Combination therapy with plasma exchange and glucocorticoid may be effective for severe COVID-19 infection. -A retrospective observational study

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Running title

Plasma exchange for COVID-19

Abstract

We retrospectively analyzed the characteristics and outcomes of five patients with COVID-19 who were received glucocorticoid (with or without pulse therapy) and therapeutic plasma exchange. The efficacy of the treatment was determined by whether the patient was able to be transferred from the COVID-19 exclusive ICU to the general ward. In comparing patients who received prednisolone pulse therapy (3 cases) with those who did not (2 cases), 2/3 (66%) and 0/2 (0%) patients could be discharged from the COVID-19 dedicated ICU, respectively. Among five patients who was performed plasma exchange, two elderly male patients who underwent plasma exchange as early as within 8 days of disease exacerbation survived and were able to be transferred to the general ward. This observational study indicates that plasma exchange in conjunction with methylprednisolone pulse therapy at the appropriate time may be an effective treatment for elderly patients with severe COVID-19.

Keywords

COVID-19, glucocorticoid, methylprednisolone, plasma exchange, SARS-CoV-2

Introduction

COVID-19 causes systemic symptoms such as fever, cough, and general malaise. In severe cases, it causes acute respiratory distress syndrome (ARDS) resulting in acute progressive hypoxemia and may take a fatal course. The pathogenesis of ARDS is considered to be caused by a cytokine storm that results from excessive activation of the immune system in response to a COVID-19 (1,2,3). Although the optimal treatment regimen for COVID-19 has not been established, Horby et al. reported on the efficacy of short-term dexamethasone for moderate and severe cases of COVID-19 in a recovery trial (4). This study found that mortality at 28 days was significantly lower in the dexamethasone group than in the standard care group. However, subgroup analysis showed that in severe cases of COVID-19 in patients over the age of 70, survival was low, and long-term prognosis was not shown. Plasma exchange (PE) removes high molecular weight inflammatory proteins and tissue-damaging factors such as neutrophil extracellular traps that dissolve in a patient's plasma (5). It has also been reported that viral RNA is detected in the peripheral blood in severe COVID-19 cases and that PE can also be used to remove viral RNA directly (6). We therefore decided to investigate whether combination therapy with a glucocorticoid (GC) and PE could be effective treatment in COVID-19 and tested it in several patients with severe COVID-19.

Patients and Methods

We retrospectively analyzed the characteristics and outcomes of COVID-19 patients who were received GC including pulse therapy and therapeutic plasma exchange, hospitalized at the Juntendo University Hospital, a 1,051-bed, university-affiliated hospital in Tokyo, from April 13, 2020, to September 30, 2020. All patients were positive for the SARS-CoV-2 polymerase chain reaction (PCR) test and negative for other infections. The criteria for GC administration and PE were patients with ARDS (PaO2/FiO2 ratio of less than 200) and/or labored respiration and/or tracheal intubation. PE was performed using a membrane plasma separator (Plasmaflow OP-08W (Asahi Kasei Medical Co., Ltd., Tokyo, Japan). Each PE session, we used fresh frozen plasma as the replacement fluid and 2,500–3,000 ml per time in all patients. We performed a lung protective strategy in all intubated patients and daily prone position ventilation, and continued anticoagulant therapy with heparin in all patients. We also performed a comprehensive screening of bacterial and fungal infections and used empirical antibiotics. The ethical review board of our hospital approved the use of PE for COVID-19 patients. The efficacy of PE and steroids, including pulse therapy, was assessed by the outcome of whether the patient could be transferred from the COVID-19 dedicated

ICU. Written informed consent was obtained from all patients on the basis of the Declaration of Helsinki.

Results

Five patients received steroids and PE, including pulse therapy, during the eligible observation period. Four of the five patients were male, and the median age was 76 years. All patients had some history of malignancy, hypertension, or renal failure. All patients received some GC and also PE, even if the timing was uneven. Three of the five patients received methylprednisolone pulse therapy. Two patients refused to be ventilated of their own volition, so even if they were hypoxemic, only three out of five patients were administered ventilatory management. The median number of PE performed was 6, and the median time from admission to PE was 11 days. As for apheresis besides plasma exchange, continuous hemodiafiltration (CHDF) was performed in 3 patients, and polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) was performed in 2 patients. The outcome of discharge from the dedicated ICU ward was achieved in 2 of 5 patients, both of whom received prednisolone pulse therapy. This means that two of the three patients who received prednisolone pulse therapy were discharged to the general ward, and the two patients without prednisolone pulse therapy did not achieve the outcome. In addition, the two patients who achieved the outcome started PE 6 and 7 days after admission, respectively, which was relatively early compared to the other patients. A brief summary of patient profiles and outcomes is shown in Table 1. The course of each case is described in detail as below.

