【 CASE REPORT 】

Two Cases of Severe COVID-19 Pneumonia Effectively Treated with Extracorporeal Membrane Oxygenation in Addition to Favipiravir and Corticosteroid

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Abstract:

Case 1: A 65-year-old man with novel coronavirus infection (COVID-19) complicated with acute respiratory failure. On admission, the patient was started on favipiravir and corticosteroid. However, due to a lack of significant improvement, he was introduced to mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Although iliopsoas hematoma occurred as a complication, the patient recovered. Case 2: A 49-year-old man with COVID-19 had been started on favipiravir and corticosteroid. Due to progressive respiratory failure, the patient underwent mechanical ventilation and ECMO. The patient recovered without complications. We successfully treated these severe cases with a multimodal combination of pharmacological and non-pharmacological supportive therapy.

Key words: COVID-19, favipiravir, corticosteroid, extracorporeal membrane oxygenation, mechanical ventilation

Introduction

Coronavirus disease 2019 (COVID-19) was first identified in December 2019 in Wuhan, China, and has since rapidly spread globally. At present, there are few established treatments for COVID-19 with confirmed efficacy, resulting in numerous deaths.

Globally, as of August 1, 2020, 17,396,943 confirmed cases and 675,060 deaths related to COVID-19 have been reported to WHO, and the mortality rate is 3.9% (1). The overall hospital mortality rate from COVID-19 is approximately 15% to 20%, increasing to 40% among patients requiring ICU admission. By age, the hospital mortality rate is 35% for patients 70 to 79 years old and 60% for patients 80 to 89 years old (2). The mortality in COVID-19 patients who develope severe respiratory compromise and require mechanical ventilation is high.

Favipiravir obtained manufacturing and marketing approval in March 2014 for "new or re-emerging influenza virus infections (provided that other anti-influenza virus drugs were ineffective)". With regard to the mechanism of action of this drug, favipiravir taken up into cells is metabolized and converted by intracellular enzymes to become favipiravir ribofuranosyl triphosphate, which selectively inhibits viral RNA-dependent RNA polymerase. Therefore, this agent may also be effective against RNA viruses other than influenza virus, and indeed, nonclinical studies have reported its efficacy against several RNA viruses, including Ebola virus (3), Arenaviridae and Bunyaviridae (4). In an open-label, controlled trial in China, the time to viral clearance of mild to moderate COVID-19 treated with favipiravir and interferon alfa was significantly shorter than that of lobinavir ritonavir and interferon alfa (5).

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Table 1. Case 1: Laboratory Findings at the Time of Hospital Admission.

TP	6.1 g/dL	WBC	8,300 /μL
alb	2.6 g/dL	neutro	87.4 %
T-bil	0.5 mg/dL	lymph	6.9 %
AST	66 U/L	mono	5.4 %
ALT	33 U/L	eosino	0.1 %
LDH	628 U/L	Hb	16.3 g/dL
γ-GTP	27 U/L	Hct	47.5 %
CK	69 U/L	Plt	27.9 ×10^4/μL
BUN	13.8 mg/dL		
Cr	0.76 mg/dL	PT-INR	1.16
UA	4.2 mg/dL	APTT	35.8 sec
Na	136 mEq/L	D-dimer	8.8 pg/mL
K	4.8 mEq/L	fibrinogen	774 mg/dL
Cl	102 mEq/L		
glu	99 mg/dL		
CRP	24.99 mg/dL		
IgG	846 mg/dL		
IgA	157 mg/dL		
IgM	36 mg/dL		
IgE	92 mg/dL	influenza	A negative
SPA	92.8 ng/mL		B negative
SPD	221 ng/mL		
KL-6	370 U/mL		
β-D-glucan	12.0 pg/mL		
NT-proBNP	125 pg/mL		
PCT	0.20 ng/mL		

TP: thyroid peroxidase, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, CK: creatine kinase, BUN; blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, IgG: immunoglobulinG, IgA: immunoglobulin A, IgM: immunoglobulin M, IgE: immunoglobulin E, SPA: surfactant protein A, SPD: surfactant protein D, KL-6: Krebs von den Lungen, NT-proBNP: N-terminal pro-brain natriuretic peptide, PCT: procalcitonin, WBC: white blood cells, Hb: hemoglobin, Hct: hematocrit, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time

There have been several reports of the efficacy of administering corticosteroids for COVID-19 patients, although opinions on this approach were initially negative (6, 7). Corticosteroids are a viable therapeutic strategy for modulating the inflammatory response in patients with COVID-19.

