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Early hydroxychloroquine and azithromycin as combined therapy for COVID-19: a case series

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a worldwide outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) has declared it as a public health emergency of international concern (PHEIC) and eventually a pandemic. Many clinical trials have been conducted to investigate potential and effective therapies for COVID-19. Here we reported the outcome of three COVID-19 cases treated early with the combination of hydroxychloroquine and azithromycin. Early treatments of suspected or confirmed positive COVID-19 cases with this combination therapy is to avoid disease progressions into a more severe and irreversible state. In these cases, clinical, radiological, and laboratory features were followed up. No complications were observed. The COVID-19 patients treated with this early combination therapy showed good clinical and virological responses.

ABSTRAK

Coronavirus diseases 2019 (COVID-19) adalah penyakit yang telah menjadi wabah di seluruh dunia dan disebabkan oleh *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). Organisasi Kesehatan Dunia (WHO) telah menetapkan kondisi ini dalam kategori *public health emergency of international concern* (PHEIC) dan juga menetapkan sebagai sebuah pandemi. Banyak uji klinis dilakukan untuk menemukan terapi potensial dan efektif untuk COVID-19. Kami melaporkan luaran dari tiga seri kasus yang mendapatkan pengobatan awal dengan kombinasi hidroksikloroquin dan azitromisin. Tujuan pengobatan terhadap pasien tersangka maupun yang telah terkonfirmasi positif COVID-19 dengan menggunakan terapi kombinasi obat ini pada tahap awal penyakit adalah untuk mengurangi progresivitas penyakit menjadi lebih parah dan ireversibel. Pemeriksaan klinis, radiologi, dan hasil laboratorium diikuti untuk melihat kondisi pasien. Tidak ada komplikasi yang ditemukan. Pasien yang diobati dengan terapi kombinasi ini menunjukkan respon klinis yang baik.

Keywords:
azithromycin;
COVID-19;
hydroxychloroquine;
SARS-CoV-2;
therapy;

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first reported in Wuhan, China on December 2019, before rapidly spreading to the rest of the world.[1-3] As of May 29, 2020, there have been more than 5.7 million cases and 350,000 deaths in more than 200 countries.[4] The World Health Organization (WHO) has declared this situation as a public health emergency of international concern (PHEIC) and eventually a pandemic. Current pieces of evidence suggest that SARS-CoV-2 can be transmitted via droplets, close contacts, and contaminated objects. The incubation period ranges from 2-14 days.[5,6]

The classic symptoms of COVID-19 include fever, dry cough, shortness of breath, sore throat, malaise, and diarrhea. Anosmia and ageusia can be found in some cases. Acute respiratory distress syndrome and septic shock have occurred in severe cases. Chest imaging has shown multiple infiltrative patches and ground glass appearance in both lungs.[6,7]

There is an urgent need to treat the disease and to limit the duration of virus carriage with an effective treatment. Among drug candidates to treat COVID-19, hydroxychloroquine (HCQ) and azithromycin (AZ) are suggested to have beneficial effects when they are simultaneously administered. Since both drugs have been shown to have antiviral activities, such combination may both act as an antiviral therapy and prevent bacterial super-infections.[8-11] Therefore, these two drugs are administered for suspected or COVID-19 positive patients. However, both drugs still have limited clinical evidence on its efficacy for COVID-19.[12] In this report, we present three cases of COVID-19 patients receiving early combined therapy with HCQ and AZ. "Early state" is defined as highly suspected COVID-19 patients, but quantitative reverse transcription-polymerase chain reaction (RT-PCR) results from nasopharyngeal swab have not been obtained.[13] Signed informed consent was received from each patient presented in this case series. All three patients were treated in the Academic Hospital of Universitas Gadjah Mada, a referral hospital in Yogyakarta, Indonesia.

CASE 1

A 70-year-old woman was referred to the emergency unit with a chief complaint of fever for two weeks. The patient also felt nauseous, shortness of breath, fatigue, and sometimes cough. The patient has a previous medical history of hypertension. The patient had a travel history to Semarang, Central Java (a local transmission region in Indonesia) two weeks before hospital admission.

