〈Case Report〉

Three cases of COVID-19 pneumonia treated with ivermectin monotherapy

Kosuke Jo[1], Hironori Goto[2], Tsunetoshi Mogi[2], Kenji Kono[1] and Takafumi Ueno[3]

[1]Department of Infectious Diseases, Fukuoka Kinen Hospital, Fukuoka, Japan
[2]General Medical Department, Fukuoka Kinen Hospital, Fukuoka, Japan
[3]Department of Cardiovascular Medicine, Fukuoka Kinen Hospital, Fukuoka, Japan

(Received for publication Mmmm dd, 2021)

We report three cases of coronavirus disease 2019 (COVID-19) pneumonia treated with ivermectin monotherapy. The patients included two men (aged 40 and 49 years) and a woman (aged 53 years), all of whom had high fever and bilateral pneumonia. We administered 0.2 mg/kg of ivermectin orally every alternate day. They defervesced soon after, the blood inflammatory markers and chest radiographic findings improved and the patients were discharged. There was no need for additional therapy. These three patients improved following ivermectin administration. Oral ivermectin may have a role to play in the home treatment of COVID-19 patients.

Introduction

Ivermectin, a Nobel Prize-winning drug, has been used worldwide since 1987 for the treatment of river blindness, lymphatic filariasis, strongyloidiasis, and scabies[1)]. It is a well-tolerated, low-cost medication. The coronavirus disease 2019 (COVID-19) pandemic began in Wuhan, China, in December 2019 and subsequently spread worldwide. In April 2020, Caly *et al.* found that ivermectin suppresses severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication *in vitro*[2)], and it has been clinically used for the treatment and prevention of COVID-19 worldwide. Numerous clinical trials have been performed in various countries to confirm the efficacy and safety of ivermectin for COVID-19. In Japan, Kitasato University is currently conducting a doctor-initiated clinical trial[1)].

Corresponding author: Kosuke Jo, Department of Infectious Diseases, Fukuoka Kinen Hospital; 1–1–35 Nishijin, Sawara-ku, Fukuoka-city, Fukuoka 814–8525, Japan, Tel: +81–92–821–4731, Fax: +81–92–821–6449, E-mail: kousuke-j@oita-u.ac.jp

Fukuoka Kinen Hospital is an acute-care hospital consisted of 239 beds. Since April 2020, three to twenty COVID-19 patients have been hospitalized at any time in dedicated isolation wards. In April 2021, off-label use of ivermectin for COVID-19 was approved by ethics committee in our hospital, and we have begun to use it for inpatients with mild or moderate disease, after obtaining informed consent. The severity of COVID-19 was defined as follows: mild: oxygen saturation (SpO_2)≧96% on room air and no respiratory symptom (coughing only, no shortness of breath), moderate I: 93%＜SpO_2＜96%, (shortness of breath and pneumonia findings), moderate II: SpO_2≦93% oxygen administration required, and severe: admission to ICU or mechanical ventilator required, according to the Severity Classification of COVID-19 in our country[3].

We administered oral ivermectin (0.2 mg/kg/day) on Days 1, 3 and 5 (where Day 1 is the first day of admission) to patients (Niaee MS, manuscript in preparation). We decided to add steroids or tocilizumab if there were persistent high fever and inflammatory markers worsened. Glycyrrhizin preparations were added if liver damage occurred.

Case Studies

Case 1

A 40-year-old man presented with a 10-days history of fever and a several-day history of diarrhea before hospitalization. A nasopharyngeal swab tested positive for SARS-CoV-2 using polymerase chain reaction (PCR) in another hospital, three days before admission to our hospital. He had no significant medical history but had been a long-time smoker (current smoker). Findings on physical examination included: SpO_2 on room air 97%, body temperature 39.3℃, blood pressure 138/98 mmHg, heart rate 100 beats/min, his height 171 cm, weight 69 kg, and body mass index (BMI) 23.6 kg/m^2. Laboratory findings included: white blood cell (WBC) count of 5,940/μL, platelet (PLT) count of 20.3×10^4/μL, mildly elevated liver enzyme levels (aspartate aminotransferase (AST) 44 IU/L, alanine aminotransferase (ALT) 55 IU/L), elevated lactate dehydrogenase (LDH) levels 389 U/L, and C-reactive protein (CRP) levels 5.67 mg/dL. Blood urea nitrogen (BUN) 12 mg/dL, creatinine (Cr) 0.95 mg/dL, D-dimer 1.80 μg/mL, ferritin 472 ng/mL, and sialylated carbohydrate antigen KL-6 251 U/mL. Chest computed tomography (CT) showed peripheral predominant, multiple ground-glass opacities (Fig. 1A). He received 15 mg ivermectin three times every other day from the date of admission (Day 1, Day 3, and Day 5). From Day 4 onwards, defervescence below 37℃ was observed along with improvement of LDH and CRP levels (Fig. 2). On Day 8, computed tomography (CT) after treatment with ivermectin showed an improvement of the pneumonia (Fig. 1B). No adverse effects of ivermectin were observed. The patient was discharged on Day 8.

