

CASE REPORT

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A case of treatment failure of hydroxychloroquine and azithromycin in a COVID-19 patient

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ABSTRACT

Introduction: The novel coronavirus disease 2019 (COVID-19) has been responsible for the current global pandemic. Currently, there are no proven medical therapies to treat this disease. Despite the lack of rigorous clinical trials, a combination of hydroxychloroquine and azithromycin has been a heavily promoted therapy. **Case Report:** We report a case of a 74-year-old man with a history of type II diabetes mellitus and paroxysmal atrial fibrillation with initial mild respiratory symptoms and a confirmed diagnosis of COVID-19 by nasal swab. As an outpatient, the patient had completed a five day course of hydroxychloroquine and azithromycin. On the sixth day the patient was hospitalized for worsening hypoxia and increased respiratory distress. The patient required mechanical ventilation and proning to treat his hypoxic respiratory failure due to COVID-19 and currently remains intubated 11 days after admission. **Conclusion:** Hydroxychloroquine and azithromycin combination therapy failed to prevent the patient from manifesting severe symptoms of COVID-19. This case report of treatment failure is in line with two preliminary studies that have not found benefit of hydroxychloroquine in the treatment of this novel disease. This highlights the need for robust controlled clinical trials to assess efficacy of novel therapeutic agents before being proclaimed to the public.

Keywords: Azithromycin, COVID-19, Hydroxychloroquine, Novel therapy

How to cite this article

Nguyen AP, Stephen FO. A case of treatment failure of hydroxychloroquine and azithromycin in a COVID-19 patient. Int J Case Rep Images 2020;11:101135Z01AN2020.

Article ID: 101135Z01AN2020

doi: 10.5348/101135Z01AN2020CR

INTRODUCTION

The SARS-CoV-2 virus responsible for coronavirus disease 2019 (COVID-19) has been responsible for a global pandemic within a few months of its discovery. Social distancing, personal hygiene, and supportive management are the current recommend measures to limit spread of disease [1]. Consequently, physicians are using a variety of novel medical therapies to combat this disease [2]. The antiretrovirals lopinavir and ritonavir have been used for COVID-19 based on clinical studies showing reduced mortality and intubation rates in 2003 outbreak of severe acute respiratory syndrome. An open-label randomized control trial has not shown a difference in clinical improvement, viral clearance, or mortality [3]. Interferon- β had demonstrated activity against the corona virus responsible for the Middle Eastern respiratory syndrome. Its effectiveness in COVID-19 is unknown given the absence of clinical trials. Tocilizumab a monoclonal antibody IL-6 receptor antagonist has the theoretical effect of dampening the "cytokine storm" seen in COVID-19. A small case series reported rapid defervescence and improved respiratory function in 91% of patients. The lack of comparison to a control group limits its interpretation of drug effect [4]. Convalescent plasma therapy is under investigation but a case series involving five patients that showed improved $\text{PaO}_2/\text{FiO}_2$ and reduced viral loads after transfusion [5]. A large randomized control trial for remdesivir, an

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Received: 25 April 2020
Accepted: 30 May 2020
Published: 24 June 2020

RNA polymerase inhibitor, has demonstrated a shorter recovery time compared to placebo [6]. Currently, it is the only medication to receive the US Food and Drug Administration approval for emergency use in critically ill COVID-19 patients.

The combination therapy of hydroxychloroquine, an antimalarial and immunomodulator, and azithromycin, an antibiotic, was reported by Gautret et al. to significantly reduce viral load [6]. From this study the drug combination became popularized due to increased media exposure, and its efficacy has been highly touted despite a lack of robust clinical trials. Here, we present a case in contrast to the current proclamations of efficacy.

CASE REPORT

A 74-year-old man with a history of paroxysmal atrial fibrillation and type II diabetes mellitus that was well managed with sitagliptin and absent any microvascular complications had a three day history of fever, nonproductive cough, and dyspnea before presenting to a local emergency department. The patient was evaluated and underwent a nasopharyngeal swab for COVID-19 testing and was discharged home. The following day, the patient was notified that he was positive for COVID-19 and was prescribed a five day course of hydroxychloroquine 400 mg per day and azithromycin 250 mg per day. On day six of therapy, the patient had continued dyspnea and fever that necessitated a return visit to the hospital. The patient's initial SpO₂ measured 84% on room air and improved to 97% on 15 L/min high flow nasal cannula at FiO₂ 60%. His chest X-ray (CXR) demonstrated patchy bilateral opacifications (Figure 1A) and his electrocardiogram demonstrated a normal sinus rhythm and a QTc of 423 ms. The patient was admitted to the intensive care unit (ICU) for close observation. A complete blood count, basic metabolic panel, procalcitonin, and lactic acid level were obtained on admission and is presented in Table 1. These values did not change significantly during this patient's hospitalization. No additional antibiotics or antiretrovirals were given as the patient's blood, sputum, and urine cultures obtained on admission had no bacterial growth and there were no viral coinfections.