Vital sign examinations on admission were: blood pressure 130/80 mmHg, heart rate 76 bpm, respiratory rate 36x/min, temperature 36.9^{o}C, SpO2 90% room air, and 97% with 4 liters per minute (lpm) oxygen via nasal cannula. No murmur or gallops were found during heart auscultations. Lung auscultation found crackles on both lungs.

Laboratory results were white blood cell (WBC) count 5500/uL, neutrophil 69.1%, lymphocyte 26.1%, monocyte 3.9%, hematocrit (HCT) 37%, hemoglobin (HB) 12.6 g/dL, platelet (PLT) 227.000/uL, potassium 3.1 mmol/L, ureum 15.5 mg/dL, creatinine 0.65 mg/dL, procalcitonin 0.09 ng/ml, positive C-reactive protein (CRP) 24 ug/ml, and postprandial blood glucose 206 mg/dL. No bacteria were detected in the sputum culture. The electrocardiogram (ECG) showed normal sinus rhythm and had a QTc interval of less than 500 ms (475 ms). Chest X-ray revealed infiltrate in the right suprahilar

region (FIGURE 1).

We performed RT-PCR for COVID-19 testing by the nasopharyngeal swab. However, the result was delayed due to overload samples in the reference laboratory in our provincial regions. At the beginning of the pandemic, there was only one reference laboratory in our province that was able to perform RT-PCR for COVID-19. Thus, the patient was diagnosed with suspected severe COVID-19, mild hypokalemia, hyperglycemia, and primary hypertension. She was treated with hydroxychloroquine 400 mg per orally (PO) BID on the first day and continued with 200 mg BID until 5 days. We combined it with azithromycin 500 mg PO QD for 5 days. We also treated her comorbid conditions (candesartan 8 mg PO QD, metformin 500 mg PO QD, paracetamol 500 mg PO TID, KSR 1 tablet PO QD, and curcuma 1 tablet PO TID).

Oxygen requirement was increased from 4 lpm oxygen via nasal cannula on arrival to 8 lpm with a non-rebreathing mask on day 2 (oxygen saturation was 95-97%). On day 3, it was given back to 4 lpm oxygen via nasal cannula. Improvement was observed on day 5 without oxygen via nasal cannula (oxygen saturation 96%). An ECG follow-up showed normal results (QTc interval 428-435 ms).

RT-PCR had not existed yet on day 6 since hospitalization, but the clinical condition was stable. We decided to discharge the patient by educating the COVID-19 protocol to prevent transmission, and we evaluated one week later after the discharge. Then, the first and second RT-PCR results were positive.

During clinical evaluation at one week after the discharge, the patient was free from any signs and symptoms. Complete blood count was within normal limit, postprandial blood glucose was 134 mg/dL, negative CRP, and chest X-ray was normal (FIGURE 1). The patient was treated for her previously established diseases (metformin 500 mg PO QD and amlodipine 10mg PO QD), and the multivitamin was given. The RT-PCR from nasopharyngeal swabs were still positive on day 21st and 22nd. RT-PCR evaluation from nasopharyngeal swabs on day 28th and 29th after onset were negative. Thus, the patient had a full recovery.

CASE 2

A 42-year-old man was admitted to the hospital with a chief complaint of shortness of breath since three days prior to admission, followed by cough, fever, and hypogeusia. The patient had a contact history with COVID-19 patient several days before admission. Vital signs on presentation included blood pressure 118/78 mmHg, heart rate 110 bpm, respiratory rate 22x/min, temperature 37.9^{o}C, SpO2 97% with 3 lpm oxygen via nasal cannula. No murmur or gallops were found, and lung auscultation found crackles on both lungs.

The laboratory results were WBC count 5800/uL, neutrophil 69.2%, lymphocyte 20.3%, monocyte 10.3%, HCT 40.1%, HB 13.6 g/dL, PLT 180000/uL, potassium 3.8 mmol/L, sodium 135 mmol/L, chloride 95 mmol/L, ureum 16 mg/dL, creatinine 0.74mg/dL, positive CRP, serum glutamic oxaloacetic transaminase(SGOT) 45 u/L, serum glutamic pyruvic transaminase (SGPT) 40 u/L, and blood gas analysis were pH 7.45, PCO2 29.0 mmHg, cHCO3 19 mmol/l, and PO2 98.7 mmHg.