The high mortality rate in severe cases is important, given the potential access to extracorporeal membrane oxygenation of venous blood, which may serve as a life-saving emergency treatment. Although the efficacy of ECMO in COVID-19 is controversial, ECMO is a proposed as a treatment option in the interim guidance document published by the WHO and interim guidance for clinical management of COVID-19 patients provided by the United States Centers for Disease Control (8).

We herein report two cases of COVID-19 in which the early introduction of ECMO was extremely effective for managing patients whose pneumonia was aggravated even under the use of favipiravir and corticosteroid.

Case Reports

Case 1

A 65-year-old Japanese man with no significant medical history developed malaise at the end of March, 2020, and eventually developed pyrexia, cough and dyspnea. He visited a local clinic 9 days later. Because the patient presented with decreased percutaneous oxygen saturation (SpO_2) and ground-glass opacities in both lungs, he was suspected of having COVID-19 pneumonia. On the same day, he was taken to our hospital by an ambulance, where he was immediately admitted. He had neither a history of close contact with COVID-19-positive patients nor any recent travel history. He was a former smoker (37.5 packs per year).

At the time of admission, the patient had no disorientation, with a body temperature of 37.5℃, blood pressure of 140/78 mmHg, pulse rate of 72 beats per minute (regular), respiratory rate of 24 breaths per minute and SpO_2 of 82% on room air. At the time of admission, a marked increase was observed in lactate dehydrogenase and C-reactive protein (CRP), being 628 U/L and 24.99 mg/dL, respectively. Although no increase was found in white blood cell count, an increased neutrophil fraction and decreased lymphocyte fraction were detected. Surfactant protein D increased to 221 ng/mL (Table 1).

At the time of hospital admission, chest radiography showed diffuse ground-glass opacities in both lungs (Fig. 1a), and plain chest computed tomography (CT) showed diffuse ground-glass opacities in nearly all layers of both lungs (Fig. 1b).

The patient was found to have progressive acute respiratory failure and started to receive high-flow nasal cannula oxygen therapy [delivery of 50 L of flow; fraction of inspired oxygen (FiO_2) of 50%]. Methylprednisolone pulse therapy (administered at 1 g/day for 3 days) was started to treat the progressive acute respiratory failure as empirical treatment for severe pneumonia and acute interstitial pneumonia. Intravenous infusion of meropenem (1 g every 8 hours) and azithromycin (500 mg every 24 hours) was started under suspicion of severe bacterial pneumonia, and continuous intravenous infusion of sivelestat (400 mg/day) was also started to treat acute respiratory distress syndrome (ARDS).

A COVID-19 real-time polymerase chain reaction (RT-PCR) test was performed, and the patient was found to be positive for COVID-19 on Day 3 of hospitalization. With the patient's consent, treatment with favipiravir was started on a compassionate-use basis. On Day 5, further progression of respiratory failure required the patient to be intubated and moved to mechanical ventilation. On the same day, venovenous (V-V) ECMO was employed for this patient with severe progressive COVID-19 pneumonia with no irreversible underlying disease because mechanical ventilation was considered insufficient to sustain the cardiorespiratory system
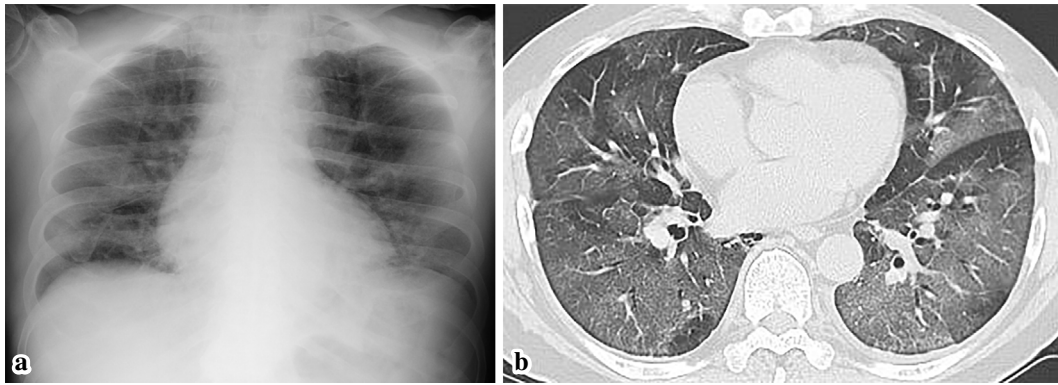
Figure 1. Case 1: Imaging findings at the time of hospital admission. (a) Chest radiography shows diffuse ground-glass opacities in both lungs. (b) Chest CT shows diffuse ground-glass opacities in nearly all layers of both lungs.

