

What are the data regarding use of hydroxychloroquine sulfate (Plaquenil®) in combination with azithromycin (Zithromax®/Z-Pak®) for the treatment of COVID-19?

Background

- Chloroquine and hydroxychloroquine sulfate (HCQ) have been used for over 50 years to treat malaria.¹
- HCQ is also approved for the treatment of systemic lupus erythematosus and rheumatoid arthritis.²
- Both drugs have similar safety profiles with warnings for adverse cardiac effects including ventricular arrhythmias, torsades de pointes, QT interval prolongation, and cardiomyopathy.² Patients at higher risk include those with renal or hepatic impairment or receiving other QT-prolonging drugs.
- Chloroquine and HCQ have *in-vitro* activity against multiple coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2 (COVID-19).^{3, 4}
- Azithromycin is a macrolide antibiotic approved to treat mild to moderate infections caused by susceptible bacteria.² The label carries warnings for potentially fatal hepatotoxicity and QT interval prolongation.

Pertinent Literature

- Multiple clinical trials have been launched in hospitals in China.⁵ The first results from more than 100 patients with COVID-19 demonstrated that treatment with chloroquine reduced exacerbation of pneumonia, duration of symptoms, and hospital stays when compared to a control group.⁶ This led to a consensus recommendation in China for dosing chloroquine at 500 mg by mouth twice a day in patients with mild, moderate, and severe forms of COVID-19 pneumonia.⁷
- Since chloroquine and HCQ have similar mechanisms of action, French researchers have suggested that HCQ could also be used and estimated a dose of 600 mg/day would produce a concentration of 1 µg/mL, noting that additional research is needed to determine if a loading dose would be required.³
- In a non-randomized, open-label French clinical trial of hospitalized patients with confirmed COVID-19:⁸
 - Thirty-six patients were included: 20 received HCQ 600 mg/day and 16 were controls (refused treatment and/or did not receive HCQ). Viral load was tested daily via nasopharyngeal swabs.
 - Depending on their clinical presentation, azithromycin was added to treatment at 500 mg on day 1, followed by 250 mg/day for the next 4 days. Criteria for adding azithromycin were not reported.
 - Absence of COVID-19 at day 6 was the primary objective. At day 6 post-inclusion, 100% (6/6) of patients treated with the combination of HCQ and azithromycin were virologically cured compared to 57.1% (8/14) treated with HCQ only, and 12.5% (2/16) in the control group (p<0.001).
- The American College of Cardiology (ACC) published guidance addressing ventricular arrhythmia risk due to HCQ-azithromycin treatment for COVID-19, in which they outline safety considerations for inpatient and outpatient use of HCQ and recommend monitoring for arrhythmias in the context of potential drug benefit, drug safety, resource availability, and quarantine considerations.⁹

Information from the Centers for Disease Control and Prevention (CDC) – March 2020

- There are no drugs or other therapeutics approved by the United States Food and Drug Administration to prevent or treat COVID-19.¹⁰
- Hydroxychloroquine and chloroquine are under investigation in clinical trials for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection, and treatment of patients with mild, moderate, and severe COVID-19.¹⁰

Conclusion

- As of March 25, 2020, there is very little information related to the use of HCQ in combination with azithromycin for the treatment of COVID-19 infection. Both HCQ and azithromycin can prolong the QT interval. Information related to the dosing and duration of HCQ therapy is evolving.