On hospital day two, the patient had increased labored breathing and required progressively higher FiO₂ to maintain his oxygen saturation above 90%. The patient was subsequently intubated and mechanically ventilated at 6 mL/kg/min with an initial positive end expiratory pressure (PEEP) of 9 cm H₂O (Figure 1B). The patient had severe acute respiratory distress syndrome with a pre-intubation PaO₂/FiO₂ ratio of 55. He was chemically paralyzed and placed prone for 16 hours a day for two days. During this time, his highest PEEP requirement was 12 cm H₂O and highest FiO₂ was 0.8. On hospital day 5, the patient tolerated lying supine without the need to increase his FiO₂ or PEEP. The patient has remained

intubated for 11 days as of this writing and current therapy has been supportive, e.g., furosemide to maintain euvolemia, nutrition by way of tube feeding, and venous thromboembolic prevention dosing of enoxaparin. The biochemical markers C-reactive protein, lactate dehydrogenase, and ferritin were not checked until hospital day 3 and d-dimer levels were not tested until hospital day 4, these values are presented in Figure 2.

Table 1: Baseline characteristics

Weight (kg)	78.1
Height (cm)	172.7
BMI (kg/m ²)	26.2
Temperature (Celsius)	38.5
Blood pressure (mmHg)	111/58
Heart rate	93
Respiratory rate	22
WBC (10 ³ /uL)	10.4
Lymphocyte (10 ³ /uL)	0.5
Hemoglobin (g/dL)	13.1
Platelet (10 ³ /uL)	409
Sodium (mmol/L)	141
Potassium (mmol/L)	3.8
Chloride (mmol/L)	108
HCO ₃ (mmol/L)	23
BUN (mg/dL)	20
Creatinine (mg/dL)	1.3
Lactate (mmol/L)	1.8
Total bilirubin (mg/dL)	0.8
AST (u/L)	131
ALT (u/L)	116
Procalcitonin (ng/mL)	0.07

BMI: body mass index; WBC: white blood cell; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

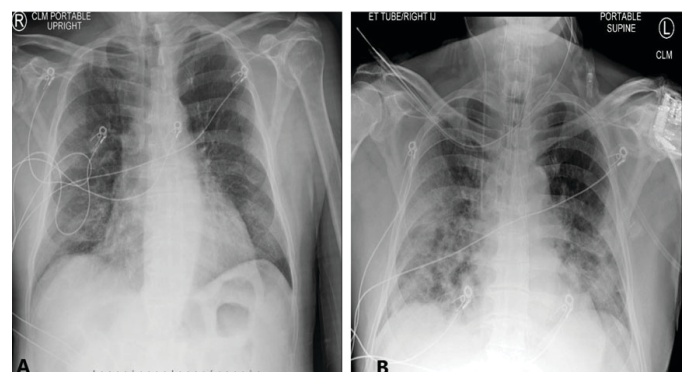


Figure 1: (A) Admission CXR demonstrating bilateral patchy opacification. (B) Post-intubation CXR on hospital day 2 demonstrating worsening bilateral opacification.

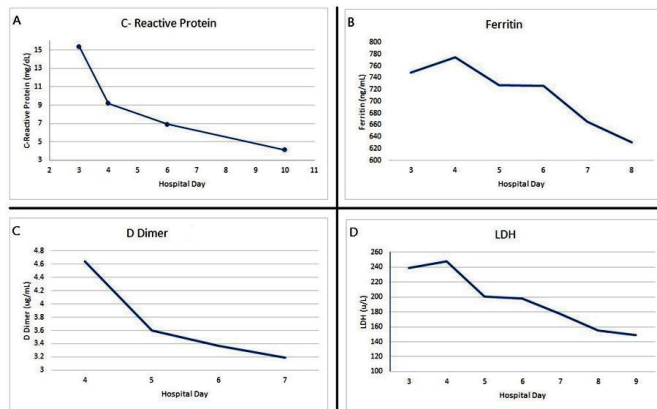


Figure 2: Trends for (A) C-reactive protein, (B) ferritin, (C) D-dimer, and (D) lactate dehydrogenase.