Case 1

Case 1 was a 66-year-old man who was receiving peritoneal dialysis because of an IgA nephropathy. His chief complaints were fever and dyspnea at rest. His chest computed tomography (CT) scan showed diffuse ground glass opacities and consolidation on the pleural side of both lungs (Figure 1A). We performed tracheal intubation and administered methylprednisolone (mPSL) (equivalent to 1 mg/kg) to improve his ARDS. In addition, we performed hemoadsorption using PMX-DHP. We also continued CHDF using an AN69ST cytokine-absorbing hemofilter. Because his oxygenation improved, we withdrew the mPSL after 10 days. His oxygenation, however, worsened again on the 14th day in hospital, and we restarted the GCs and performed PE starting on the 17th day in hospital. However, his oxygenation worsened day by day and he died on the 29th day in hospital (Figure 1B).

Case 2

Case 2 was a 63-year-old woman with breast cancer who was treated with surgery and radiation therapy. She had a fever and cough, and her chest CT scan showed diffuse ground glass opacities (Figure 2A). She was admitted to our hospital on suspicion of radiation pneumonitis. After admission, it was found that her SARS-CoV-2 PCR test was positive. Because her oxygenation worsened, we performed tracheal intubation and started her on a mPSL (equivalent to 1 mg/kg). We also performed PMX-DHP, and the mPSL was withdrawn on the 6th day in hospital. Her oxygenation worsened, so we continued CHDF using polymethylmethacrylate (PMMA)-based dialysis and performed PE starting on the 12th day in hospital. She died on the 18th day in hospital (Figure 2B).

Case 3

Case 3 was an 84-year-old man receiving hemodialysis because of chronic renal failure. He also had a hepatocellular carcinoma and was undergoing radiofrequency ablation treatment. Two days before admission, he was febrile and subsequently tested positive in a SARS-CoV-2 PCR test. On admission, his chest CT scan showed almost no abnormalities (Figure 3A). Although his oxygenation worsened, he decided of his own free will not to be intubated. We administered intravenous mPSL (1,000 mg/day) pulse therapy for 3 days starting on his 7th day in hospital and performed PE twice. In addition, CHDF using PMMA-based dialysis was continued. His oxygenation improved temporarily, but subsequently worsened again. He received his second mPSL pulse therapy for 3 days starting on the 20th day in hospital and then a third mPSL pulse therapy for 3 days starting on the 30th day in hospital; he restarted PE every other day. However, all additional treatments were unsuccessful, and he died on the 38th day in hospital (Figures 3B and 3C).

Case 4

Case 4 was a 76-year-old man with a history of diabetes, hypertension, and prostate cancer. His chief complaints were fever, cough, and dyspnea that began 5 days before being admitted. His chest CT scan showed diffuse ground glass opacities on the pleural side of both lungs (Figure 4A). After admission, he tested positive for SARS-CoV-2 PCR test. His oxygenation worsened, and we performed tracheal intubation. We performed PE on the 5th, 6th, 7th, and 9th days in hospital. He was then extubated on the 12th day in hospital. Because his oxygenation worsened again, we performed reintubation on the 19th day in hospital (Figure 4B) and performed PE twice, but his oxygenation did not improve (Figure 4C). We added mPSL pulse therapy (mPSL 1,000 mg/day) for 3 days and continued GC treatment with prednisolone (PSL, equivalent to 1 mg/kg) after that. These GC treatments were extremely effective, with his respiratory condition improving markedly, as shown on his chest CT scans (Figure 5A). We tapered his PSL and withdrew it on the 62nd day in hospital (total GC therapy duration was 37 days). Because he showed severe dysphagia and respiratory muscle weakness, he received a tracheostomy on the 62nd day in hospital and was subsequently transferred to a general ward (Figure 5B).

Case 5

Case 5 was an 86-year-old man with a previous cerebral infarction and subdural hematoma, as well as an untreated prostate cancer. He had a fever and had a positive SARS-CoV-2 PCR test. On admission, his chest CT scan showed slightly ground glass opacities (Figure 6A). His oxygenation worsened (Figure 6B) but he decided of his own free will not to be intubated. We performed mPSL pulse therapy for 3 days starting on his 5th day in hospital, and we performed PE 7 times. We started treatment with daily PSL (equivalent to 1 mg/kg), which was gradually tapered to every 7 days. His oxygenation improved as well as his lungs, as shown on chest CT scans (Figure 6C), and he was discharged on the 46th day in hospital (Figures 6D).