The ECG result was normal sinus rhythm and had a QTc interval of less than 500 ms (344 ms). The chest X-ray revealed bilateral pneumonia (FIGURE 1). The first RT-PCR from nasopharyngeal swab was positive for SARS-CoV-2. Thus, the patient was diagnosed with moderate COVID-19. He was treated with hydroxychloroquine 400 mg PO BID on the first day and continued with 200 mg BID for 10 days combined with

azithromycin 500 mg PO QD on the first day and continued with 250 mg QD for 4 days. Paracetamol 500 mg PO TID, multivitamin (caviplex) one tablet PO BID, N-acetylcysteine (NAC) 200 mg PO TID, and vitamin C injection 200mg TID were given as supportive treatment. There were no fever and shortness of breath, only cough remained on day 3.

The second RT-PCR from nasopharyngeal swab was still positive on day 4. No symptoms were reported but the CRP test was still positive on day 5. Follow-up ECG showed normal results (QTc interval 409-423 ms). The chest X-ray showed improvement and RT-PCR nasopharyngeal swabs were negative on day 11 and 12, consecutively. The chest X-ray showed further improvement on day 18 (FIGURE 1). The patient was discharged on the 19th day.

CASE 3

A30-year-old woman was admitted to the hospital with a chief complaint of fever for 3 days. The patient also complained of cough and sore throat. She had close contact with her husband who died of COVID-19. Vital signs on presentation included: blood pressure 110/70 mmHg, heart rate 110 bpm, respiratory rate 20x/min, temperature 37.8^{o}C, SpO2 98% at room air. Heart and lung examinations were within normal limits. The laboratory results were WBC count 4300 u/L, neutrophil 49.1%, lymphocyte 42.1%, monocyte 8.6%, HCT 43.8%, HB 15.0 g/dL, PLT 111000 u/L, positive CRP, and negative immunoglobulin (Ig) G and M (IgG/IgM) of SARS-CoV-2 antibody test. ECG revealed sinus tachycardia (heart rate 122 bpm) and had a QTc interval of less than 500 ms (390 ms). The patient was diagnosed with acute upper respiratory infection and acute pharyngitis. Mild infection of SARS-CoV-2 was suspected. Since the clinical diagnosis of this patient was acute upper respiratory infection, we did not perform chest X-ray examination.

She was treated with hydroxychloroquine 400 mg PO BID on the first day and continued with 200 mg PO BID for seven days. We also treated her with azithromycin 500 mg PO QD for 6 days. Paracetamol 500 mg PO TID, multivitamin (caviplex) 1 tablet PO BID, curcuma 1 tablet PO TID, N-acetylcysteine (NAC) 200 mg PO BID, and vitamin C injection 200 mg TID as supportive treatment. We did an RT-PCR test for SARS-CoV-2 from nasopharyngeal swab on day 2 and day 3 and the results were positive. The diagnosis of mild COVID-19 was established. CRP test was negative on day 6. There were no symptoms since day 3 but ECG still showed sinus tachycardia and had QTc interval 370-419 ms until day 7. The ECG was normal on day 8. We conducted IgG/IgM SARS-CoV-2 antibody test on day 9 and the result was positive. RT-PCR from nasopharyngeal swab was delivered on day 13 and day 14, and the results were negative. The patient was later discharged after 17 days of hospital admission.

