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Case report

Combination treatment of short-course systemic corticosteroid and favipiravir in a successfully treated case of critically ill COVID-19 pneumonia with COPD

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ABSTRACT

Use of systemic corticosteroids for the treatment for coronavirus disease 2019 (COVID-19) among chronic obstructive pulmonary disease (COPD) patients is not well described. A 58-year-old man with fever and progressive dyspnea was admitted to the Showa University Hospital, and showed severe respiratory failure which needed mechanical ventilation. His chest computed tomography scanning showed emphysema and bilateral ground-glass opacity caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. He received 30 mg prednisolone for five days with antiviral drug of favipiravir, and was successfully extubated on day five. A SARS-CoV-2 polymerase chain reaction (PCR) test became negative on day 15. He was discharged on day 21. Serum IgM and IgG antibodies against SARS-CoV-2 converted to positive on day 7 and they kept positive on day 54 for both IgM and IgG. Combination treatment of short-course systemic corticosteroid and favipiravir might improve the prognosis for critically ill COVID-19 pneumonia with COPD without negative influence on viral clearance or antibody production.

1. Introduction

The coronavirus disease 2019 (COVID-19) is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has high morbidity and mortality, and there is an urgent need to establish a treatment method [1]. Treatment strategies for severe cases of COVID-19 focus on two targets: reduction of viral load in the body by use of antiviral drugs, and control of inflammatory cytokines in the body, which are produced in response to viral antigens [2].

Favipiravir (Avigan®), lopinavir/ritonavir (Kaletra®), remdesivir, and the antimalarial drug, hydroxychloroquine, are currently being tested as antiviral treatment candidates in clinical studies [3]. Favipiravir acts by selectively inhibiting RNA-dependent RNA polymerase of RNA viruses to suppress viral replication [4]. Initially developed as a treatment drug for novel influenza virus infection, it has shown to have an antiviral effect on SARS-CoV-2 [3]. There have been reports that clinical course improved in severe COVID-19 patients who received favipiravir empirically, however, all of these cases are currently being examined at the case report basis, and clinical trials designed for more objective evaluation of efficacy are currently underway.

Chronic obstructive pulmonary disease (COPD) is considered to be a risk factor of severe COVID-19, and more careful treatment is necessary

Abbreviations: ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; GOLD, The Global Initiative for Chronic Obstructive Lung Disease; ICU, intensive care unit; MERS, middle east respiratory syndrome; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; SFTSV, severe fever with thrombocytopenia syndrome virus; SpO_2, peripheral capillary oxygen saturation; SRAS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell.

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in cases exhibiting COPD [5]. While systemic corticosteroid treatment is recommended in cases of COPD exacerbation, liberal use of systemic corticosteroid in COVID-19 cases with COPD is not recommended due to potential risks of steroid-related complications, secondary infections, and delayed viral shedding [6]. At present, there are few case reports related to cases of COVID-19 with COPD as an exacerbating complication.

In this study, we report our experiences in treating a critically ill patient with COVID-19, complicated by COPD, who exhibited ground glass shadows on emphysematous lungs and needed mechanical ventilation. This patient exhibited a favorable prognosis after being administered a combination treatment of short-course systemic corticosteroid and favipiravir, and eventually came out mechanical ventilatory support without any negative impact on viral clearance and antibody production against SARS-CoV-2. Off-label use of favipiravir for COVID-19 was approved by the ethical committee of Showa University. The written informed consent was obtained from the patient for use of favipiravir and publication of this case report.