Discussion

Although dexamethasone and remdesivir have been reported to be useful in the treatment of COVID-19 (4,7), it is still reported that even with multidisciplinary treatment, there is a high risk of the condition being fatal in men older than 65 years, and in patients with diabetes, hypertension, and heart disease (8). So far, numerous reports on the efficacy of PE for severe COVID-19 have been published, including case reports and case series (9,10,11,12,13).

Liu J et al reported that PE was used in 9 of 23 patients admitted to the ICU and a decrease in blood cytokines after PE (14). Gluck WL et al performed five sessions of PE over eight days in ten patients with increased oxygen demand (15). Ventilated patients also reported an average 78% improvement in PaO2/FiO2 ratio, and significant decreases in blood levels of C-reactive protein (CRP) and cytokines. These reports show that PE can removes high molecular weight inflammatory proteins and cytokines that dissolve in a patient's plasma. Although we did not evaluate major cytokines in this study, we found a decrease in CRP and an improvement in PaO2/FiO2 ratio after PE in all cases.

Dogan L et al reported that 6 of 53 patients admitted to the ICU with encephalitis symptoms were treated with PE with albumin replacement, and 4 of the 6 patients improved in consciousness, mostly after 1-3 sessions (9). Faqihi F et al reported a prospective study of 10 patients who deteriorated within 24 hours of ICU admission. 9 patients survived after 5-7 PEs (16). Khamis F et al, in a study of 31 patients with severe COVID-19, reported a higher extubation rate in 11 patients who underwent PE (17). They also reported that 28-day mortality was significantly low (0% vs. 35%). Jaiswal V et al reported that 14 intubated COVID-19 patients received only one session of PE followed by convalescent plasma (18). Ten patients were released from the ventilator at a median of 5 days after treatment. 28-day mortality was 21.4% and 28.6%, respectively. Kamran SM et al retrospectively analyzed 280 COVID-19 patients (19). 71 patients underwent PE and 209 patients did not. Propensity score matching was used to analyze each of the 45 patients with a uniform patient background. The mortality rate was zero in the 43 patients who received PE within the first 12 days, whereas the mortality rate was 17.9% (5 deaths) in the other 28 patients. These reports suggest that early PE may contribute to improved survival rate.

Gucyetmez B et al studied 73 patients with COVID-19 in 5 hospitals, divided into high d-dimer ($\geq$2 mg/L) group (53 patients) and low d-dimer group (20 patients) (20). The high d-dimer group was further divided into two groups: those who received PE (18 patients) and those who did not (35 patients). The median day for the starting PE was three. Among the high d-dimer group, the mortality rate was 16.7% in the group receiving PE and 45.7% in the group not receiving PE, which was more pronounced after propensity score matching (8.3% and 58.3%, respectively). In COVID-19 patients, it has been known that abnormal blood coagulation occurs because of damage to vascular endothelial cells and an abnormal coagulation system, and prevention of thrombosis using anticoagulation therapy determines prognosis (21,22,23). This report suggests that correcting the coagulation system to a normal state and removing substances that cause excessive inflammation by performing apheresis may be an effective treatment.

Thus, these reports show that the efficacy of PE in patients with severe COIVD-19, and the efficacy seems to be higher when the treatment is administered early after an exacerbation. In addition, the possibility of directly removing SARS-CoV-2 from the bloodstream by apheresis has been speculated (24). Further investigation is needed to determine why PE is shown to be effective in the treatment of severe COVID-19 and what characteristics of patients should be treated with PE. Furthermore, the results of a prospective randomized controlled trial, which is currently underway to provide evidence for the efficacy of PE, are also awaited (25,26,27,28,29,30).

The efficacy of CRRT in patients with acute kidney injury and hypercytokinemia has also been reported (31), however, results have been inconsistent. Similarly, in our observation, the efficacy of CHDF and PMX-DHP has not been clearly demonstrated. In case 1 and 3, CHDF was performed during hospitalization because of chronic renal failure, and in case 2, blood purification with PMMA membrane was performed to adsorb cytokines as part of multidisciplinary treatment, but the improvement in oxygen demand was not clear. We also performed one to three sessions of PMX-DHP as part of our multidisciplinary treatment. There are some reports that PMX-DHP was effective in treating severe COVID-19 (32,33,34), but further investigation is needed. In this observation, two patients who were able to be transferred from the COVID-19 ICU to the general ward both showed a rapidly increasing oxygen demand and exacerbation on chest CT within a few days after admission. However, early treatment (within 8 days after admission) with multidisciplinary therapy combining steroid pulse therapy and PE improved the condition and reduced the oxygen demand.