due to the patient's poor oxygenation even at an FiO_2 of 1.0. ECMO cannulae were placed in the superior and inferior vena cavae, draining blood from the right femoral vein and returning it to the right internal jugular vein after extracorporeal oxygenation with a flow of 3.0 L/min. From days 3 to 5, platelets decreased from 24.5×10^4 to 17.8×10^4/μL, fibrinogen decreased from 426 to 54 mg/dL, and D-dimer increased from 68.1 to 98.2 μg/mL. No bleeding tendency, circulatory failure due to microthrombus, or multiple organ failure was observed. Since the criteria established by the Japanese Association for Acute Medicine for disseminated intravascular coagulation (DIC) were met, we administered recombinant thrombomodulin. His oxygenation promptly improved after the start of ECMO therapy. For pulmonary protection, the mode of the mechanical ventilator was set as follows: pressure-controlled ventilation (PCV), FiO_2 of 0.35, positive end-expiratory pressure (PEEP) of 9 cmH_2O, inspiratory pressure of 7 cmH_2O and respiratory frequency of 10 per minute. After introduction of mechanical ventilation and ECMO, the patient's blood pressure decreased. Based on the echocardiographic and electrocardiographic findings, the patient was diagnosed with concurrent takotsubo cardiomyopathy, for which treatment with noradrenaline was started.

The patient's condition gradually improved in terms of inflammatory reaction and infiltrative opacities in both lungs. His blood oxygen level stabilized even when the level of oxygen received through ECMO was reduced. Therefore, he was weaned from ECMO on Day 12. He was extubated on Day 14. As an adverse event, the patient developed left iliopsoas bleed that required a number of blood transfusions, which resulted in transfusion-associated circulatory overload. The patient was re-intubated and placed on mechanical ventilation on Day 15. His condition improved after fluid management, and he was extubated again on Day 23. The radioopaque areas in the lung fields became smaller. The flow of supplemental oxygen was decreased to 1 L/min/cannula on Day 33. The patient was discharged on Day 41 (Fig. 2).

Case 2

A 49-year-old Japanese man with bronchial asthma presented with pyrexia, malaise and dyspnea at the middle of April, 2020, and visited a local clinic. Due to his poor response to any symptomatic treatments given, the patient was taken by ambulance to our hospital 3 days later. He had had close contact with his wife, who had contracted COVID-19 pneumonia. He was suspected of also having COVID-19 pneumonia based on chest CT findings and was admitted to the hospital on the same day. He had no smoking history.

At the time of admission, the patient had no disorientation, with a body temperature of 39.9℃, blood pressure of 142/88 mmHg, pulse rate of 126 beats per minute, regular, respiratory rate of 22 breaths per minute and percutaneous oxygen saturation (SpO_2) of 97% on room air, and a slight increase in CRP (0.70) was observed. Although no increase was found in white blood cell count, an increased neutrophil fraction and decreased lymphocyte fraction were noted (Table 2).

Chest radiography at admission showed nodular opacity in the right upper lobe (Fig. 3a), and plain chest CT showed numerous circular ground-glass opacities and consolidation in the right upper lobe and left lower lobe, which were most obvious around the bronchovascular bundle on the peripheral side (Fig. 3b).

