REVIEW

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Chloroquine and Hydroxychloroquine in Treatment of COVID-19 Disease

Fatma YILDIRIM[1]

[1]University of Health Sciences, Diskapi Yıldırım Beyazıt Research and Education Hospital, General Surgery and Medical Intensive Care Units, Ankara, Turke

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Corresponding Author: Fatma Yildirim
E mail: fatma_bodur2000@yahoo.com

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ABSTRACT

The use of chloroquine and its derivatives as an anti-viral agent is supported by pre-clinical in-vitro studies and its clinical safety is known in the term of its other indications. But there is insufficient clinical data to support its use in critically ill patients with The noval corona virus disease 2019 (COVID-19). Nevertheless, it is recommended that these drugs, which are supported by the urgency of the COVID-19 pandemic in many national guidelines and consensus reports, including our country, should be applied in accordance with the guidelines.

Keywords: Chloroquine, Hydroxychloroquine, Suggestion, Corona-19

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) first broke out in Wuhan (China) and subsequently spread worldwide. With the declaration on March 11th, 2020, by the World Health Organization that corona virus disease 2019 (COVID-2019) is a pandemic, Chloroquine (CQ) and Hydroxychloroquine (HCQ) have been sporadically used in treating SARS-CoV-2 infection due to their proposed immunomodulatory effect and also proposed usefulness in controlling the cytokine storm. This review aims to explain the mechanism of action of these compounds and to present the available clinical data for the use of CQ/ HCQ in COVID-19.

Proposed mechanisms for chloroquine and hydroxychloroquine

Chloroquine and HCQ were initially developed as antimalarial agents. The antimalarial actions of these compounds are related to a heavy accumulation of these drugs in the acidic lysosomes of the parasites resulting in lysis of the malarial parasite. Immunomodulatory and anti-inflammatory effects of these agents include inhibition of ligand-based toll-like receptor stimulation, inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) pathways in macrophages with resultant reduction in the generation of pro-inflammatory cytokines, reduced processing of the endogenous and exogenous ligands through lysosomes and endosomes with resultant reduction in the availability of processed antigens for presentation to the major histocompatibility complex–T cell receptor interactions, and downstream activation of cellular immunity (1-3).

Hydroxychloroquine is known to have significant effects on many mechanisms that drive the viral entry into the host cells. Its most prominent action on the angiotensin converting enzyme (ACE) II receptors. The original experiments during the SARS epidemic suggested that SARS-CoV-1 binds to ACE II receptors, primarily present in the lung, heart, kidney, and intestine for its entry into the host system. Chloroquine inhibits the intracellular glycosylation of the ACE II, and thus inhibits the addition of sialic acid part, which then leads to reduced ligand recognition and internalization of the virus. Once the virus is bound to the cell membrane, endosomes play an important role in the fusion of viral particles and their internalization. Thus, neutralization of the acidic pH of the endosome by CQ or HCQ may prevent the fusion of SARS-CoV-2 with the host cell inhibiting the primary entry (4-7). SARS-CoV infects the type 2 pneumocytes in

the alveolar epithelium through its ACE II receptor attachment. This results in a local inflammatory reaction with local neutrophils and macrophage activation as well as activation of the cellular immunity arm with T helper 1 (Th1) response. The resultant cytokine storm and disruption of epithelial permeability lead to the development of acute respiratory distress syndrome and associated morbidity and mortality related to COVID-19 (8). CQ/HCQ reduces the secretion of the proinflammatory cytokines, in particular the Th1 cytokines, especially interleukin (IL)-1, IL-6 tumor necrosis factor-α and interferon-gamma by the alveolar macrophages (9). Therefore these drugs may have a role in reducing the peak inflammatory response in COVID-19. Together with the immunomodulatory properties and antiviral effects CQ/HCQ are promising, and over the past 3 months, multiple studies have been started to clear clinical advantages of these drugs.

Clinical evidence of chloroquine/hydroxychloroquine on SARS-CoV-2

Chloroquine and HCQ have been investigated in Ebola virus disease, human immunodeficiency virus infection, Middle East Respiratory Syndrome (MERS) and SARS-CoV-1 infection (4,6,8,10) and their promising action against SARS-CoV-1 has provided the basis for their possible benefits in treating SARS-CoV-2 infection. Genetic analysis of SARS-CoV-2 has shown about 80% nucleotide similarity with SARS-CoV-1, causing the evaluation of these drug compounds for COVID-19 (11).

There is only limited clinical trial data available to date to evaluate use of CQ and HCQ for treatment or prevention of COVID-19. Clinical experience in treating patients with COVID-19 is accumulating; some studies reported possible clinical benefits, including decrease in viral load and duration of illness (12-15). Majority of data to date involves use in patients with mild or moderate COVID-19; only limited clinical data is available their use in patients with severe disease (18).