DISCUSSION

The use of chloroquine in COVID-19 began with evaluating whether existing antiviral medications were effective against the SARS-CoV-2 virus. Chloroquine had previously been reported to have a potential for antiviral properties. In an in vitro study, it was demonstrated to have inhibitory effects against the virus at cell entry and postentry. Its 90% maximal effective concentration against the virus was measured to be 6.90 μM which the authors postulated could be achieved clinically with 500 mg of chloroquine [7, 8]. Hydroxychloroquine has a chemical structure similar to chloroquine and believed to have similar inhibition activity against the SARS-CoV-2 virus.

There are currently 21 clinical trials in China alone evaluating the therapeutic effects of chloroquine/hydroxychloroquine on COVID-19. An early pilot randomized control trial from Shanghai compared 15 hospitalized COVID-19 positive patients taking a 5-day course of hydroxychloroquine 400 mg once per day in addition to conventional care to 15 patients undergoing conventional care alone. Conventional care was defined as bed rest, oxygen therapy, symptom management, and all patients received inhaled interferon- α . The primary end point was viral clearance by polymerase chain reaction (PCR) at day 7 and mortality at day 14. At day 7, 13 patients in the treatment group and 14 patients in the control group had tested negative for the virus. By 14 days, all patients in the study were virus free and there was no mortality [9]. The major weakness of this study was that patients were not well controlled. Seventy-three percent of the patients were simultaneously treated with arbidol hydrochloride, a novel antiretroviral, and 2 patients in the treatment arm was also treated with lopinavir and ritonavir. In addition, all patients in this study were considered mild cases of COVID-19.

A second study compared hydroxychloroquine to standard of care [6]. In this non-randomized open labeled study, 26 patients were enrolled into the

hydroxychloroquine group. These patients were treated with hydroxychloroquine 200 mg three times a day for ten days and 6 of the patients were prescribed azithromycin 500 mg on day one and 250 mg per day for the next four days. Sixteen patients were enrolled as control patients. All 42 patients were hospitalized while in treatment. Six patients in the treatment group were excluded from the analysis, with 3 patients having worsening progression of disease requiring transfer to the ICU. One patient died on day three of treatment, and two patients withdrew after enrollment. The data was published earlier than the primary end point due to favorable results. The authors reported that by day 6, 70% in the treatment arm were PCR negative, with 100% of the patients treated with hydroxychloroquine and azithromycin compared to 12.5% in the control group. There have been many criticisms about the trial, most prominent being that it was a non-randomized control trial and the 6 patients who left the treatment arm were not included in the analysis. There were multiple confounding factors as well. The question of why azithromycin was chosen was not well described. Also, the treatment group was all obtained from a single center, while patients in the control group were pooled from various medical centers and they included patients who had not agreed to the study.

Though hydroxychloroquine has a reduced toxicity profile compared to chloroquine, it is not without risks [10]. Potential side effects include cardiomyopathies, a prolonged QTc, and Torsades de Pointes [11, 12]. To date, there have been no published multicenter randomized control trials to address the question of whether hydroxychloroquine or a combination of hydroxychloroquine and azithromycin is effective, and the optimal duration of therapy and dosing for treatment of COVID-19. Despite the lack of rigorous testing, the therapy has been heavily touted by the President of the United States.

We have presented a case in which a patient with mild symptoms due to COVID-19 infection was indeed treated with hydroxychloroquine and azithromycin as an outpatient. Despite, completing a five day course, his symptoms worsened, necessitating hospitalization and mechanical ventilation. Hence, this medical regimen provided no demonstrable clinical benefit in this case. While this represents only a single treatment failure, this case is in concert with the preliminary findings of two recent studies which also have not demonstrated clinical efficacy of hydroxychloroquine or chloroquine. The first study was a multicenter controlled trial of 181 patients from France, in which no clinical benefit was identified in patients with documented SAR-CoV-2 pneumonia compared to placebo [13]. The second was a preliminary study from Brazil looking at different dosages of chloroquine, which found no clinical efficacy or increased viral clearance with chloroquine, and increased toxicity with higher dosages [14].

CONCLUSION

We believe that more robust trials are required before broad public proclamations can be made regarding the efficacy of chloroquine, hydroxychloroquine, and other novel treatment regimens for COVID-19. We also support the Infectious Disease Society of America recommendations to use novel medications only in the context of a clinical trial.

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Author Contributions

Albert Phan Nguyen – Conception of the work, Design of the work, Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

F Otis Stephen – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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