Treatment was started with intravenous infusion of methylprednisolone (80 mg/day) and azithromycin (500 mg every 24 hours) to alleviate inflammation, ceftriaxone (2 g every 24 hours) in consideration of bacterial pneumonia and peramivir (600 mg/day on Day 1 and 300 mg/day from Day 2 onward) as an antiviral agent (Fig. 4). The patient showed positive results of a COVID-19 RT-PCR test on Day 3 of hospitalization when treatment with favipiravir was started. Pyrexia in the patient persisted, and respiratory failure progressed even after the initiation of favipiravir. The dose of methylprednisolone was increased to 250 mg/day from Day 6 onward. On Day 7, continuous intravenous infusion of sivelestat (400 mg/day) was started. Since the platelet count had decreased to 13.9×10^4/μL and COVID-19 often causes abnormal coagulation, intravenous infusion of recombinant thrombomodulin (32,000 U/day) was also started. The D-dimer level slightly increased to 1.8 μg/mL on Day 10 but
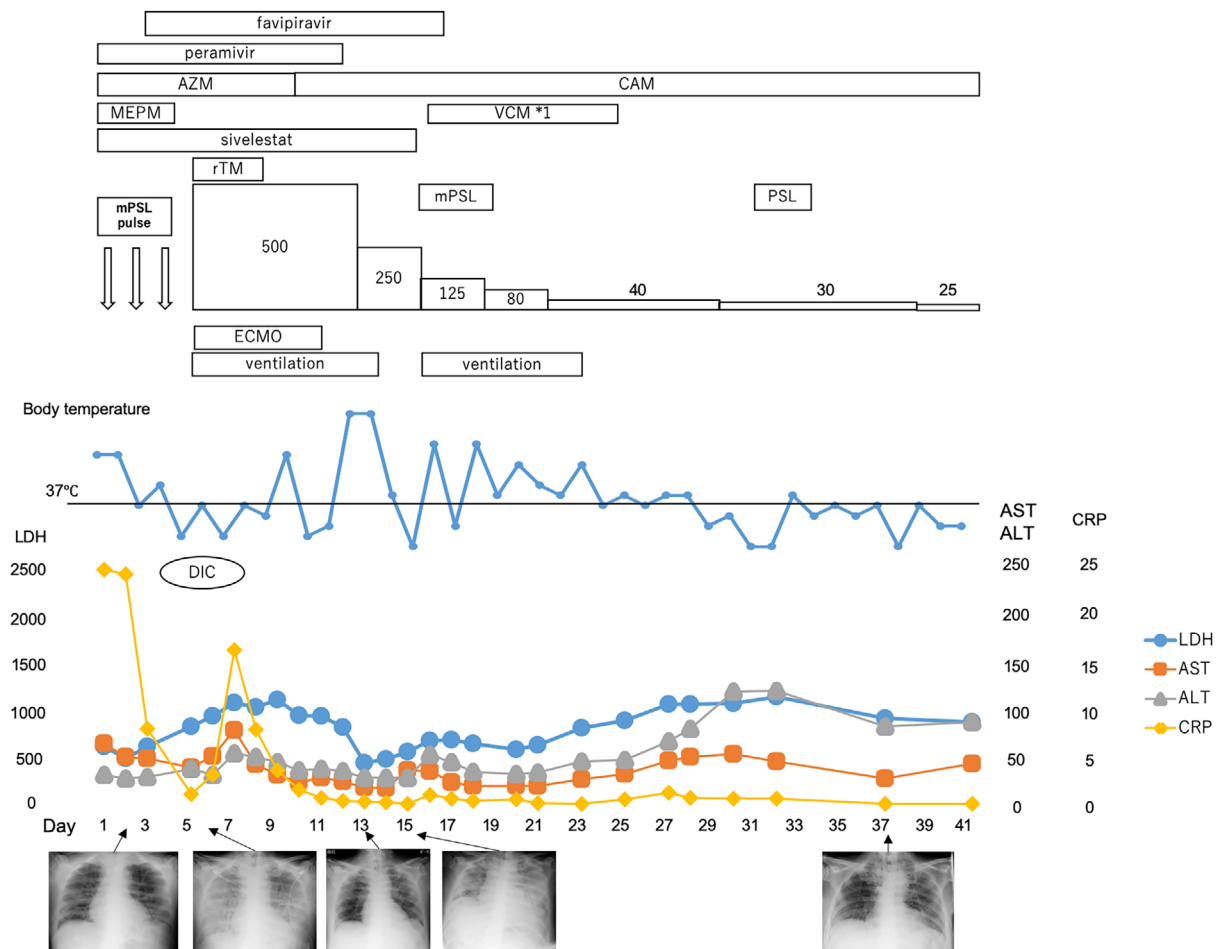
Figure 2. Case 1: Clinical course after hospital admission.

improved thereafter.

The further progression of respiratory failure necessitated noninvasive intermittent positive-pressure ventilation on Day 8 and intubation and mechanical ventilation on Day 9. On Day 10, V-V ECMO was employed for this patient with severe progressive COVID-19 pneumonia with no irreversible underlying disease and poor oxygenation, even at an FiO_2 of 1.0. ECMO cannulae were placed in the superior and inferior vena cavae, draining blood from the right femoral vein and returning it to the right internal jugular vein after extracorporeal oxygenation with a flow of 3.5 L/min. His oxygenation promptly improved after the start of ECMO therapy. For pulmonary protection, the mode of the mechanical ventilator was set as follows: PCV, FiO_2 of 0.21, PEEP of 8 cmH_2O, inspiratory pressure of 8 cmH_2O and respiratory frequency of 12 per minute.

The patient's condition gradually improved in terms of inflammatory reaction and infiltrative opacities in both lungs. His blood oxygen level stabilized even when the level of oxygen received ECMO was reduced. Therefore, he was weaned from ECMO on Day 15. He was extubated on Day 19. No ECMO-associated adverse events were observed. The patient no longer required supplemental oxygen supply on Day 23. The patient was discharged on Day 32 (Fig. 4).