2. Case report

The patient was a 58-year-old man with COPD, having a smoking history of 38 pack-years. He had no apparent contact history with COVID-19 patients. In March 2020, he had a fever of 38 °C seven days prior to hospital admission, and had been prescribed to use loxoprofen sodium at home. His fever and malaise persisted, and he began experiencing dyspnea one day before admission, and then he was subsequently brought to the emergency department of the Showa University Hospital. Upon arrival, his vital signs were body temperature, 37.1 °C; blood pressure, 120/80 mmHg; heart rate, 114 beats/min; respiratory rate, 24 breaths/min; auscultation, clear breathing sounds without murmurs; consciousness, clear and lucid. Marked hypoxemia as 55% of peripheral capillary oxygen saturation (SpO_2) at room air was observed. Blood biochemistry testing revealed lymphocytopenia and high inflammatory response as white blood cell (WBC) count 7200/μL (lymphocytes 5.5%), C-reactive protein (CRP) 23.67 mg/dL (Table 1).

A chest X-ray revealed decreased lung permeability due to bilateral lung field consolidation and ground-glass shadows, and chest computed tomography (CT) scanning also showed bilateral ground-glass opacity with significant emphysematous changes in the bilateral apex of the lung, and bilateral pleural effusion (Fig. 1a and c). SpO_2 was 84% even when oxygen was administered at 12 L/min using a non-rebreather mask. Endotracheal intubation was performed immediately as the patient was transferred to the intensive care unit (ICU) to receive ventilator management.

Table 1
Laboratory findings.

WBC,/μL	7200	TP, g/dL	5.8
Neutrophils, %	91.0	Albumin, g/dL	2.6
Lymphocytes, %	5.5	T-Bil, mg/dL	1.5
Monocytes, %	2.0	BUN, mg/dL	23.5
RBC,/μL	342×10^4	Creatinine, mg/dL	1.06
Hb, g/dL	13.1	AST, IU/L	100
Platelets,/μL	16.6×10^4	ALT, IU/L	73
PT-INR	0.94	LDH, IU/L	889
APTT, sec	28.1	ɤ-GTP, IU/L	194
Fibrinogen, mg/dL	811	CK, IU/L	48
D-Dimer, μg/mL	5.40	Na, mEq/L	136.2
		K, mEq/L	4.8
Arterial blood gas	O_2: mask 12L/min	Cl, mEq/L	100.0
pH	7.292	CRP, mg/dL	23.67
$PaCO_2$, mmHg	57.1	KL-6, U/mL	540.0
PaO_2, mmHg	71.2	SP-D, ng/mL	194.1
HCO_3^-, mmol/L	27.0	SP-A, ng/mL	81.3
BE, mmol/L	−0.6	procalcitonin, ng/mL	0.18
Lactate, mmol/L	0.85	Ferritin, ng/mL	2342

Abbreviations: ALT; alanine aminotransferase, AST; aspartate aminotransferase, APTT; activated partial thromboplastin time, BE; base excess, BUN; blood urea nitrogen, CK; creatine kinase, CRP; C-reactive protein, KL-6; sialylated carbohydrate antigen Krebs von den Lungen-6, LDH; lactate dehydrogenase, PT-INR; prothrombin-international normalized ratio, RBC; red blood cells, SP-A; surfactant protein-A, SP-D; surfactant protein-D, T-Bil; total bilirubin, TP; total protein.

