Ivermectin as a Potential Therapeutic Agent for COVID-19 – case studies

Natalia Sisca Wijaya, Sidharta Salim
Mitra Kemayoran Hospital, Jakarta, Indonesia

ABSTRACT

In December 2019, an outbreak of a novel coronavirus (SARS-CoV-2) started in Wuhan, China, and has since become a global threat to human health. To date, the worldwide response to the COVID-19 outbreak has been limited mainly to monitoring/containment. Several types of drug, as well as vaccination, are still under investigation and clinical trials worldwide. Recently, a study demonstrated ~5000-fold reduction in SARS-CoV-2 virus at 48h in cell culture after a single treatment of ivermectin. A clinical study at the University of Utah found that the administration of ivermectin during COVID-19 illness in hospitalized patients is associated with lower mortality and hospital length of stay. We report three confirmed cases of COVID-19 infection with significant improvement clinically and radiologically, with following treatment single dose of ivermectin

Keywords: Ivermectin, SARS-CoV-2, COVID-19

ABSTRAK

Pada Desember 2019, wabah yang disebabkan oleh varian baru coronavirus (SARS-CoV-2) dimulai di Wuhan, China, dan saat ini telah menjadi ancaman global bagi kesehatan manusia. Hingga saat ini, respons dunia terhadap wabah COVID-19 masih terbatas pada pemantauan dan isolasi. Di seluruh dunia, beberapa jenis obat dan juga vaksinasi masih menjalani tahap investigasi dan uji klinis. Baru-baru ini, sebuah studi mendemonstrasikan bahwa satu dosis ivermectin mampu mengurangi ~5000-kali kadar SARS-CoV-2 virus dalam 48 jam pada kultur sel. Sebuah uji klinis di Universitas di Utah juga membuktikan bahwa ivermectin terbukti menurunkan angka mortalitas dan juga lama perawatan pasien COVID-19 rawat inap. Kami melaporkan tiga pasien dengan konfirmasi positif COVID-19 yang menunjukkan kemajuan signifikan klinis dan radiologis setelah pengobatan dengan satu dosis *ivermectin*. **Natalia Sisca Wijaya, Sidharta Salim. *Ivermectin* sebagai Agen Terapeutik Potensial untuk COVID-19 – studi kasus**

Kata kunci: *Ivermectin*, SARS-CoV-2, COVID-19

INTRODUCTION

In December 2019, an outbreak of a novel coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in Wuhan, China, and has since become a global threat to human health. The number of confirmed cases of 2019 coronavirus disease (COVID-19) has reached 3.4 million people worldwide as of May 3, 2020. Many cases of COVID-19 are acute and resolve quickly, but the disease can also be fatal, with a mortality rate of around 3% worldwide.[1]

Although several clinical trials are now underway to test possible therapies, the worldwide response to the COVID-19 outbreak has been largely limited to monitoring/containment. Several types of drugs and vaccination are under investigation and clinical trials worldwide.[1] A collaborative study by Monash University's Biomedicine Discovery Institute and the Peter Doherty Institute of Infection and Immunity, both from Australia, demonstrated that the anti-parasitic drug ivermectin might be effective against SARS-CoV-2, the virus which causes COVID-19 pandemic. It has been postulated that a single treatment of ivermectin could effect ~5000-fold reduction in virus at 48h in cell culture.[2] A clinical study on the usefulness of ivermectin in COVID-19 illness was also performed at the University of Utah with findings that ivermectin administration during COVID-19 illness in hospitalized patients is associated with lower mortality and hospital length of stay. These findings, however, still require confirmation in randomized controlled trials.[3]

We report three confirmed cases of COVID-19 infection with clinically and radiologically significant improvement after treated with ivermectin as a compassionate treatment.

CASES

Patient 1

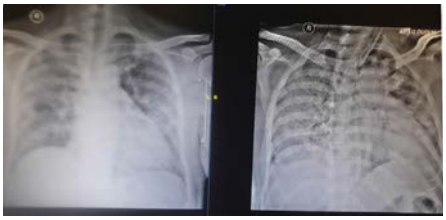
A 57-year old male patient with an underlying history of hypertension presented to the hospital with a four-day history of cough, fever, and shortness of breath. He admitted the previous contact with confirmed COVID-19 case two weeks before his symptoms. His initial blood pressure at presentation was elevated at 160/80 mmHg; he was tachycardic with a heart rate of 108 bpm, slightly tachypneic with a respiratory rate of 22-24 times per minute, subfebrile at 37.6oC and his oxygen saturation was 97% without oxygen supplementation.

Alamat Korespondensi *email: acispunya@gmail.com*


The blood test showed normal Hb at 15.9 g/dl, normal white blood cell count at 5,760/ul, lymphopenia at 12% with neutrophil to lymphocyte ratio of 6.1, slightly decreased platelet level of 184,000/ul, elevated CRP at 19.6 mg/L and elevated D-dimer at 0.52 ug/ml. IgG/IgM nCoV-2 was negative. A chest x-ray showed bilateral pneumonia and a repeat chest CT scan showed ground-glass opacities on both lungs.