The use of GCs against ARDS in COVID-19 has been controversial, and the World Health Organization did not initially recommend its use. In contrast, some studies suggested that GCs were effective (35), and COVID-19's Surviving Sepsis Campaign Guidelines somewhat recommended it for severe cases (36). Currently, the effectiveness of GCs has been demonstrated (4), and it has become the standard treatment worldwide. As of December 2020, however, there are no randomized controlled trials comparing GC types, doses, and durations. In this study, all survivors were over 70 years old, which was older than patients in the recovery trial (4). Our retrospective, single-center, small case study suggests that the combination of GC including steroid pulse therapy and membrane-based PE administered at an early and appropriate time may be effective even in severe cases in elderly COVID-19 patients who have a history of hypertension, diabetes, and cerebrovascular disease.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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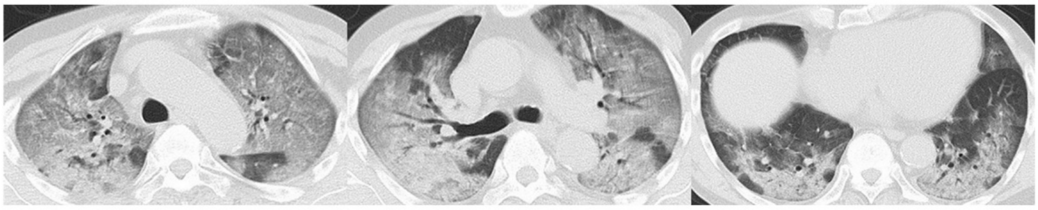
Table1

	Case1	Case2	Case3	Case4	Case5
Age	66	63	84	76	86
sex	M	F	M	M	M
Underlying health condition	IgA nephropathy on peritoneal dialysis	Breast cancer	Cronic renal failure on hemodialysis Liver cancer	diabetes hypertension Prostate cancer	Cerebral infarction Subdural hematoma prostate cancer
Steroid pulse(mPSL 1000mg/d)	No	No	Yes	Yes	Yes
Maximum daily steroids dose without pulse	mPSL 60mg	mPSL 50mg	PSL60mg	PSL50mg	PSL60mg
Other medication	Nafamostat mesilate Hydroxychloroquine Gamma-globulin	Hydroxychloroquine	Remdesivir Favipiravir Ciclesonide	Remdesivir Favipiravir Ciclesonide Gamma-globulin	Favipiravir
Intubation	Yes	Yes	No	Yes	No
Time from onset to admission(days)	probably 14	7	probably 7	probably 11	probably 2
Time from admission to PE(days)	17	12	11	5	8
Total times of PE	6	3	5	6	7
Other theraeutic apheresis	CHDF PMX-DHP	CHDF PMX-DHP	CHDF		
Outcome（transferred from ICU）	No	No	No	Yes	Yes
Time from admission to outcome(days)	died on the 29th days	died on the 18th days	died on the 38th days	62	40

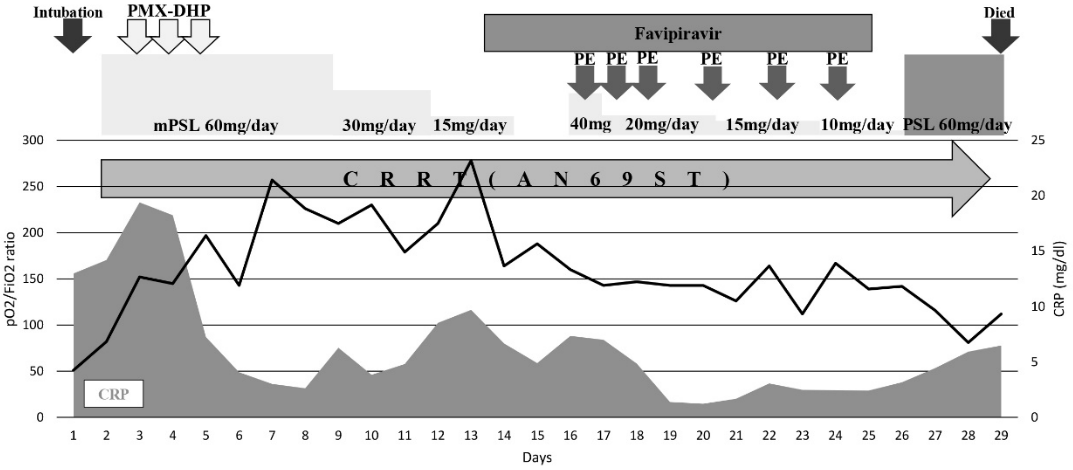
CHDF: continuous hemodiafiltration, mPSL: methylprednisolone, PE: plasma exchange, PMX-DHP: polymyxin B-immobilized fiber column direct hemoperfusion, PSL: prednisolone