As empiric therapy for severe pneumonia, tazobactam piperacillin (4.5 g every 8 hours) was infused intravenously, and azithromycin (500 mg every 24 hours) was administered via nasogastric tube for three days. As there was a tendency for CO_2 retention in his arterial blood gas, we diagnosed him as COPD exacerbation and 30 mg/day of prednisolone was administered for five days to control COPD exacerbation. On day four of hospitalization, a polymerase chain reaction (PCR) assay of SARS-CoV-2 obtained via nasal swab was found to be positive, and the patient was diagnosed with COVID-19 pneumonia. Oral administration of favipiravir was started on the same day. On the first day of treatment, 1800 mg/body were administered every 12 hours, and from the second day, 800 mg/body were administered every 12 hours via nasogastric tube (Fig. 2). Venous thromboembolism was suspected as D-dimer tended to increase after admission, thus the patient began receiving continuous intravenous heparin infusions. On day five of hospitalization, the patient's respiratory condition was improved, and the ventilatory support was discontinued. On day 10 of hospitalization, as his symptoms and chest X-ray findings improved, the treatment of antibiotics were discontinued. A contrast-enhanced CT scan performed on day 13 of hospitalization revealed the presence of thrombosis in the right pulmonary artery, and from the left common iliac vein to the femoral vein, which were diagnosed as a pulmonary embolism and deep vein thrombosis, respectively. The continuous infusion of heparin was changed to oral edoxaban of 60 mg/day. In addition, as WBC tended to decrease to 3400/μL (neutrophils 60%, lymphocytes 29.1%), administration of favipiravir was terminated on day 13 (total administration of 10 days). On day 15 of hospitalization, a SARS-CoV-2 PCR test of a nasal swab sample became negative. Oxygen administration terminated on day 19 of hospitalization. Chest radiological and CT images were improved (Fig. 1b and d), and the patient was discharged on day 21. His blood seropositivity for SARS-CoV-2 antibodies was retrospectively analyzed using GenBody COVID-19 IgM/IgG kit (GenBody Inc., Republic of Korea). Negative results of his IgM and IgG antibody against SARS-CoV-2 on admission turned out positive on day 7 and 15 for both IgM and IgG, and their positivity sustained on day 54 during his visit at the outpatient clinic.

3. Discussion

Favipiravir is an RNA-dependent RNA polymerase inhibitor that inhibits RNA virus replication. Favipiravir was approved in 2014 in Japan as a treatment for novel influenza virus infections [4]. The efficacy of favipiravir against the Ebola virus became known during the Ebola outbreak in West Africa, from 2014 to 2015 [7]. In addition, findings indicate the efficacy of favipiravir in cases of infection by severe fever with thrombocytopenia syndrome virus (SFTSV) [8]. In a study using type I interferon receptor knockout mice, as a result of infecting the mice with SFTSV and administering favipiravir or control, all mice in the control group died, whereas all the mice in the favipiravir group survived; no weight loss was observed, and recovery mice were also noted in production of neutralizing antibodies during the treatment period. Based on the above findings, favipiravir is also expected to have a viral replication inhibitory effect on SARS-CoV-2. In view of favipiravir's pharmacological action, this drug is thought to be effective in suppressing viral replication [3], supposed to be administered as a treatment for the virus during the early stages of infection. However, at present, use of this drug has been studied only in severe cases. As of June 2020, Japanese phase III clinical trials of favipiravir are ongoing, and the effect of adding favipiravir to the standard of care treatment is being investigated (JapicCTI-205238).

