Should hydroxychloroquine with azithromycin be used in the treatment of COVID-19?

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*This rapid review summarizes the available evidence on the efficacy and safety of **hydroxychloroquine with azithromycin** in treating patients with COVID-19. This may change as new evidence emerges.*

KEY FINDINGS

There is no high-quality evidence proving the efficacy and safety of hydroxychloroquine with azithromycin for the treatment of COVID-19, and treatment with the combination should only be in the realm of compassionate use.

- The current major guidelines (WHO, CDC, Canada, etc.) state that there is no definitive treatment for COVID-19. Management is largely supportive, tailored according to individual presentations and background medical history. Prevention of spread is paramount, as nations globally enforce community quarantines and lockdowns, impose physical distancing, highlight respiratory etiquette and emphasize frequent and correct handwashing.
- Hydroxychloroquine is an antimalarial drug which demonstrates in-vitro activity against SARS-CoV-2 and possible immunomodulating properties. Azithromycin is an antibiotic in the macrolide family, and is thought to prevent bacterial superinfection as well as exert immunomodulatory properties.
- There is no high-quality evidence proving the efficacy and safety of hydroxychloroquine with azithromycin for COVID-19.
- There is only one clinical trial, an open label non-randomized study by Gautret et al., that investigated this combination. However, this study had a very small sample size, and it had various methodological flaws in participant selection, treatment assignment, outcome measures, and data analysis.
- There are three planned randomized clinical trials designed to investigate the combination of hydroxychloroquine with azithromycin for CoVID-19, but all of these have yet to start recruitment.
- The drugs of the combination are not without possible risk. The common adverse events associated with both hydroxychloroquine and azithromycin are cardiac arrythmias (e.g., prolongation of the QT interval) and significant drug interactions. Hydroxychloroquine also poses risk of retinal damage, and should be used with caution in patients with diabetes and glucose-6-phosphate dehydrogenase (G6PD) deficiency.

RESULTS

Two studies were included in this review, and they both came from the French team of Gautret et al.

The French team of Gautret and co-authors enrolled patients above 12 years of age, who had PCR-documented SARS-CoV-2 carriage in the admission nasopharyngeal swab regardless of clinical presentation. The experimental arm consisted of 26 patients from The Mediterranee Infection Hospital Institute in Marseille, while the control arm had 16 patients taken from the other French medical centers (Nice, etc). The outcome was virologic clearance at Day 6 post-inclusion. Twenty-six patients were enrolled in the experimental group but there were six lost to follow-up, leaving 20 in the final analysis (hydroxychloroquine 14 patients, hydroxychloroquine plus azithromycin, six patients). Hydroxychloroquine was given at a dose of 200 mg three times a day for ten days; azithromycin at 500 mg for Day 1, followed by 250 mg for four days. The control group received "symptomatic treatment and antibiotics." The investigators reported that at the time of assessment, 100% of those given hydroxychloroquine and azithromycin were virologically cured, compared to 57.1% of those given hydroxychloroquine alone, and 12.5% in the control group, and this was statistically significant ($p<0.001$).

This study had a very small sample size and was prone to selection bias. There was no randomization, no allocation concealment, and no blinding. Not all patients were analyzed in the groups to which they were assigned, and the patients who were lost to follow-up were not included in the analysis. The study endpoint did not include clinical parameters (days to improvement, hospitalization duration, etc.) but looked only at virologic clearance.10 Furthermore, the baseline characteristic were not comparable among the participants; those in the hydroxychloroquine with azithromycin group – who were all found to be cleared of virus on Day 6 – actually had lower viral load at the start of the study compared to those in the other two groups.

The later study of Gautret et al., which enrolled 80 patients, claimed to be an observational study (descriptive, with no comparison group). The study declared as endpoints 1) clinical outcome, 2) contagiousness as measured by PCR and culture, and 3) length of stay in an infectious disease unit. It included in the analysis six patients from the open-label trial who received the combination regimen. The authors reported that patients with no contraindications were offered 200 mg of oral HCQ (three times a day for ten days) combined with azithromycin (500mg on the first day, then 250 mg for the following four days). Out of 80 patients, 79 were managed this way. The majority of patients (81.3%) had favorable outcome and were discharged from the unit "at the time of writing (not indicated)." Ninety-three percent (93%) of patients were negative for viral load on Day 8 of treatment, and none of the patients were considered contagious on Day 12. The average time from initiation of treatment to discharge was 4.1 days. Seven out of 80 patients had adverse events of nausea and vomiting, diarrhea and blurring of vision (reported five days after treatment).

No conclusions can be made from this study, however, owing to its descriptive nature.

CONCLUSION

There is no high-quality evidence proving the efficacy and safety of hydroxychloroquine and azithromycin for the treatment of COVID-19. Cognizant of this and the risks associated with each drug, the intervention should only be offered to patients under the realm of compassionate use, and decision-making shared between them and their healthcare professional. If so chosen, critical monitoring of hospital course and expected adverse events is warranted. In the meantime, the conduct and results of adequately-powered randomized controlled trials of larger sample sizes are awaited for more definitive conclusions.