Fig1

A



B



Intubation
PMX-DHP
Favipiravir
Died
PE
PE
PE
PE
PE
PE
mPSL 60mg/day
30mg/day
15mg/day
40mg
20mg/day
15mg/day
10mg/day
PSL 60mg/day
CRRT(AN69ST)
pO2/FiO2 ratio
CRP (mg/dl)
CRP
Days

Fig2

A

B

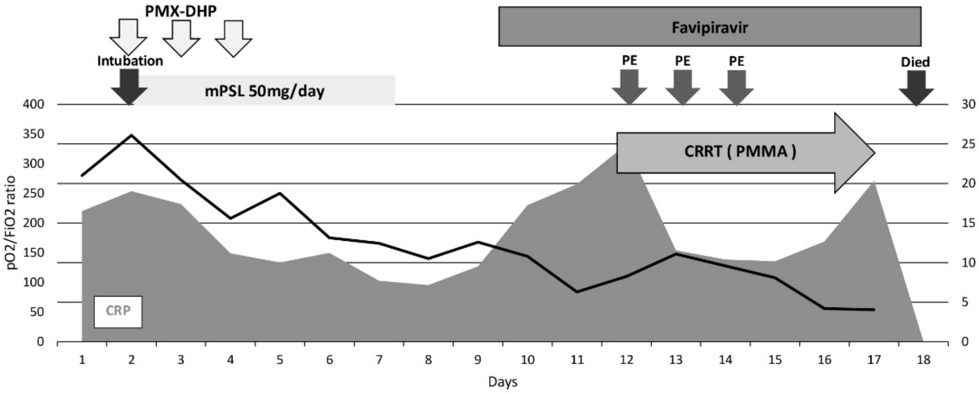
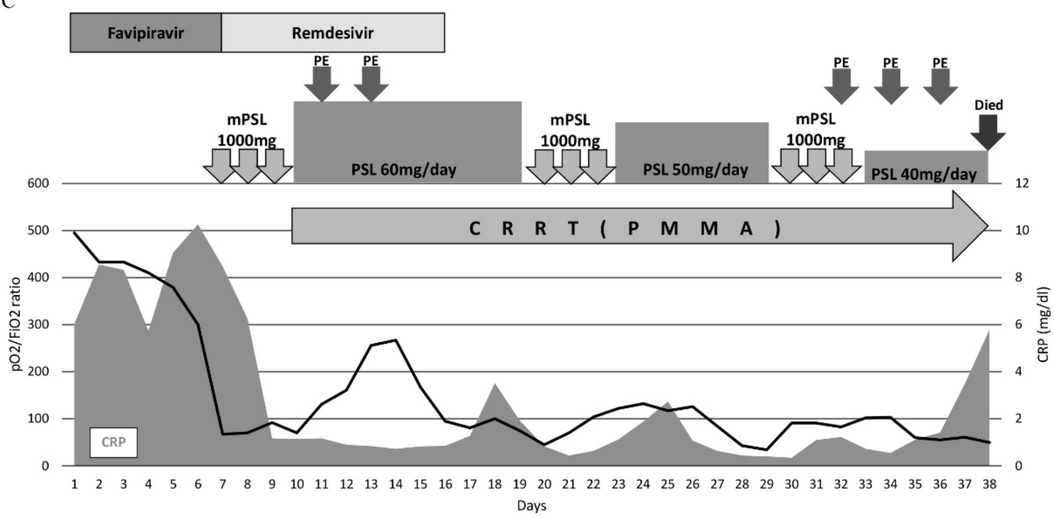

PMX-DHP
Intubation
mPSL 50mg/day
Favipiravir
PE
PE
PE
Died
CRRT (PMMA)
CRP
pO2/FiO2 ratio
CRP (mg/dl)
400
350
300
250
200
150
100
50
0
30
25
20
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Days

