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

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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 lopinavir ritonavir and interferon alfa (5).
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 (ECMO) 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.

| Table 1. Case 1: Laboratory Findings at the Time of Hospital Admission. |
|-----------------|-----------------|-----------------|
| TP              | alb             | T-bil           |
| 6.1 g/dL        | 2.6 g/dL        | 0.5 mg/dL       |
| WBC             | neutro          | lymph           |
| 8,300 /μL       | 87.4 %          | 6.9 %           |
| AST             | 66 U/L          | 628 U/L         |
| 33 U/L          | 66 U/L          | 27 U/L          |
| ALT             | mono            | Hct             |
| 5.4 %           | 16.3 g/dL       | 47.5 %          |
| LDH             | cosino          |                |
| 27 U/L          |                |                |
| γ-GTP           |                |                |
| 69 U/L          |                |                |
| CK              |                |                |
| 13.8 mg/dL      |                |                |
| BUN             |                |                |
| Cr              |                |                |
| 0.76 mg/dL      |                |                |
| UA              |                |                |
| 4.2 mg/dL       |                |                |
| Na              |                |                |
| 136 mEq/L       |                |                |
| K               |                |                |
| 4.8 mEq/L       |                |                |
| 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        |                |
| SPA             | 92.8 ng/mL      | influenza       |
| SPD             | 221 ng/mL       | A negative      |
| KL-6            | 370 U/mL        | B negative      |
| 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: immunoglobulinA, IgM: immunoglobulinM, IgE: immunoglobulinE, SPA: surfactant proteinA, SPD: surfactant protein D, KL-6: Krebs von den Lugen, 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.
due to the patient’s poor oxygenation even at an FiO₂ 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 24.5×10⁴ to 17.8×10⁴/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), FiO₂ of 0.35, positive end-expiratory pressure (PEEP) of 9 cmH₂O, inspiratory pressure of 7 cmH₂O 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 radiopaque 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°C, 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 (SpO₂) 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 13.9×10⁴/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...
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 FiO2 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, FiO2 of 0.21, PEEP of 8 cmH2O, inspiratory pressure of 8 cmH2O 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.

| Test | Value               |
|------|---------------------|
| TP   | 7.1 g/dL            |
| alb  | 4.1 g/dL            |
| T-bil| 0.52 mg/dL          |
| AST  | 22 U/L              |
| ALT  | 32 U/L              |
| LDH  | 190 U/L             |
| γ-GTP| 17 U/L              |
| CK   | 65 U/L              |
| BUN  | 8.8 mg/dL           |
| Cr   | 0.99 mg/dL          |
| UA   | 6.4 mg/dL           |
| Na   | 139 mEq/L           |
| K    | 3.4 mEq/L           |
| Cl   | 107 mEq/L           |
| glu  | 112 mg/dL           |
| CRP  | 0.70 mg/dL          |
| IgG  | 1.186 mg/dL         |
| IgA  | 297 mg/dL           |
| IgM  | 37 mg/dL            |
| IgE  | 223 mg/dL           |
| SPA  | 16.1 ng/mL          |
| SPD  | 25.6 ng/mL          |
| 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: immunoglobulin G, 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.
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). TtD-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 syndromes. 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

![Image](image_url)

**Figure 4.** Case 2: Clinical course after hospital admission.
patients with refractory hypoxemia in the ECMO cohort was refractory respiratory failure in 2018, the use of ECMO was based on the finding that the mortality in patients using SAR study) (20) demonstrated the efficacy of ECMO therapy vs. ECMO for severe adult respiratory failure (CEA (H1N1) 2009, the results of ECMO database-based cohort treatment of ARDS (17). In the treatment of novel influenza damage to the lung. Respiratory ECMO is regarded as a life-supporting method used in patients with severe respiratory failure at the time of the diagnosis of COVID-19. 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.

The authors state that they have no Conflict of Interest (COI).
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