Declaration of Conflict of Interest

No conflict of interest

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12. Gautret P, Lagier J, Parola P, Hoang V, Meddeb, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study
    Running title: Hydroxychloroquine-Azithromycin and COVID-19

Appendix 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings as reported
1	Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.	Open-label, non-randomized trial	France	French-confirmed COVID-19 patients above 12 years of age	26 patients on HCQ or HCQ with Azithromycin HCQ: 200 mg three times a day for ten days, Azithromycin 500 mg on Day 1, followed by 250 mg for four days All from The Mediterranee Infection Hospital Institute in Marseille	16 patients in the control arm received "supportive treatment and antibiotics All from the other medical centers (Nice, etc.)	Outcome: virologic clearance at Day 6 post-inclusion	100% of those given HCQ and azithromycin were virologically cured, compared to 57.1% of those given HCQ alone, and 12.5% in the control group ($p<0.001$).
2	Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study Running title: Hydroxychloroquine-Azithromycin and COVID-19	Observational study	France	Confirmed COVID-19 patients	Hydroxychloroquine (200 mg of oral HCQ three times a day for ten days) and Azithromycin (500mg on the first day, then 250 mg for the following four days) Regimen given for at least three days in patients with at least a six-day follow-up period	None	1) Clinical outcome, 2)Contagiousness as measured by PCR and culture, and 3) length of stay in an infectious disease unit	81.3% had favorable outcome and were discharged from the unit Ninety-three percent (93%) of patients negative for viral load on Day 8 of treatment, None of the patients contagious on Day 12. Mean time from start of treatment to discharge was 4.1 days. 7/80 had adverse events: nausea and vomiting, diarrhea and blurring of vision (reported five days after treatment).

Appendix 2. Characteristics of clinical trials

Most recent search of clinicaltrials.gov conducted 03 April 2020

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04329572 Open, Multicentric, Non Randomized, Exploratory Clinical Trial to Assess the Efficacy and Safety of Hydroxychloroquine and Azithromycin for the Treatment of Acute Respiratory Syndrome (COVID-19) Caused by SARS-CoV-2 Virus	Not yet recruiting	Apr 3-May 31, 2020	Open-label, multicentric, non-randomized exploratory clinical trial Single group assignment Patients who do not consent to participate or do not fulfill eligibility criteria will be invited to participate as control group and will receive standard care only.	Brazil	400 participants Adults with COVID-19, on mechanical ventilation	HCQ 400 mg BID on D1 and 400 mg/day on D2 to D5 and azithromycin (AZT) 500 mg/ 5 days on top of standard treatment	Standard care only	Primary Outcome Measures : Evolution of acute respiratory syndrome, oxygen saturation hemodynamic stability Secondary Outcome Measures Viral load Change in Clinical Condition Evolution of Acute Respiratory Syndrome Hospital discharge Rate of mortality within 28-days Evaluation of change in acute respiratory syndrome
2	NCT04322123 An Open-label, Randomized Controlled Trial of Hydroxychloroquine and Azytromicyn for COVID-19 Infection on Hospitalized, Noncritical Patients	Not yet recruiting	Apr 6-Aug 30, 2020	Open-label, randomized controlled trial	Brazil	630 participants Patients 18 years and above with suspected or confirmed COVID-19 admitted to inpatient units and intensive care units	Hydroxychloroquine 400mg 2x/day, 12/12h for 07 days. Hydroxychloroquine 400mg 2x/day, 12/12h + azythromycin 500mg 1x/day for 07 days	Standard treatment protocol for 2019-nCoV infection.	Primary Endpoints: Evaluation of the clinical status Secondary Outcome Measures Evaluation of the clinical status of patients on the 7th day after randomization Need of intubation and mechanical ventilation Need of intubation and mechanical ventilation up to the 7th day after randomization Use of mechanical ventilation during hospital stay Use of mechanical ventilation during hospital stay Use of non-invasive ventilation

									Hospital Length of Stay All-cause mortality Thromboembolic complications Acute renal disfunction
3	NCT04321278 Evaluation of the Safety and Clinical Efficacy of Hydroxychloroquine Associated With Azithromycin in Patients With Pneumonia Caused by Infection by the SARS-CoV2 Virus - Coalition COVID-19 Brasil II - Severely-ill Patients	Not yet recruiting	March 28 - August 30, 2020	Open-label Parallel assignment, Randomized Interventional Trial	Brazil	440 participants Adults with probable or confirmed infection by SARS-CoV2	Hydroxychloroquine [400mg 2x/day, 12/12h] + azithromycin [500mg 1x/day]) for 10 days. Standard treatment is according to the treatment protocol for 2019-nCoV infection.	Hydroxychloroquine [400mg 2x/day, 12/12h] for 10 days. Standard treatment is according to the treatment protocol for 2019-nCoV infection.	Primary Outcome Measures : Evaluation of the clinical status Secondary Outcome Measures All-cause mortality Number of days free from mechanical ventilation Duration of mechanical ventilation Duration of hospitalization Length of hospital stay on survivors Other secondary infections Time from treatment start to death
4	NCT04322396 Proactive Prophylaxis With Azithromycin and Chloroquine in Hospitalized Patients With COVID: A Randomized, Placebo-controlled Double-blinded Trial Evaluating Treatment With Azithromycin and Hydroxychloroquine to Patients With COVID-19	Not yet recruiting	Apr 1 – Oct 31, 2020	RCT, quad-blinded	Denmark	226 participants Child, adult, older adult with COVID-19	Standard care, HCQ, Azithro	Standard care, placebo HCQ, placebo Azithro	Primary outcome measure: Number of days alive and discharged from hospital within 14 days Secondary Outcome Measures Categorization of hospitalization status Admitted to ICU Have used Non-invasive ventilation (NIV) Mortality Length of hospitalization Days alive and discharged from hospital Mortality, 90 days Mortality, 365 days Number of readmissions (all causes) Number of days using non-invasive ventilation (NIV) Change in patient's oxygen partial pressure Delta PaO2 measured in arterial puncture

									Change in patient's carbon dioxide partial pressure Delta PaCO2 measured in arterial puncture Level of pH in blood Time for no oxygen supplement