In COVID-19 cases, the presence of COPD is considered to be a risk

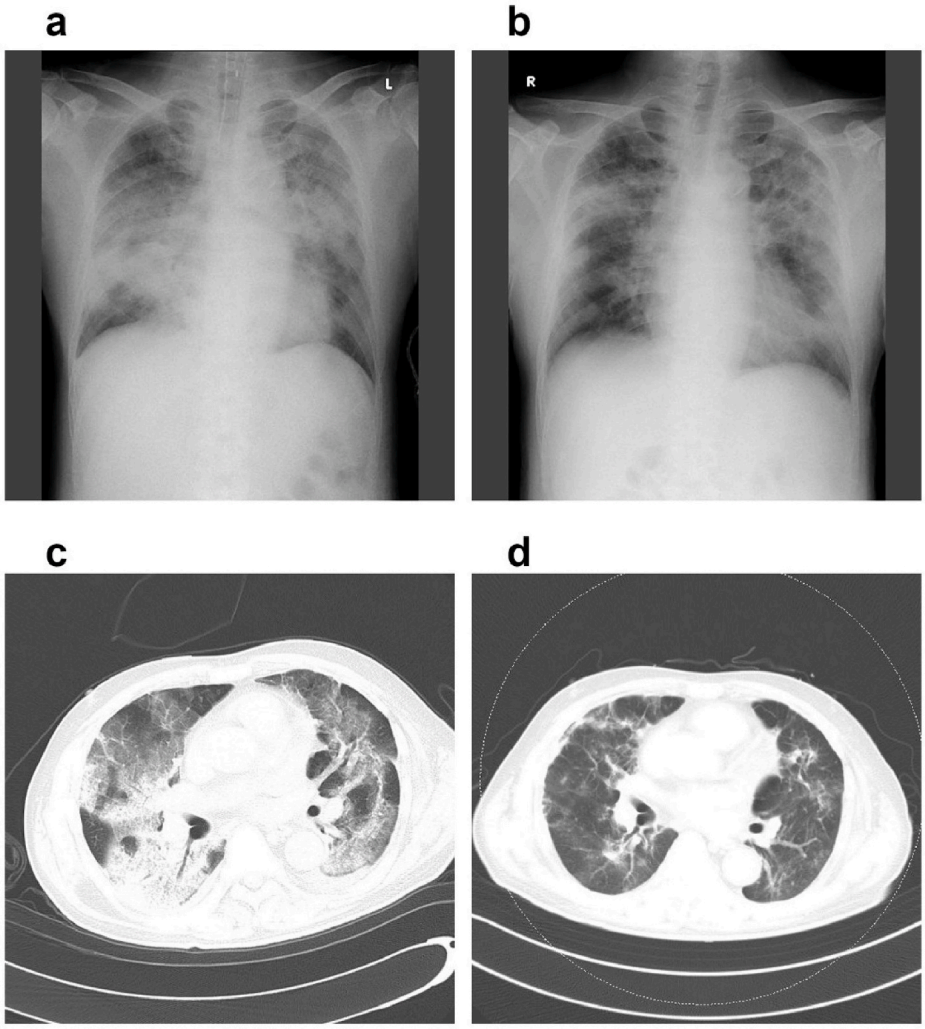

Fig. 1. Radiologic and CT images. Chest X-ray shows consolidation and ground-glass opacities in both lung fields on the day of admission (a), which improved on a day before discharge (b). Chest CT indicates upper-lobe predominant emphysema and bilateral ground-glass opacity with traction bronchiectasis on the day of admission (c), which also improved on a day before discharge (d). Bilateral pleural effusion was also observed in this case.

factor for worse prognosis, alongside hypertension, heart disease, and diabetes. In a study of 344 patients requiring ICU treatment, there were significantly more patients with COPD in the non-surviving group (n = 133) [9]. Low pulmonary function due to COPD is believed to be a poor prognostic factor when respiratory failure is presented. In terms of susceptibility of COVID-19 among COPD patients, analysis of multiple studies revealed that the rate of complication by COPD among COVID-19 cases was 1.0–2.9% of all cases [10,11]; and whether COPD is a significant risk factor for developing COVID-19 requires further consideration, taking confounding factors into account. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend continuing normal medical care including inhaled corticosteroids for COPD patients during the COVID-19 epidemic [12]; and stabilizing the COPD control is believed to be the best treatment strategy to minimize the risk SARS-CoV-2 infection.

