysis showed that a significantly higher weighted proportion of patients treated with combined therapy (10.8%) or HCQ alone (10.7%) experienced QTc prolongation (≥500 ms) compared to control (5.88%). Furthermore, meta-analysis of means revealed that the concurrent use of HCQ and AZ resulted in the greatest change in QTc interval from baseline. Comparison of weighted means between the combined treatment arm and the two monotherapy groups found that the differences were significant.

Although comprehensive in nature, this review has several limitations. During an ongoing pandemic, conducting well-designed trials is fraught with challenges. Due to significant heterogeneity among the studies with respect to patient demo-

graphics, disease severity, dosages used, time to treatment, and reported outcomes, the generalizability of our results is limited. In addition, for ethical reasons, no study employed a true control arm, in which potentially life-saving drugs, such as steroids and intravenous immunoglobulins, would be restricted. Therefore, the efficacy of HCQ/CQ with or without AZ cannot be definitively confirmed.

Conclusion

Although the present review examined data from the largest cohort of COVID-19 patients treated with CQ, HCQ, and/or AZ to date, no conclusive statements can be definitively made. The therapeutic efficacy of these experimental agents is best assessed through randomized clinical trials, which are difficult to conduct properly in the setting of an ongoing global outbreak.

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