Discussion

Although the majority of cases of COVID-19 result in mild, reversible symptoms, some patients develop dyspnea and hypoxemia within about a week of the onset of the disease. Wang et al. reported that 26.1% of patients hospitalized with COVID-19 pneumonia required treatment in the intensive-care unit (ICU); 61.1% of these patients in the ICU had ARDS, and the mortality rate was approximately 4.3% (9). A total of 60 patients with COVID-19 pneumonia had been admitted to our hospital as of the middle of May, 2020. Eight of these 60 patients required intubation and mechanical ventilation, including the 2 presently reported patients who also required the use of ECMO.
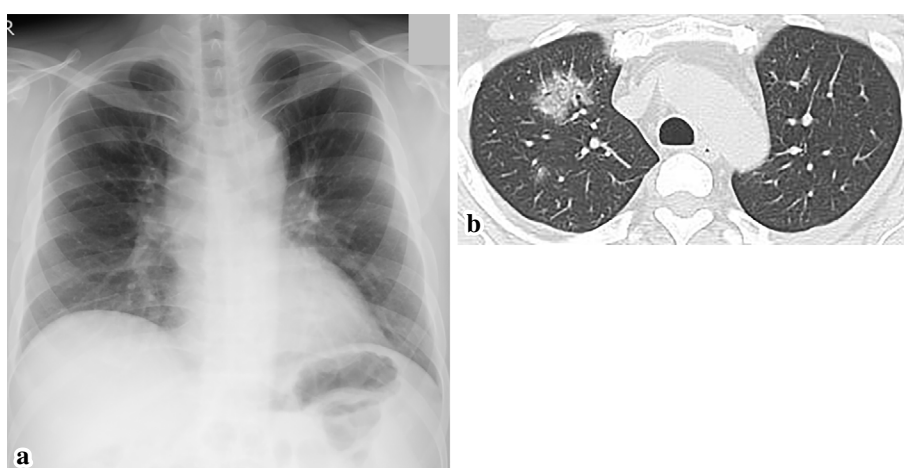
ARDS is characterized by excessive local inflammation in the lung, which can progress to an "out-of-control" state. Excessive production of mediators, such as cytokines (e.g., interleukin-6, tumor necrosis factor alpha, interleukin-8) and arachidonate metabolites (i.e., cytokine storm), interstitial lung edema caused by enhanced pulmonary vascular permeability, and diffuse alveolar damage induce a rapid decrease in oxygenation and the accumulation of carbon dioxide (10). Antiviral treatment and pharmacological and non-pharmacological supportive therapies are considered to serve

Table 2.   Case 2: Laboratory Findings at the Time of Hospital Admission.

TP	7.1 g/dL	WBC	5,500 /μL
alb	4.1 g/dL	neutro	80.6 %
T-bil	0.52 mg/dL	lymph	11.2 %
AST	22 U/L	mono	8.2 %
ALT	32 U/L	eosino	0 %
LDH	190 U/L	Hb	16.0 g/dL
γ-GTP	17 U/L	Hct	46.2 %
CK	65 U/L	Plt	20.2 ×10^4/μL
BUN	8.8 mg/dL		
Cr	0.99 mg/dL	PT-INR	1.07
UA	6.4 mg/dL	APTT	35.0 sec
Na	139 mEq/L	D-dimer	0.4 pg/mL
K	3.4 mEq/L	fibrinogen	334 mg/dL
Cl	107 mEq/L		
glu	112 mg/dL		
CRP	0.70 mg/dL		
IgG	1,186 mg/dL	influenza	A negative
IgA	297 mg/dL		B negative
IgM	37 mg/dL		
IgE	223 mg/dL	Pneumococcal urinary antigen test	negative
SPA	16.1 ng/mL		
SPD	25.6 ng/mL	Legionella urinary antigen test	negative
KL-6	165 U/mL		
β-D-glucan	5.1 pg/mL		
NT-proBNP	16 pg/mL		
PCT	0.04 ng/mL		

TP: thyroid peroxidase, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, CK: creatine kinase, BUN; blood urea nitrogen, Cr: creatinine, CRP: C-reactive protein, IgG: immunoglobulinG, IgA: immunoglobulin A, IgM: immunoglobulin M, IgE: immunoglobulin E, SPA: surfactant protein A, SPD: surfactant protein D, KL-6: Krebs von den Lungen, NT-proBNP: N-terminal pro-brain natriuretic peptide, PCT: procalcitonin, WBC: white blood cells, Hb: hemoglobin, Hct: hematocrit, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time