Currently there is no clear treatment guideline as to whether systemic corticosteroids should be administered, as usual, to patients with COPD that develop COVID-19. Regarding the administration of corticosteroids, studies on severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), influenza, and respiratory syncytial virus (RSV) have revealed a delay in the rate of viral shedding [6]. Although at present there is no data for SARS-CoV-2, a delay in viral excretion due to administration of systemic corticosteroids is expected. The current consensus is that systemic corticosteroid therapy should not be strongly recommended in patients with respiratory failure due to SARS-CoV-2 infection [6]. However, there are reports indicating that systemic corticosteroids were effective in COVID-19 cases of acute respiratory distress syndrome (ARDS) [13]. A retrospective study of 201 COVID-19 patients hospitalized in Wuhan, China, found that 84 cases (41.8%) worsened to ARDS. Although 44 (52.4%) of these ARDS cases resulted in death, treatment with methylprednisolone reduced the risk of death (hazard ratio: 0.38; 95% CI: 0.20–0.72). As a possible mechanism, it has been suggested, that in severe COVID-19 cases, excessive inflammatory cell infiltration resulting from SARS-CoV-2 infection may cause a cytokine storm, resulting in systemic inflammation. In such cases, immunomodulatory agents such as corticosteroids and anti-IL-6 antibody may be effective. However, there is no clear evidence regarding the amount and duration of corticosteroid administration, further cases need to be evaluated, and corticosteroids should be administered with caution. In the present case, the progressive respiratory failure associated with CO_2 retention was a major contributor to the exacerbation of the patient's COPD, and systemic corticosteroid therapy was co-administered with favipiravir. Even if a COPD patient develops COVID-19, the similar treatment as the exacerbation of COPD associated with other viral infections may contribute to a favorable course. The GOLD guidelines [12] indicate that administration of systemic corticosteroids during COPD exacerbation shortens the duration of treatment and hospitalization, improves oxygenation, and improves

