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Short Communication

# Triple therapy with hydroxychloroquine, azithromycin, and ciclesonide for COVID-19 pneumonia



Nobuaki Mori <sup>a,\*</sup>, Mitsuya Katayama <sup>a</sup>, Shigenari Nukaga <sup>b</sup>

<sup>a</sup> Department of General Internal Medicine and Infectious Diseases, National Hospital Organization, Tokyo Medical Center, Tokyo, Japan

<sup>b</sup> Department of Respiratory Medicine, National Hospital Organization, Tokyo Medical Center, Tokyo, Japan

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## KEYWORDS

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Therapy;  
Reverse  
transcription-PCR

**Abstract** No specific therapy is available for COVID-19. We report the effectiveness and adverse effects of triple therapy with hydroxychloroquine, azithromycin, and ciclesonide in patients with COVID-19 pneumonia. The clinical condition of the patients improved within 5 days in response to the therapy.

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## Introduction

Coronavirus disease 2019 (COVID-19), first being reported in Wuhan, Hubei, China in December 2019, has been declared a pandemic.<sup>1</sup> Although several investigational

approaches are being explored for the treatment for COVID-19 pneumonia, there are no proven or approved treatments. Hydroxychloroquine is commonly used to treat systemic lupus erythematosus, rheumatoid arthritis, and malaria. A representative study reported that patients with COVID-19 who were administered hydroxychloroquine had greater severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clearance and a shorter time to fever normalization than those in the control group.<sup>2</sup> However, an observational study showed hydroxychloroquine administration was not associated with the lower the risk of intubation or death.<sup>3</sup>

\* Corresponding author. Department of General Internal Medicine and Infectious Diseases, National Hospital Organization, Tokyo Medical Center, 2-5-1 Higashigaoka, Meguro-ku, Tokyo 152-8902, Japan. Fax: +81 3 3412-9811.  
E-mail address: [nobuaki.m@icloud.com](mailto:nobuaki.m@icloud.com) (N. Mori).

**Table 1** Basic and clinical patient characteristics, treatment, and outcome.

Patient No.	Age (years)	Sex	Underlying diseases	Smoking history	ACE-I or ARB medication	Principal symptoms	Maximum body temperature (°C)	Arterial oxygen saturation on admission (ambient air)	Oxygen support
1	68	M	CKD, HT, bladder cancer, renal pelvic cancer	Past	No	fever, headache, fatigue, diarrhea, vomiting, cough, dyspnea, myalgia, arthralgia, hypogeusia	38.3	91%	Low-flow nasal cannula
2	71	F	DM, HL, HT	Current	Yes	Loss of appetite, loss of consciousness, dyspnea	38.1	93%	Low-flow nasal cannula
3	49	F	HT	Current	Yes	fever, headache, arthralgia, dyspnea	39.6	85%	Low-flow nasal cannula
4	60	M	None	Past	No	fever, cough, fatigue	39.8	85%	Low-flow nasal cannula
5	51	M	None	Unknown	No	fever, dyspnea, rhinorrhea, fatigue, headache, myalgia, hypogeusia	40	96%	None
Day of starting triple therapy from symptom onset	Daily dose and duration of hydroxychloroquine	Daily dose and duration of azithromycin	Daily dose and duration of ciclesonide	Other antibiotic treatment	Additional treatment	Time to fever and respiratory symptoms normalization	Adverse event	Time from administering triplet therapy to development of adverse events	Outcome
14	400 mg for 10 days	500 mg IV for 3 days	2 × 200 mcg puffs tds for 14 days	CTRX	None	4 days	None	—	Cure
6	200 mg for 10 days	500 mg IV for 3 days	2 × 200 mcg puffs tds for 10 days	CTRX	None	7 days	None	—	Cure
8	200 mg for 8 days	500 mg po for 3 days	2 × 200 mcg puffs tds for 16 days	CTRX	DMX	11 days	QTc prolongation	8 days	Cure
13	200 mg for 10 days	2 g po for 1 days	2 × 200 mcg puffs tds for 5 days	CTRX, TAZ/PIPC	Favipiravir	—	None	—	Intubation
14	400 mg for 5 days	500 mg po for 3 days	2 × 200 mcg puffs bd for 12 days	CTRX	None	3 days	Liver dysfunction	5 days	Cure

Abbreviations: ACE-I, angiotensin converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; HL, hyperlipidemia; HT, hypertension; bd, twice a day; CTRX, ceftriaxone; DMX, dexamethasone; IV, intravenously; po, per os (oral); TAZ/PIPC, tazobactam and piperacillin; tds, 3 times a day.