Fig3

A

B

C



Favipiravir
Remdesivir
PE
PE
PE
PE
PE
mPSL
1000mg
PSL 60mg/day
mPSL
1000mg
PSL 50mg/day
mPSL
1000mg
PSL 40mg/day
Died
C R R T (P M M A)
CRP
pO2/FiO2 ratio
CRP (mg/dl)
Days
0
100
200
300
400
500
600
0
2
4
6
8
10
12
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38

Fig4

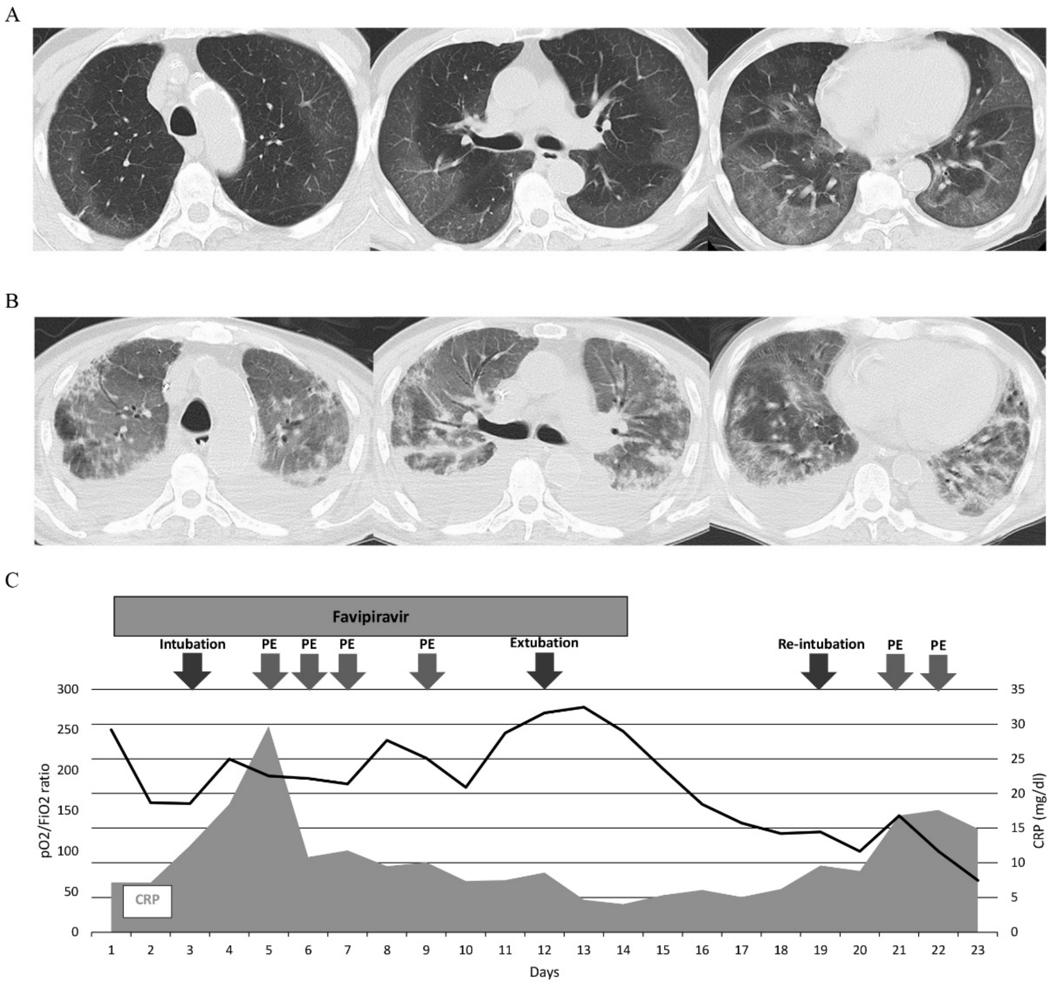
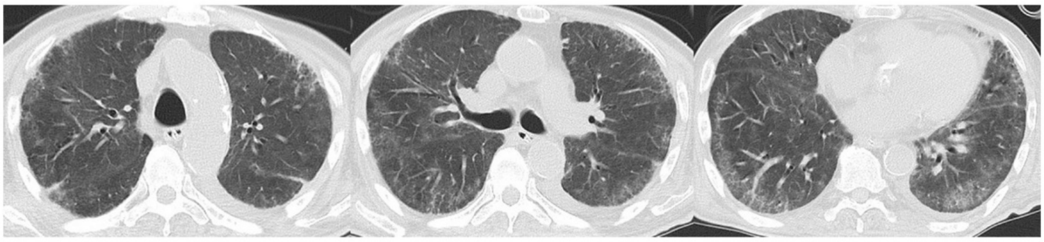