Fig. 1. (A) Chest computed tomography on admission showed multiple ground glass opacities in both lung fields. (B) On Day 8, chest computed tomography showed improvement of the pneumonia

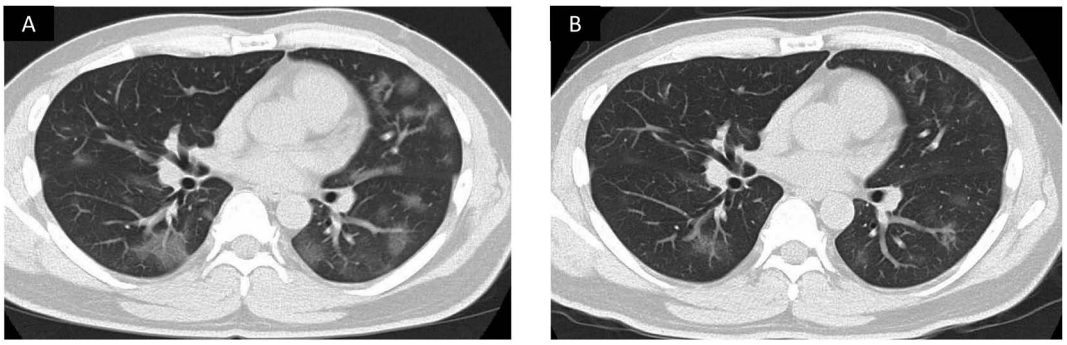
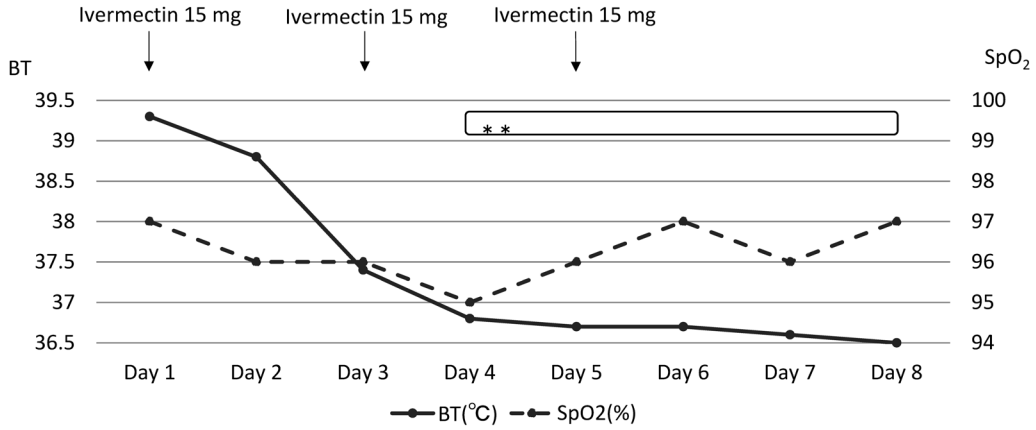


Fig. 2. Clinical course of Case 1



AST/ALT(IU/L)	44/55	68/121	42/117
LDH(U/L)	389	364	237
CRP(mg/dL)	5.67	1.93	0.65
D-dimer(μg/mL)	1.80	2.00	5.80

** glycyrrhizin preparation
Abbreviations: AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; BT, body temperature; SpO_2, oxygen saturation

Case 2

A 49-year-old man presented with fever persisting for nine days. He was referred to our hospital and was admitted immediately. On admission, a nasopharyngeal swab tested positive for SARS-CoV-2 using reverse transcription-loop-mediated isothermal amplification (LAMP). His medical history included hypertension, myocardial infarction, and borderline diabetes. Findings on physical examination included: SpO_2 on room air 93%, body temperature 38.8℃, blood pressure 129/84 mmHg, heart rate 86 beats/min, his height 174 cm, weight 91.0 kg, and BMI 30 kg/

Fig. 3. (A) Chest computed tomography on admission showed multiple ground glass opacities around bronchovascular bundles bilaterally. (B) On Day 8, chest computed tomography showed improvement of the pneumonia