Hydroxychloroquine in combination with azithromycin has been found to be associated with faster virologic clearance than hydroxychloroquine monotherapy.<sup>4</sup> Early, not yet peer-reviewed data, suggest ciclesonide, an inhaled corticosteroid used to treat asthma, inhibits the replication of the SARS-CoV-2 *in vitro*.<sup>5</sup> However, the clinical effectiveness of combination therapy with these three agents for COVID-19 pneumonia is not known.

Herein, we report the effectiveness and safety of triple therapy with hydroxychloroquine, azithromycin, and ciclesonide in adult patients with COVID-19 pneumonia.

## Materials and methods

This case-series study was conducted at the National Hospital Organization Tokyo Medical Center located in Tokyo, Japan, from March to April 2020.

Patients aged 18 years or older were eligible if the reverse transcriptase-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 in their nasopharyngeal swab specimens was positive and they had pneumonia confirmed by chest imaging. The following data were collected from the medical charts for all patients: age, sex, underlying diseases, smoking history, symptoms, use of angiotensin converting-enzyme inhibitor or angiotensin II receptor blocker medication, body temperature, oxygen saturation in the ambient air on admission, duration of triple therapy from symptom onset, time to fever and respiratory symptom normalization, adverse events, and outcome.

## Results

Five patients with COVID-2019 pneumonia were administered triple therapy during the study period. The basic and clinical patient characteristics of the patients are shown in [Table 1](#). Their median age was 60 years (range: 49–71 years), and three of them were men. Three patients had underlying diseases, including cancer, hypertension, and diabetes mellitus, and four patients were current or former smokers. All patients had flu-like symptoms and, two patients had hyposmia. Four patients required low-flow nasal cannula oxygenation at admission.

The median time from symptom onset to the initiation of triple therapy was 13 days (range: 6–14 days) ([Table 1](#)). All patients also received other antibiotics. Two patients (Patients 3 and 5) had adverse events, including liver dysfunction and QT prolongation, and discontinued hydroxychloroquine. Three patients (Patients 1, 2, and 5) improved within 5 days and completely recovered from fever and respiratory symptoms within 7 days of triple therapy initiation. However, one patient (Patient 3) showed worsening of their respiratory condition on the day after triple therapy initiation. With the administration of dexamethasone, the patient's condition gradually improved. The fourth patient (Patient 4) who experienced progressive respiratory deterioration was additionally administered favipiravir, intubated, and transferred to a high care center.

## Discussion

We evaluated the clinical characteristics and outcomes of five patients with COVID-19 pneumonia treated with triple therapy. Most patients started triple therapy over 7 days after the onset. Their clinical condition improved within 5 days of initiating triple therapy.

There are no proven treatments for COVID-19 pneumonia. There are some therapeutic strategies for SARS-CoV-2 infection<sup>6</sup>: inhibiting SARS-CoV-2 cell entry, endocytosis and membrane fusion; inhibiting RNA synthesis; suppressing inflammation. Hydroxychloroquine blocks viral entry into cells by inhibiting the glycosylation of host receptors, proteolytic processing, endosomal acidification, and attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells.<sup>6</sup> Although azithromycin belongs to a class of antibiotics used to treat several bacterial infections, its use as potential antiviral has come to light in the recent years through studies on its immunomodulatory and anti-inflammatory effects.<sup>7,8</sup> Adding azithromycin to the treatment regimen may also be effective to treat underlying potential secondary infections. Ciclesonide has an anti-inflammatory effect on respiratory epithelium.<sup>5</sup> Although there is no clear evidence, we expected an additive or synergistic effect of using ciclesonide which has anti-inflammatory effect on respiratory epithelium in COVID-19 pneumonia, in addition to the viral clearance effect of the combination of hydroxychloroquine and azithromycin. In our study, response within 5 days from administering triple therapy lead to favorable outcome. However, the difference in host factors influencing the response to triple therapy is unknown. The Infectious Diseases Society of America COVID-19 guideline warns about the potential for QT prolongation with the combination of hydroxychloroquine and azithromycin.<sup>7</sup> Although combination therapies with different mechanisms of action generally have an additive or synergistic effect, it is also necessary to consider the risk of synergistic adverse effects. Therefore, if there is no response to therapy within 5 days, it should be discontinued because of the risk of adverse events. As our study had a small sample size and lacked a control group, it is necessary to evaluate appropriate triple therapy in clinical trials.

In conclusion, our study showed the potential benefits and risks of using the combination of hydroxychloroquine, azithromycin, and ciclesonide for COVID-19 pneumonia.

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All the authors declare that they have no financial, non-financial and personal conflicts of interest.

## Ethical approval

This study was approved by the National Hospital Organization Tokyo Medical Center Ethics Committee (R20-048).

The need for patient consent was waived owing to the retrospective nature of the study.

### Declaration of competing interest

All authors do not have any conflicts of interest to declare.

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