A
B
C
Favipiravir
Intubation
PE
PE
PE
PE
Extubation
Re-intubation
PE
PE
300
250
200
150
100
50
0
pO2/FiO2 ratio
35
30
25
20
15
10
5
0
CRP (mg/dl)
CRP
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Days

Fig5

A



B

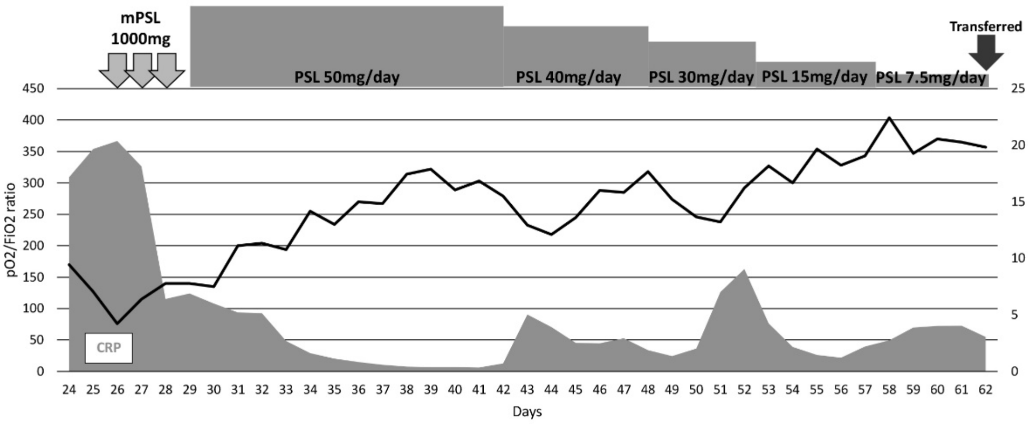
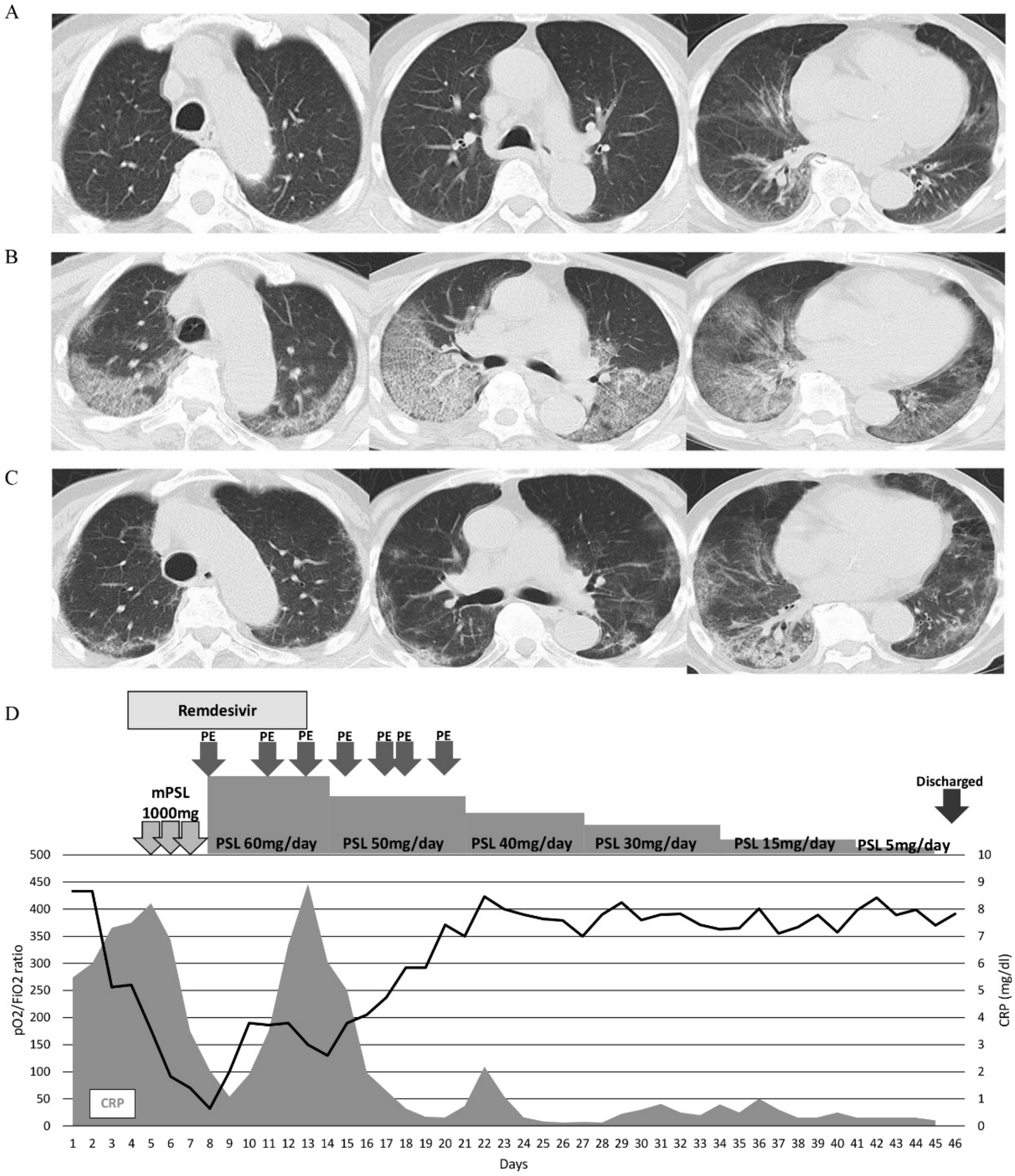