Figure 3.   Case 2: Imaging findings at the time of hospital admission. (a) Chest radiography shows nodular opacity in the right upper lobe. (b) Chest CT shows numerous circular ground-glass opacities and consolidation in the right upper lobe and left lower lobe, which were most obvious around the bronchovascular bundle on the peripheral side.
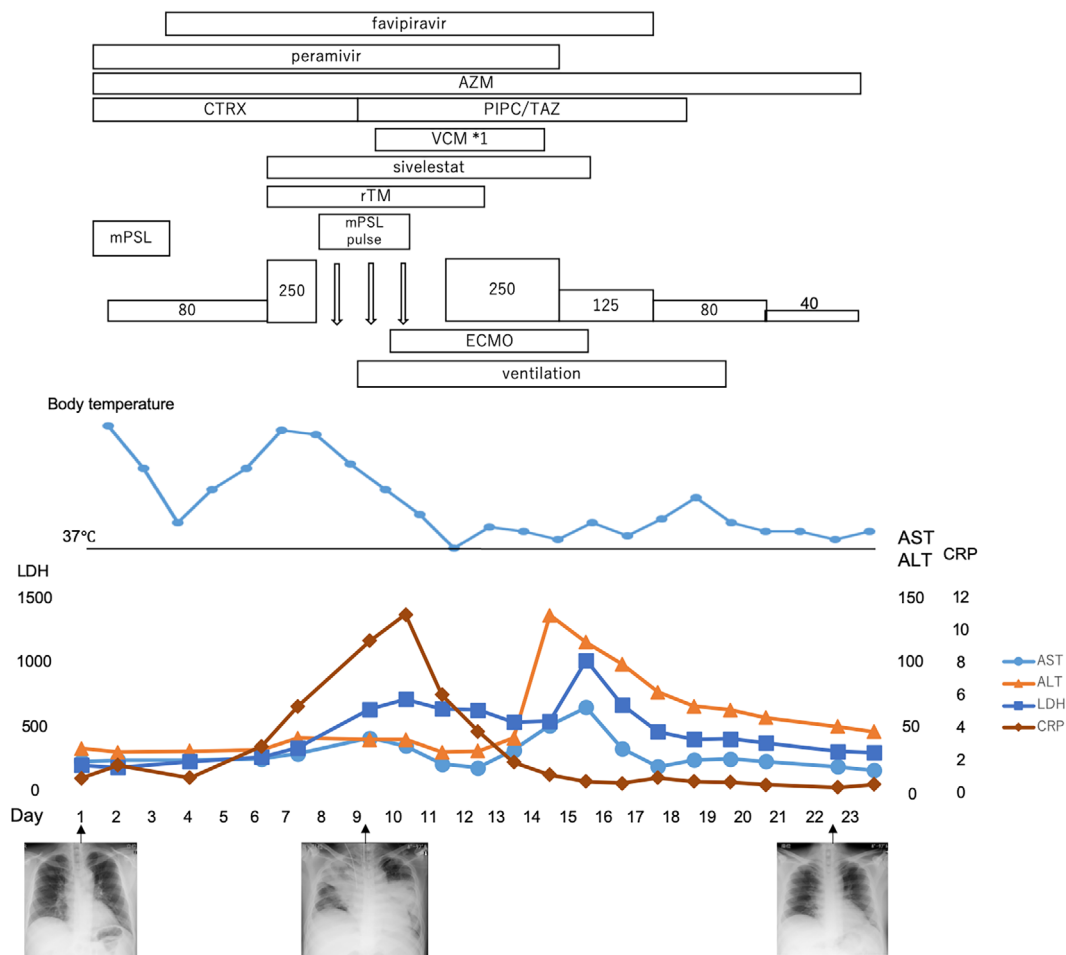
Figure 4. Case 2: Clinical course after hospital admission.

as important therapeutic strategies for COVID-19 pneumonia patients with ARDS.

It was previously reported that the fulminant activation of coagulation and consumption of clotting factors occur in severe cases of COVID-19. Inflammation of lung tissues and endothelial cells causes microthrombi formation, leading to thrombotic complications, such as deep venous thrombosis, pulmonary embolism and thrombotic arterial complications (11). T tD-dimer and fibrinogen degradation product (FDP) levels were increased in both of the present cases. Furthermore, in Case 1, the patient developed DIC and pulmonary thromboembolism despite the use of anticoagulants.

DIC in patients with COVID-19 has previously been described, and its characteristics include a lack of bleeding risk, mildly low platelet counts and elevated plasma fibrinogen levels, none of which are seen in typical DIC. Therefore, instead of DIC, these data might more closely resemble complement-mediated thrombotic microangiopathy (TMA) syndromes. Importantly, another essential aspect of DIC seen in COVID-19 is the detection of both COVID-19 and complement components in regions of TMA. Mediators of TMA syndromes overlap with those released by cytokine storm, suggesting close connections between ineffective immune responses to COVID-19, severe pneumonia and life-threatening microangiopathy (12). Although the diagnostic

criteria for DIC were met in case 1, TMA syndrome might have occurred in both cases (particularly in case 2) because of the lack of typical symptoms of DIC.