He was initially given 4 liters of oxygen via nasal cannula and treated with hydroxychloroquine 200 mg BID and azithromycin 500 mg BID and high dose vitamin C (3 g OD). However, on his following days of hospitalization, the patient continuously has increasing requirements of oxygen. On his fourth day, he had to be hooked to BIPAP at 15 liters per minute. The subsequent result of nasopharyngeal swab PCR was confirmed to be positive for SARS-CoV-2.

On his seventh day of hospitalization, he experienced a sudden drop in blood pressure and desaturation as low as 70%. Repeat blood test showed leukocytosis at 22,870/ul, lymphopenia at 4% with neutrophil to lymphocyte ratio of 22.5, and further elevated D-dimer at 80.90 ug/ml. Blood gas analysis showed respiratory acidosis with pH of 7.272, pCO2 of 76.1, pO2 of 141, and P/F ratio of 141. Repeat chest x-ray showed progression of pneumonia and signs of acute respiratory distress syndrome.



Six hours after the administration of ivermectin, the patient showed clinical improvement. Blood pressure was improving with decreasing requirement of inotropes and his oxygen saturation raised to 100%. A repeat chest x-ray showed significant improvement. Blood test one day after also showed improvement with decreasing WBC at 15,360/ul, reducing D-dimer at 5.43 ug/ml and improving blood gas analysis with pH of 7.481, pCO2 of 39.4, pO2 of 143.9.

Figure1. Patient 1 :**left** : chest x-ray prior and **right** : after the administration of ivermectin.

He was immediately intubated and mechanically ventilated. Two inotropes (dopamine 10 mcg/kg/min and norepinephrine 0.5 mcg/kg/min) had to be administered to maintain his systolic blood pressure above 90 mmHg and heparin intravenous drip at 15,000 unit/24h was also administered to prevent further blood clotting. Despite the maximum setting of the mechanical ventilator and maximum FiO2 of 100%, his oxygen saturation level was below expectations at 88%. With his family consent, we administered ivermectin at a dose of 0.2mg per kg body weight per NGT.

Patient 2

A 48-year old female patient without any underlying disease, presented to hospital with one-week history of fever and cough, with progression to shortness and difficulty of breathing for two days. She denied any prior contact with confirmed COVID-19 cases. Her initial blood pressure at presentation was 120/70 mmHg; she was tachycardic with heart rate of 110 bpm; tachypneic with respiratory rate of 24-26 times per minute; subfebrile at 37.5°C and her oxygen saturation was 86% without oxygen supplementaion.

Her blood test showed Hb 10.5 g/dl, normal white blood cell count 5,950/ul, normal lymphocyte count at 36% with neutrophil to lymphocyte ratio 1.52; normal platelet count 221,000/ul; CRP was elevated at 60 mg/L and initial IgG/IgM nCoV-2 was negative. Chest x-ray showed bilateral pneumonia with cardiomegaly. She was immediately given 8 liters of oxygen via simple mask, raising her oxygen saturation level to 93%. With the patient's consent, the patient was treated with combination of azithromycin 500mg BID and single dose of ivermectin at 0.2mg/kgBW.

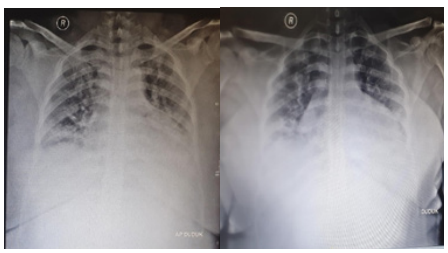


Figure 2. Patient 2 :**left** : chest x-ray prior and **right** : after the administration of ivermectin.

One day after ivermectin administration, the patient showed immediate clinical improvement. Her heart rate has normalized at 92 bpm; she was less tachypneic with respiratory rate of 20-22 times per minute and her oxygen saturation improved at 98% with only 3 liters of nasal cannula. Her repeat chest x-ray also showed significant improvement **(Fig.2).** Blood test however, showed slight elevation of WBC at 11,270/ul and lymphopenia at 19%;but decreasing CRP at 15.4 mg/L. Her repeat IgG/IgM nCoV-2 was noted to be positive.

Patient 3

A 34-year old female, without underlying comorbidities, presented at the hospital with a history of fever and cough for five days. She is a nurse caring for COVID patients. Her blood pressure at examination was 120/70 mmHg, heart rate f 88 bpm, respiratory rate 20 times per minute, temperature 37.2oC, and oxygen saturation 97% without oxygen supplementation.