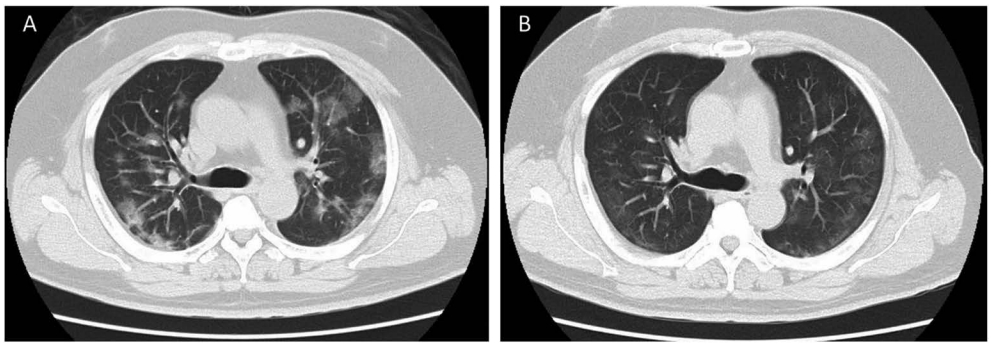
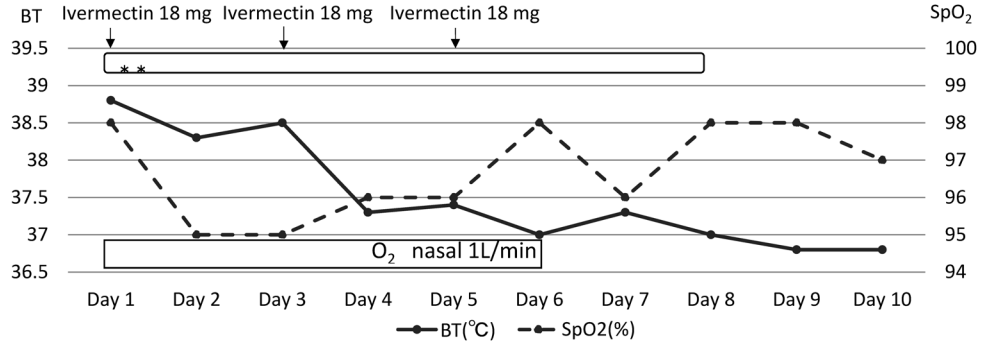


Fig. 4. Clinical course of Case 2



AST/ALT(IU/L)	64/66	69/70	76/113	28/65	23/53
LDH(U/L)	416	429	346	244	214
CRP(mg/dL)	5.63	6.90	1.93	0.45	0.15
D-dimer(μg/mL)	1.70	1.60	1.80	1.70	1.30

** glycyrrhizin preparation
Abbreviations: AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; BT, body temperature; SpO_2, oxygen saturation

m^2. Laboratory findings included: WBC count of 4,400/μL, decrease in PLT $9.8\times10^4/\mu$L, elevated liver enzyme AST 64 U/L, ALT 66 U/L, LDH 416 U/L, BUN 9 mg/dL, Cr 0.97 mg/dL, CRP 5.63 mg/dL, D-dimer 1.70 μg/mL, ferritin 406 ng/mL. Chest CT showed multiple ground-glass opacities around bilateral bronchovascular bundles (Fig. 3A). He received 18 mg ivermectin three times every other day and oxygen inhalation at 1 L/min from the date of admission. From Day 4 onwards, defervescence was observed along with improvement of LDH and CRP levels. Oxygen inhalation was discontinued on Day 6 (Fig. 4). On Day 8, chest CT showed improvement in the pneumonia (Fig. 3B).

Fig. 5. Chest computed tomography on admission showed wide ground glass opacity with interlobular septal thickening in the right middle lobe