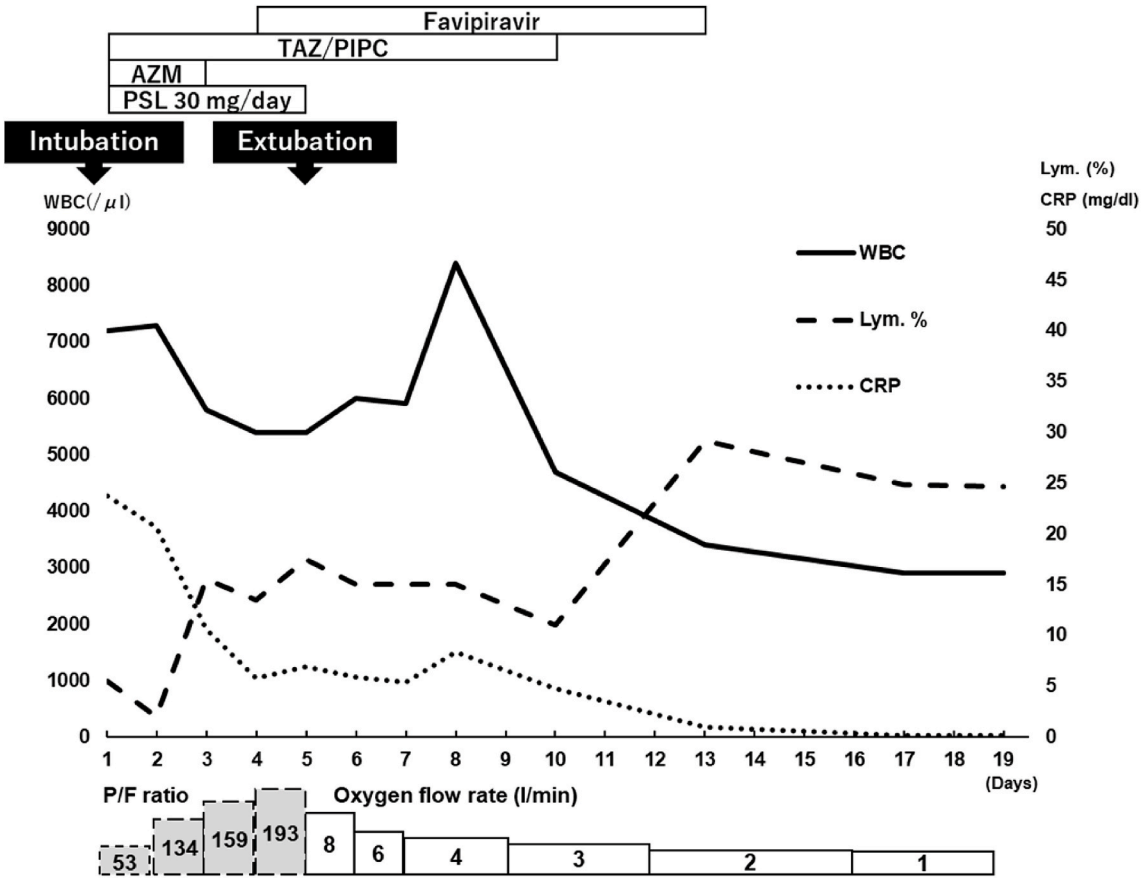

Fig. 2. Clinical course. Treatment and oxygen supplementation course and changes in blood cell counts and C-reactive protein (CRP) in the patient. Abbreviations: AZM: azithromycin, Lym: lymphocytes, P/F ratio: a ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2), PSL: prednisolone, TAZ/PIPC: tazobactam/piperacillin.

respiratory function. The recommended corticosteroid treatment is 40 mg of prednisolone for five days. While there are currently no negative reports concerning systemic corticosteroid administration in COVID-19 patients with COPD, further evidence is needed to establish a conclusive evidence.

Caution in the use of systemic corticosteroid for COVID-19 pneumonia is proposed in terms of delayed viral clearance and impaired antibody production [6]. In our case report, a PCR assay of SARS-CoV-2 from a nasal swab sample returned to be negative on day 15 of hospitalization. In a study of 18 cases of COVID-19 in Singapore, the median day from the first positive SARS-CoV-2 PCR result to the last positive nasopharyngeal swab was 12 days (range; 1–24 days) [14]. Although systemic corticosteroids were administered in this case, no obvious delay in viral clearance was observed. Moreover, both of IgM and IgG antibodies against SARS-CoV-2 sustained as positive during follow-up period after discharge. A short course of prednisolone (30 mg/day for 5 days) in combination with the antiviral drug favipiravir may not interfere virus shedding as well as antibody production against SARS-CoV-2.

As limitations, this is a case report, and an objective clinical trial is necessary to evaluate the efficacy of favipiravir and systemic steroid administration. In addition, in this case, no pulmonary testing was performed or no drug therapy for COPD had been administered prior to the onset of COVID-19 symptoms. The relationship between severity of COPD and COVID-19 has not been fully investigated. The efficacy and safety of inhaled corticosteroids for SARS-CoV-2 infection with COPD remains to be elucidated in future studies.

4. Conclusion

Here, we have reported a case of COVID-19 pneumonia complicated with COPD. The patient developed severe respiratory failure necessitating mechanical ventilation, which was successfully improved by administration of short-course systemic corticosteroid and antiviral drug of favipiravir with negative PCR test and antibody seropositivity against SARS-CoV-2. These results suggest that combination treatment of short-course systemic corticosteroid and favipiravir may be effective in COVID-19 pneumonia complicated by COPD without negative impact on viral shedding or seroconversion against SARS-CoV-2.

Credit authorship contribution statement

Hideki Inoue: Writing manuscript and final approval for submission, Megumi Jinno: Writing manuscript draft and making figures and table, Shin Ohta: Laboratory testing, data curation, and critical revision of the manuscript, Yasunari Kishino: Data curation, Tomoko Kawahara: Data curation, Hatsuko Mikuni: Data curation, Haruna Sato: Writing manuscript draft, Mayumi Yamamoto: Data curation, Yoko Sato: Data curation, Chisato Onitsuka: Data curation, Yuiko Goto: Data curation, Hitoshi Ikeda: Data curation, Hiroki Sato: Data curation, Tomoki Uno: Data curation, Yoshitaka Uchida: Data curation, Tomoyuki Kimura: Data curation, Yoshito Miyata: Data curation, Kuniaki Hirai: Study design, Tetsuya Homma: Conceptualization of the study, Yoshio Watanabe: Data curation, Sojiro Kusumoto: Data curation, Shintaro Suzuki: Data curation, Issei Tokimatsu: Data curation, Akihiko Tanaka: Critical revision of the manuscript, Hironori Sagara: Conceptualization and supervision of the study

Declaration of competing interest

The authors declare no conflicts of interest (COI) to disclose.

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