A small pilot study was conducted in China by Chen et al (17). Fifteen treatment-naive patients received HCQ sulfate (400 mg daily for 5 days) with conventional treatments and 15 patients received conventional treatments alone. Both groups received interferon and most patients also received umifenovir (Arbidol®) or lopinavir/ritonavir. Primary end point was conversion to negative PCR in pharyngeal swabs on day 7. Negative PCR reported at day 7 in 13 patients (86.7%) treated with HCQ and 14 patients (93.3%) not treated with the drug. Median duration from hospitalization to negative conversion and to temperature normalization were similar in both groups. Radiological progression on CT was seen in 5 patients treated with the drug and 7 patients not treated with the drug. All ptatients showed improvement at follow-up (13).

Thirty-one patients with COVID-19 and pneumonia received HCQ sulfate (200 mg twice daily for 5 days) and standard treatment (O2, antiviral agents, antibacterial agents, immunoglobulin, with or without corticosteroids) and other 31 patients received standard treatment alone (control group) in a randomized, parallel group study in China (ChiCTR2000029559). Exclusion criteria included severe and critical illness. Patients assessed at baseline and 5 days after treatment initiation for time to clinical recovery (defined as normalization of fever and cough relief maintained for >72 hours), clinical characteristics, and changes on chest CT. It was concluded that HCQ was associated with symptom relief since time to fever normalization was shorter in HCQ group (2.2 days) vs control group (3.2 days), time to cough remission was shorter in HCQ group, and pneumonia improved in 25/31 patients (80.6%) in HCQ group vs 17/31 pts (54.8%) in control group. Total of 4 patients progressed to severe illness (all in the control group) (17).

In a randomized, parallel group, open-label study in hospitalized adults with mild to moderate COVID-19 in China; 150 patients (148 with mild to moderate disease and 2 with severe disease) were randomized 1:1 to receive HCQ (1200 mg daily for 3 days, then 800 mg daily for total treatment duration of 2-3 weeks) with standard of care or standard of care alone. Mean time from onset of symptoms to randomization was 16.6 days (range: 3-41 days). Standard of care included IV fluids, O2, various antivirals (e.g., umifenovir, lopinavir/ritonavir), antibiotics, and/or glucocorticoid therapy. By day 28, 73% of patients (53 treated with HCQ with standard of care and 56 treated with standard of care alone) had converted to negative for SARS-CoV-2. The probability of negative conversion by day 28 in those treated with HCQ was similar to that in those treated with standard of care alone; the median time to negative seroconversion (6 and 7 days) also was similar in both groups. Adverse effects reported in 30% of those treated with HCQ and 9% of those treated with standard of care alone (14).

Combination of HCQ with azithromycin investigated in a uncontrolled, retrospective, observational study in France conducted by Gautret et al (18). 80 adults with confirmed COVID-19 were treated with HCQ sulfate (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5). Majority (92%) were considered low risk for clinical deterioration only 15% had fever; 4 pts were asymptomatic carriers; mean time from onset of symptoms to treatment initiation was 4.9 days. Clinical outcome, contagiousness as assessed by nasopharyngeal PCR assay and culture, and length of stay in ward were evaluated in patients who were treated for at least 3 days and followed for at least 6 days. Favorable outcome was reported for 81.3%; 15% required O2; 3 patients transferred to intensive care unit; 1 patient died; mean time to discharge from ward was 4.1 days. At day 8, PCR results were negative in 93% of those tested; at day 5, viral cultures were negative in 97.5% of those tested (18).

Another uncontrolled, observational, retrospective analysis was made in France by Million et al (15). Data for 1061 patients with PCR (+) SARS-CoV2 RNA who were treated with a regimen of HCQ sulfate (200 mg 3 times daily for 10 days) and azithromycin (500 mg on day 1, then 250 mg daily on days 2-5) were analyzed for clinical outcomes and persistence of viral shedding. Patients were included in the analysis if they received the combined regimen for at least 3 days and were clinically assessable at day 9. There were 56 asymptomatic and 1005 symptomatic patients; the majority (95%) had relatively mild disease and were considered low risk for clinical deterioration; median age was 43.6 years (range: 14-95 years) and mean time between onset of symptoms and initiation of treatment was 6.4 days. Within 10 days of treatment, good

clinical outcome reported in 973 patients (91.7%) and poor clinical outcome reported in 46 patients (4.3%). Persistent nasal carriage of SARSCoV-2 reported at completion of treatment in 47 patients (4.4%); 8 patients died (15).