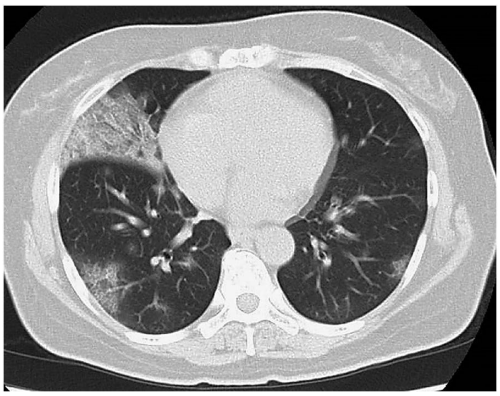
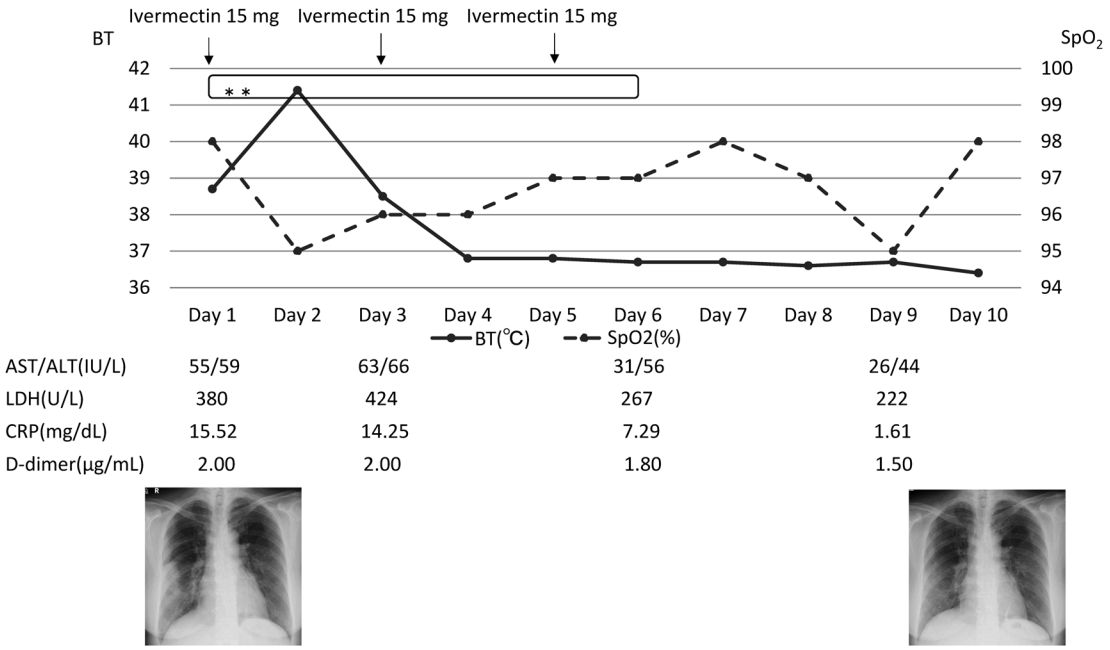


Fig. 6. Clinical course of Case 3



AST/ALT(IU/L)	55/59	63/66	31/56	26/44
LDH(U/L)	380	424	267	222
CRP(mg/dL)	15.52	14.25	7.29	1.61
D-dimer(μg/mL)	2.00	2.00	1.80	1.50

** glycyrrhizin preparation
Abbreviations: AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; BT, body temperature; SpO_2, oxygen saturation

Case 3

A 53-year-old woman presented with a sore throat and cough for six days prior to hospital admission. She had a fever of 40℃ the day before admission. A nasopharyngeal swab tested positive for SARS-CoV-2 using PCR in a clinic, one day prior to admission to our hospital. She had no significant past medical history. Findings on physical examination included; SpO_2 on room air 98%,

body temperature 38.7℃, blood pressure 112/82 mmHg, heart rate 113 beats/min, her height 165 cm, weight 72 kg, and BMI 26.4 kg/m^2. Laboratory findings included: WBC count of 5,220/μL, PLT 20.3$\times$10^4/μL, elevated liver enzyme AST 55 U/L, ALT 59 U/L, LDH 380 U/L, BUN 10 mg/dL, Cr 0.71 mg/dL, marked increase of CRP levels 15.52 mg/dL, D-dimer 2.0 μg/mL, KL-6 208 U/mL, ferritin 962 ng/mL. Chest CT showed multiple subpleural ground-glass opacities and widespread opacity with thickening of alveolar septum in the right middle lobe (Fig. 5). She received 15 mg ivermectin three times every other day. From Day 4 onwards, defervescence below 37℃ was obtained, and CRP levels decreased until discharge on Day 10. Chest radiography on discharge showed improvement of the infiltrative shadow in the right lung (Fig. 6).

Discussion

Ivermectin is a potent inhibitor of SARS-CoV-2 *in vitro*[2]. Many small-sized clinical trials of ivermectin have been conducted worldwide, and they reveal the efficacy of ivermectin at various end points, such as on length of hospital stay, mortality, and symptom improvement[4,5]. Thus, ivermectin is a candidate for the treatment of COVID-19, although it has not been formally approved in Japan. We referred to a randomized phase II clinical trial conducted in Iran, in which there was significant difference between Ivermectin groups and Control groups in improvement of inflammatory marker and mortality. Administration of 0.2 mg/kg ivermectin three times every other day was one of four regimens in Ivermectin groups. The administered dose of 0.2 mg/kg is the dose for indication disease of ivermectin in Japan, so we thought this regimen would be safer than high dose regimens.