CXR on admission CXR on discharged

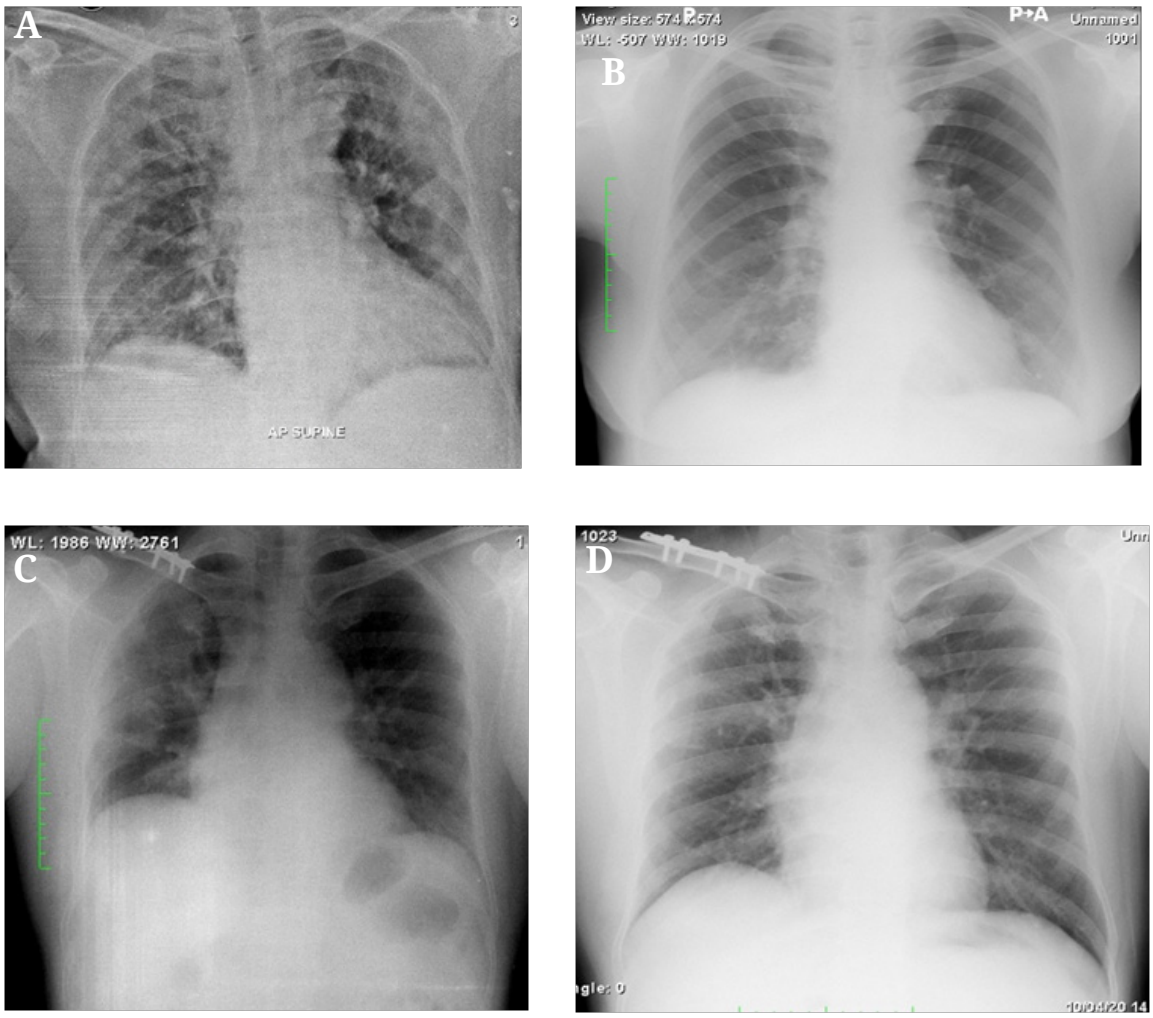

FIGURE 1. Chest X-ray examination for patient 1 (A and B) and patient 2 (C and D), both on admission (A and C) and discharge (B and D).

The clinical course of all cases are summarized in TABLE 1.