Magagnoli et al (19) investigated HCQ (with or without azithromycin) in a retrospective trial and made the analysis of patients hospitalized with COVID-19 in US Veterans Health Administration medical centers. Data for 368 males (median age >65 years) treated with HCQ in addition to standard supportive care were analyzed for death rate and need for mechanical ventilation. Death rate was 27.8% (27/97) in those treated with HCQ, 22.1% (25/113) in those treated with HCQ and azithromycin, and 11.4% (18/158) in those not treated with HCQ; rate of mechanical ventilation was 13.3%, 6.9%, and 14.1%, respectively. Use of HCQ alone (but not use of HCQ and azithromycin) was associated with increased overall mortality compared with no HCQ; use of HCQ with or without azithromycin did not reduce the risk of mechanical ventilation (19).

Two different retrospective studies analyzed outcome data for hospitalized patients

with confirmed COVID-19 in New York. They assessed the effects of treatment with HCQ with or without azithromycin. Rosenberg et al (20) analyzed data for 1438 patients (735 received HCQ with azithromycin, 271 received HCQ alone, 211 received azithromycin alone, 221 received neither drug) and assessed in-hospital mortality (primary outcome). Overall, in-hospital mortality was 20.3%; in-hospital mortality was 25.7%, 19.9%, 10%, or 12.7% in those treated with HCQ with azithromycin, HCQ alone, azithromycin alone, or neither drug, respectively (20). Geleris et al (21) analyzed data of 1376 patients (811 received HCQ [486 of these also received azithromycin] and 565 did not receive HCQ [127 of these received azithromycin]) and assessed the primary end point of time from study baseline to intubation or death. Overall, 346 patients (25.1%) progressed to intubation and/or death and death was not affected by HCQ treatment (intubation or death reported in 32.3% of patients treated with HCQ and 14.9% of patients not treated with the drug). (21).

Borba et al (22) conducted a double-blind randomized phase IIb study in Brazil to evaluate two different CQ dosages as adjunctive therapy in hospitalized adults with severe COVID-19 (NCT04323527). The first 81 patients were randomized 1:1 to receive high-dose CQ (600 mg twice daily for 10 days) or lower-dose CQ (450 mg twice daily on day 1, then 450 mg once daily on days 2-5). All patients also received azithromycin and ceftriaxone and some also received oseltamivir. An interim analysis was performed and the high-dose arm of the study was stopped because of toxicity concerns (particularly QTc prolongation and ventricular tachycardia, and because more deaths were reported in this arm). By day 13, 16/41 patients (39%) treated with the high-dose regimen had died vs 6/40 (15%) treated with the lower-dose regimen. QTc >500 msec occurred more frequently in the high-dose group (18.9%) than in the lower-dose group (11.1%). The high-dose arm included more patients face to cardiac complications than the lower-dose arm. Study is continuing using only the lower dosage (22).

National Institutes of Heath (NIH) COVID-19 Treatment Guidelines Panel states that clinical data are insufficient to recommend either for or against use of HCQ for the treatment of COVID-19 Also panel recommends against the use of a combined regimen of HCQ and azithromycin for the treatment of COVID-19, except in the context of a clinical trial. NIH Panel does not recommend the use of any agents, including HCQ for preexposure prophylaxis or postexposure prophylaxis for prevention of SARS -CoV-2 infection outside of clinical trials (16).

Infectious Diseases Society of America (IDSA) recommends that HCQ should be used for the treatment of COVID-19 in the context of a clinical trial. IDSA recommends that a combined regimen of HCQ and azithromycin should be used for the treatment of COVID-19 only in the context of a clinical trial (23).

Food and Drug Administration (FDA) issued a safety alert regarding adverse cardiac effects (e.g., prolonged QT interval, ventricular tachycardia, ventricular fibrillation) reported with use of CQ or HCQ (either alone or in conjunction with azithromycin or other drugs known to prolong QT interval) in hospital and outpatient settings; FDA cautions against use of CQ or HCQ outside of a clinical trial or hospital setting and urges healthcare professionals and pts to report adverse effects involving these drugs to FDA MedWatch (24).

Multiple clinical trials to evaluate chloroquine for the treatment of COVID-19 are registered at clinicaltrials.gov. Some can be listed as NCT04323527, NCT04328493 NCT04331600, NCT04333628, NCT04353336, NCT04360759, NCT04362332. Several clinical trials to evaluate chloroquine for prevention of COVID-19 in the healthcare setting are also registered at clinicaltrials.gov (NCT04303507 NCT04333732, NCT04349371 etc.) (25).

Conclusion

- Optimal dosage and duration of CQ/HCQ treatment in COVID-19 is not known.
- Efficacy and safety of hydroxychloroquine for treatment or prevention of COVID-19 is not established.
- Additional data is needed to determine whether in vitro activity against SARSCoV-2 corresponds with clinical efficacy for treatment or prevention of COVID-19.
- Additional data is needed regarding toxicity profile when used in patients with COVID-19.

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