The mechanism of ivermectin's antiviral action is thought to be due to inhibition of importin α/β1-mediated nuclear import of viral proteins, resulting in the reduction of viral RNA replication[2, 5, 6]. One of the prominent features of severe COVID-19 is cytokine release syndrome (CRS) which activates monocytes and macrophages resulting in the secretion of various cytokines such as IL-6[5,7]. Fortunately, ivermectin has antiviral and anti-inflammatory properties, which decreases the production of TNF-α, IL-1, and IL-6 *in vivo* and *in vitro*[5,8]. Therefore, ivermectin administration may not only be effective in the early stages of infection, but also could have a role in the later stages because of its anti-cytokine properties[9,10]. Indeed, in our cases the duration from disease onset to ivermectin administration was 6 to 10 days, suggesting that they may not have been in the early stages of disease. Re-ascent of CRP, suggestive of CRS, was not observed in all cases, and clinical symptoms, physical examination, and clinical parameters improved concurrently after administration of ivermectin.

In Japan, the COVID-19 pandemic has rapidly reduced the number of available hospital beds. Moreover, there are currently no therapeutic agents available for outpatients. Remdesivir is not suitable for home treatment because it is administered intravenously and is not recommended

for mild disease[3]. To solve these problems, a home treatment plan for outpatients with mild COVID-19 must be established immediately[11]. Case 1 and 3 were healthy adults who did not have any significant past medical history and did not require oxygen inhalation. If it were possible to prescribe ivermectin for the treatment of COVID-19 out of hospital, they could recover at home. Outpatient ivermectin use may lead to an increased availability of hospital beds. Case 2 had underlying diseases that were risk factors for severe infection[12]. In addition, the demand for inhaled oxygen made us consider the administration of steroids[13]. However, ivermectin monotherapy was followed by an improvement in the patient's overall status. Ivermectin monotherapy without steroid administration, could bring a significant benefit to patients who have underlying diseases which get worse by administering steroids, such as diabetes mellitus and immunocompromised state.

In conclusion, oral ivermectin monotherapy has the potential to be a therapeutic agent, especially for patients with mild COVID-19. A large randomized controlled trial of ivermectin home treatment is needed to validate its efficacy and safety. If successful, this could prevent a shortage of hospital beds for COVID-19 patients in our country.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical statement

Consent to publish the details of their case was obtained from the patient.

References

1) Yagisawa M, Foster PJ, Hanaki H, Omura S: Global trends in clinical studies of ivermectin in COVID-19. Jpn J Antibiot. 2021; 74: 44–95.
2) Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM: The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020; 178: 104787.
3) The Ministry of Health, Labour and Welfare: Clinical management of patients with COVID-19. A guide for front-line healthcare workers Version 5 (in Japanese). 2021.5.26. https://www.mhlw.go.jp/content/000785119.pdf
4) Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ: Use of ivermectin is associated with lower mortality in hospitalized patients with Coronavirus disease 2019: the ivermectin in COVID nineteen study. Chest. 2021; 159: 85–92.
5) Kory, P, Meduri, GU, Varon, J, Iglesias J, Marik, PE: Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19. Am J Ther. 2021; 28: e299–e318.
6) Martin AJ, Jans DA: Antivirals that target the host IMPα/β1-virus interface. Biochem Soc Trans. 2021; 49: 281–95.
7) Subbarao K, Mahanty S: Respiratory virus infections: understanding COVID-19. Immunity. 2020;

52: 905–9.
8) Zhang X, Song Y, Ci X, *et al.*: Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res. 2008; 57: 524–9.
9) Heidary F, Gharebaghi R: Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. J Antibiotics. 2020; 73: 593–602.
10) DiNicolantonio JJ, Barroso-Arranda J, McCarty M: Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19. Open Heart. 7: e001350, 2020.
11) Ayaz CM, Dizman GT, Metan G, Alp A, Unal S: Out-patient management of patients with COVID-19 on home isolation. Infez Med. 2020; 28: 351–6.
12) Gandhi RT, Lynch JB, Del Rio C: Mild or moderate Covid-19. N Engl J Med. 2020; 383: 1757–66.
13) Recovery Collaborative Group, Horby S, Lim WS, *et al.*: Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021; 384: 693–704.