TABLE 1. Clinical course of each case (day 1 refers to day on admission)

Case Number	Highly suspected covid-19	Treatment start	Confirmed COVID-19 based on first RT-PCR	Clinical improvement	Negative RT-PCR
1	Day 1	Day 1	Day 10	Day 5	Day 20
2	Day 1	Day 1	Day 6	Day 3	Day 8
3	Day 1	Day 1	Day 11	Day 3	Day 12

DISCUSSION

The therapeutic management of patients is an urgent need to treat symptoms, shortening viral shedding, and avoiding progression to a serious state. By administering hydroxychloroquine in combination with azithromycin in early state, we were able to observe improvement in all three cases. It is necessary to avoid a worsening progression, which usually occurs around the tenth day and may result in acute respiratory distress syndrome, the prognosis of which, in particular in the elderly, is poor.[12]

The protocol in our hospital is that patient with highly suspected COVID-19 should get additional examination (complete blood count, chest X-ray, ECG, RT-PCR on day 1 and day 2, and other examinations based on clinical indications). RT-PCR is only performed to person under surveillance who has positive rapid diagnostic test or patient under observation. If there is no contraindication, the patient will be given hydroxychloroquine and azithromycin in the early state. Vitamin C and symptomatic treatment can be given as supportive treatment. This protocol is in accordance with the guideline of COVID-19 treatment in Indonesia.[13] Then, the patient should be followed up for clinical signs and symptoms, ECG, and chest X-ray (if there is pneumonia). If the results of RT-PCR were positive, the third and fourth RT-PCR should be performed. The patient can be discharged if the third and fourth results of RT-PCR were negative. The additional examination should be performed based on the indication of evaluation. If the results were still positive, fifth and sixth RT-PCR should be performed. The RT-PCR is continually repeated until there are two consecutive negative results.

Severity of the disease is associated with high viral RNA load in COVID-19 patients. In these cases, the combination of hydroxychloroquine and azithromycin is found to be effective in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients within only three to six days.[8] We might have seen better results than three to six days. However, due to the sampling protocol in our hospital, we could only obtain specimen for re-examination when there is resolution of clinical signs and symptoms. These results appear to be superior because a recent study from China has shown that the mean duration of viral shedding in COVID-19 patients without specific treatment was 20 days (even 37 days for the longest duration).[14,15] The rapid decrease in viral load is a synergistic effect of the combination between hydroxychloroquine and azithromycin. The combination of these drugs has a positive role to limit the duration of viral shedding that later can slow down the epidemic.[16]

We observed prolonged positivity (more than 20 days since hospital admission) of RT-PCR results in Case 1. A previous study showed that this observation was more commonly found in patients aged ≥65 years old, similar to our present case.[17] This study also showed that 26.3% of samples remained positive for SARS-CoV-2 after 4 weeks (>28 days), suggesting prolonged viral replications in those groups of patients.[17] Interestingly, another study reported that viral infectivity (defined by observed viral growth in cell culture) was low when positive RT-PCR results were obtained more than 8 days after symptom onset.[18] This study suggests that prolonged positive RNA detections may represent the presence of non-viable virus, although we could not confirm in our patients due to lack of viral cell culture facilities.

Hydroxychloroquine is a relatively safe drug with a promising profile against SARS-CoV-2. However, hydroxychloroquine also has toxic effects. The incidence of hydroxychloroquine

overdose is low. It can be occurred when dosing at 20 mg/kg and has been fatal at over 30 mg/kg. The effects of overdose are nausea, drowsiness, visual disturbance, hypokalemia, convulsion, shock, and death.[19] The combination of hydroxychloroquine and azithromycin has a potential risk to induce severe QT prolongation. Therefore, we need to consider to perform ECG before starting the treatment. Hospitalizing patients with ECG monitoring can help in preventing cardiac side effects through early detection. In a few studies, there is possible toxicity from this drug combination.[20,21] However, in our case series, there was no observed toxicity.

Further studies of this treatment should be conducted to evaluate its double effects as antibacterial and antiviral therapy for COVID-19. These effects can eliminate the infection, hence reduce viral transmission in order to curb the spread of this pandemic. The possibility of this treatment being an international strategy to fight COVID-19 should be considered.

CONCLUSION

Since the emergence of the COVID-19 pandemic, there is an urgent need to effectively treat the disease and limit the duration of virus carriage. Many clinical trials have been conducted to investigate the potential therapies for COVID-19. We have shown that early combination therapy with hydroxychloroquine and azithromycin shows good clinical and virological (clearance) responses in our COVID-19 patients with no observable side effects. Therefore, further comprehensive studies are highly required to explore the role of this treatment for COVID-19.

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