For the two cases presented in this report, favipiravir administration was started as an antiviral treatment immediately after the diagnosis of COVID-19. At a meeting of the Japanese Association for Infectious Diseases, we presented an immediate report on cases of COVID-19 pneumonia with progressive respiratory failure, for which favipiravir may have worked promptly and effectively (13). However, rapid progression of respiratory failure was observed in the patients in this report despite the initiation of treatment with favipiravir. This can be interpreted as suggesting that the clinical benefit of treatment with an antiviral agent alone is limited in patients with concurrent ARDS. At present, multiple clinical trials of favipiravir are underway in patients with mild to severe COVID-19 pneumonia. Future data from these trials may provide new insights into the drug's clinical benefits.

As a pharmacological supportive therapy, we administered methylprednisolone (an anti-inflammatory agent for inhibiting cytokine storm), sivelestat (a neutrophil elastase inhibitor) and macrolide antibiotics with an immunoregulatory function (14) effective for suppressing hyperimmunization and excessive inflammation. The World Health Organization

(WHO) has advised against the use of corticosteroids to treat COVID-19. The interim WHO guidance on the management of patients with severe acute respiratory infection caused by COVID-19 presents negative views on the use of steroids in the treatment of this patient population ("routine use of steroids should be avoided unless the patient has symptoms including bronchial asthma, aggravated chronic obstructive pulmonary disease, and septic shock") based on data from studies of steroid therapy in patients with severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) or influenza (15). However, a study by the RECOVERY Collaborative Group showed that the use of dexamethasone in hospitalized COVID-19 patients resulted in a lower 28-day mortality than in those who were solely receiving either invasive mechanical ventilation or oxygen (6). In addition, Wu et al. performed a retrospective cohort study in patients with COVID-19 pneumonia and reported that the mortality in a cohort using methylprednisolone was lower than that in a cohort not using methylprednisolone, although the number of severe cases included in the former cohort was larger than that in the latter cohort (7). In our hospital, we have actively used steroids in patients with hypoxemia and achieved good outcomes. Based on these experiences, we are considering participating in a clinical study conducted to evaluate the efficacy of steroids in patients with COVID-19 pneumonia to verify the clinical effects of steroids in this patient population. Regarding macrolides, some researchers have reported that macrolide therapy was effective for reducing mortality in patients with ARDS (16). Although the mechanism underlying this reduction in mortality has not been fully elucidated, macrolides are likely to have effects on cytokine production and the neutrophil function (16).

As non-pharmacological supportive therapy, intubation, mechanical ventilation and ECMO were employed. ECMO is a life-supporting method used in patients with severe respiratory or cardiac failure (used particularly as a resuscitative measure taken for patients in cardiopulmonary arrest), called "respiratory ECMO" and "cardiac ECMO", respectively. Respiratory ECMO is indicated for patients with reversible acute respiratory failure. Its use is considered for patients for whom conventional mechanical ventilation is insufficient for sustaining life or in whom continuous use of the mechanical ventilation system can result in irreversible damage to the lung. Respiratory ECMO is regarded as a treatment of ARDS (17). In the treatment of novel influenza A (H1N1) 2009, the results of ECMO database-based cohort studies (18, 19) and the study on conventional ventilatory support vs. ECMO for severe adult respiratory failure (CESAR study) (20) demonstrated the efficacy of ECMO therapy based on the finding that the mortality in patients using ECMO was significantly lower than that in patients not using ECMO. In a retrospective study in MERS patients with refractory respiratory failure in 2018, the use of ECMO was required as an emergency treatment. The mortality in MERS patients with refractory hypoxemia in the ECMO cohort was significantly lower than that in the non-ECMO cohort (65% vs. 100%; p = 0.02) (21). Although little evidence for the efficacy of ECMO has been obtained with respect to COVID-19 pneumonia, results from two retrospective studies have been reported. In a retrospective study by Yang et al., of 52 patients admitted to the ICU with severe COVID-19 pneumonia, 32 died within 28 days of admission. ECMO was introduced to 6 patients, of whom 5 died, while the other was still on ECMO at the time of the endpoint assessment (22). In a retrospective study by Zhang et al., 48 of 221 patients with COVID-19 pneumonia had concurrent ARDS, and 10 of these 48 patients required mechanical ventilation and ECMO therapy. Of these 10 patients, 2 were successfully treated and discharged from the hospital, and 3 died. The other five patients were still on ECMO at the time of the endpoint assessment (23). According to the interim WHO guidance, ECMO, despite little evidence for its efficacy, is regarded as an emergency treatment of COVID-19 patients who have concurrent refractory hypoxemia even after being treated with lung-protective ventilation strategy (15). The condition of the two patients in the present case report was improved by intubation, mechanical ventilation and the prompt introduction of ECMO. COVID-19 pneumonia with ARDS is associated with high mortality. Pulmonary protection initiated before obtaining clinical benefits of antiviral treatment and pharmacological supportive therapy is considered to contribute to a reduction in mortality. Concerning complications, iliopsoas hematoma was identified in Case 1. In general, hemorrhagic complications, such as cannulation site bleeding, occur in approximately 50% of patients undergoing ECMO (17). ECMO-associated bleeding, which is attributed to the effect of heparinization as well as circuit-related consumption of coagulation factors, can be severe. It may be difficult to arrest bleeding if no measures other than monitoring the patient are taken. In Case 1, although the patient required blood transfusion, bleeding was arrested during the observation of the patient's condition. Infection is another critical complication said to occur in approximately 20% of patients on ECMO (17). However, the two patients in this report were able to safely receive ECMO therapy with no ECMO-related infectious complications.