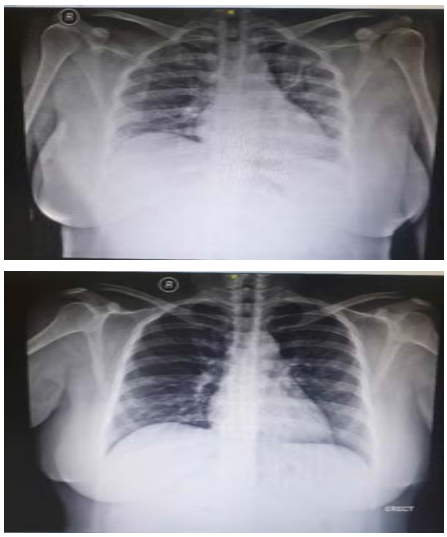


Figure 3. Patient 3, **left**: chest x-ray prior and **right**: after the administration of ivermectin

The blood test showed normal Hb of 12.8g/dl, normal WBC at 6,740/ul, normal lymphocyte count at 34% with neutrophil to lymphocyte ratio 1.8, decreasing platelet count at 146,000/ul, and elevated CRP at 22.4 mg/L. Dengue IgG and IgM were negative. IgG/IgM nCoV-2 was also negative. Chest x-ray however, showed pneumonia on the left lung. With the patient's consent, she was immediately treated with a combination of azithromycin 500 mg BID and a single dose of ivermectin at 0.2mg/kg BW. Subsequent nasopharyngeal swab PCR on the following day was confirmed to be positive for SARS-CoV-2.

After ivermectin administration, her fever started to subside, and no further febrile episode was noted after. A follow-up chest x-ray also showed significant improvement **(Figure 3).**

DISCUSSION

COVID-19 is an infectious disease caused by a newly discovered coronavirus. The virus spread rapidly, and most people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment.[1] However, in older people, and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease and cancer, serious illness is more likely to develop. [1]

Currently, there is no approved targeted therapy for COVID-19. Since the disease was first identified in Wuhan, China, in December 2019, various antiviral medicines have been studied. As of April 24, 2020, 795 clinical trials investigating potential cures for COVID-19, nearly 500 of which are interventional trials. However, as of today, none of those medications have been approved for the treatment of COVID-19. These compounds and drugs can be grouped into three broad categories: antivirals (e.g favipirapir, hydroxychloroquine, chloroquine, remdesivir, lopinavir, ritonavir), immune system-based therapies (convalescent plasma, vitamin C), and vaccines.[4]

Recently, a published study by Caly et al. reported that ivermectin, an FDA-approved anti-parasitic drug previously shown to have broad-spectrum antiviral activity in vitro, is an inhibitor of the causative virus (SARS-CoV-2) and was able to effect ~5000-fold reduction in viral RNA at 48h in cell culture.[2] Ivermectin has previously shown in vitro activity against a broad range of viruses, including human immunodeficiency virus (HIV), dengue fever, influenza, and Zika virus. It is widely used and seen as a safe drug with minimal side effects. However, since the study was done in vitro, further investigations are still needed to confirm its effectiveness in human, as well as for effective dose.[5]

On April 19, 2020, a clinical study on the usefulness of ivermectin in COVID-19 illness by Patel, *et al*, was published. The cohort study was on COVID-19 patients (including 704 ivermectin-treated and 704 controls) from 169 hospitals across 3 continents. The patients were matched for age, sex, race or ethnicity, comorbidities, and an illness severity score (qSOFA). Of those requiring mechanical ventilation, fewer patients died in the ivermectin group (7.3% versus 21.3%), and overall death rates were lower with ivermectin (1.4% versus 8.5%; HR 0.20 CI 95% 0.11-0.37, p<0.0001).[3]

In our three cases of COVID-19, after a thorough discussion with the patients and their families, including an oral and written explanation of ivermectin (in vitro only efficacy according to one study with uncertain efficacy in human and its side effects), followed by a signed written consent, we decided to treat the patient with ivermectin. Dosage of 0.2 mg/kg body weight was decided as it was the recommended dose and considered to be safe6 as antiparasitic treatment in humans.7 In all three patients, the administration of ivermectin seems to benefit as they all showed rapid clinical and radiological improvement after 24 hours.

CONCLUSION

With approximately 253,000 death from COVID-19 worldwide since the first diagnosed case in Wuhan, it is imperative to find effective vaccines and/or medicine to prevent or treat COVID-19. Ivermectin has shown efficacy as a broad-spectrum antiviral in vitro, and in our three cases, it seems also to show some degree of effectiveness for human treatment of COVID-19. Ivermectin, therefore, warrants further investigations and human trials to determine additional benefit.

REFERENCES

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med [Internet]. 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.02.06.20020974v1
2. Cally L, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-COV-2 in vitro. Science Direct 2020; DOI:10.1016/j.antiviral.2020.104787.
3. Patel AN, Desai SS, Grainger DW. Mehra MR. Usefulness of ivermectin in COVID-19 illness. SSRN [Internet]. 2020 [cited 2020 May 8]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3580524
4. Jaroslaw D, Gorovits N. COVID-19 alert. DLA Piper [Internet]. 2020 [cited 2020 May 8]. Available from: https://www.dlapiper.com/en/us/insights/publications/2020/04/therapies-for-covid19-what-is-in-the-pipeline/
5. Lundberg L, Pinkham C, Baer A, Amaya M, Narayanan A, Wagstaff KM, et al. Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis virus replication. Antivir. Res. 2013;100(3):662-72.
6. Õmura S, Crump A. The life and times of ivermectin - a success story. Nat Rev Microbiol. 2004;2:984-9. 10.1038/nrmicro1048
7. Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol. 2002;42:1122-33.