Our two patients were already suffering from severe respiratory failure at the time of the diagnosis of COVID-19. They were successfully treated by a combination of antiviral treatment with favipiravir, corticosteroid, mechanical ventilation and ECMO. The positive outcomes of these cases underscore the importance of promptly treating severe COVID-19 pneumonia after the diagnosis with non-pharmacological supportive therapy, such as mechanical ventilation and ECMO, in combination with pharmacological supportive therapy, notably favipiravir for antiviral treatment and corticosteroid for anti-inflammatory treatment.

References

1. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. [cited 2020 Aug 1]. Available from: https://covid19.who.int
2. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. Forthcoming.
3. Oestereich L, Lüdtke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral Res 105: 17-21, 2014.
4. Gowen BB, Wong MH, Jung KH, et al. *In vitro* and *in vivo* activities of T-705 against arenavirus and bunyavirus infections. Antimicrob Agents Chemother 51: 3168-3176, 2007.
5. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering. Forthcoming.
6. Horby P, Lim WS, Emberson JR, et al.; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with covid-19 - preliminary report. N Engl J Med. Forthcoming.
7. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. Forthcoming.
8. Kowalewski M, Fina D, Słomka A, et al. COVID-19 and ECMO: the interplay between coagulation and inflammation-a narrative review. Crit Care 24: 205, 2020.
9. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323: 1061-1069, 2020.
10. The Japanese Society of Intensive Care Medicine, Japanese Society of Respiratory Care Medicine, and the Japanese Respiratory Society. Clinical practice guideline for the management of acute respiratory distress syndrome (ARDS) 2016 (in Japanese).
11. Wiersinga WJ, Rhodes A, Cheng AC, et al. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. Forthcoming.
12. Merrill JT, Erkan D, Winakur J, James JA. Emerging evidence of a COVID-19 thrombotic syndrome has treatment implications. Nat Rev Rheumatol 30: 1-9, 2020.
13. The Japanese Association for Infectious Diseases [Internet]. [cited 2020 Aug 13]. Available from: http://www.kansensho.or.jp/modules/en/index.php?content_id=3.
14. Wong EH, Porter JD, Edwards MR, Johnston SL. The role of macrolides in asthma: current evidence and future directions. Lancet Respir Med 2: 657-670, 2014.
15. Clinical management of severe acute respiratory infection when novel coronavirus infection is suspected [Internet]. [cited 2020 Jun 2]. Available from: www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
16. Simonis FD, Iudibus G, Cremer OL, et al. Macrolide therapy is associated with reduced mortality in acute respiratory distress syndrome (ARDS) patients. Ann Transl Med 6: 24, 2018.
17. Brodie D, Bacchetta M. Extracorporeal membrane oxygen- ation for ARDS in adults. N Engl J Med 365: 1905-1914, 2011.
18. The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA 302: 1888-1895, 2009.
19. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA 306: 1659-1668, 2011.
20. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 374: 1351-1363, 2009.
21. Alshahrani MS, Sindi A, Alshamsi F, et al. Extracorporeal membrane oxygenation for severe Middle East respiratory syndrome coronavirus. Ann Intensive Care 8: 3, 2018.
22. Yang X, Yu Y, Shu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 8: 475-481, 2020.
23. Zhang G, Hu C, Luo L, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol 127: 104364, 2020.