mPSL
1000mg
PSL 50mg/day
PSL 40mg/day
PSL 30mg/day
PSL 15mg/day
PSL 7.5mg/day
Transferred
pO2/FiO2 ratio
CRP (mg/dl)
CRP
Days

Fig6



A
B
C
D
Remdesivir
PE
PE
PE
PE
PE
PE
PE
mPSL
1000mg
PSL 60mg/day
PSL 50mg/day
PSL 40mg/day
PSL 30mg/day
PSL 15mg/day
PSL 5mg/day
Discharged
pO2/FiO2 ratio
CRP (mg/dl)
CRP
Days

Figure legends

Fig1

Course of hospitalization and chest computed tomography(CT) findings in Case 1.

A: Chest CT scans at the time of admission showing diffuse ground glass opacities and consolidation on the pleural side of both lungs.

B: Clinical and treatment course.

CRP:C-reactive protein, CRRT:continuous renal replacement therapy, mPSL:methylprednisolone, PE:plasma exchange, PMX-DXP:polymyxin B-immobilized fiber column direct hemoperfusion, pO2/FiO2 ratio:partial pressure arterial oxygen and fraction of inspired oxygen

Fig2

Course of hospitalization and chest computed tomography(CT) findings in Case 2.

A: Chest CT scans at the time of admission showing diffuse ground glass opacities and consolidation on the pleural side of both lungs.

B: Clinical and treatment course.

CRP:C-reactive protein, CRRT:continuous renal replacement therapy, mPSL:methylprednisolone, PE:plasma exchange, PMMA:polymethylmetacrylate, PMX-

DXP:polymyxin B-immobilized fiber column direct hemoperfusion, pO2/FiO2 ratio:partial pressure arterial oxygen and fraction of inspired oxygen

Fig3

Course of hospitalization and chest computed tomography(CT) findings in Case 3.

A: Chest CT scans at the time of admission showing few abnormalities.

B: Chest CT scans taken on the 34th day in hospital showing deterioration on both sides of the lung.

C: Clinical and treatment course.

CRP:C-reactive protein, CRRT:continuous renal replacement therapy, mPSL:methylprednisolone, PE:plasma exchange, PMMA:polymethylmetacrylate, PMX-DXP:polymyxin B-immobilized fiber column direct hemoperfusion, pO2/FiO2 ratio:partial pressure arterial oxygen and fraction of inspired oxygen

Fig4

Course of hospitalization and chest computed tomography(CT) findings in Case 4 (first half).

A: Chest CT scans at the time of admission showing diffuse ground glass opacities on the pleural side of both lungs.

B: Chest CT scans just before reintubation showing marked deterioration of both lungs

C: Clinical and treatment course of the first half.

CRP:C-reactive protein, PE:plasma exchange, pO2/FiO2 ratio:partial pressure arterial oxygen and fraction of inspired oxygen

Fig5

Course of hospitalization and chest computed tomography(CT) findings in Case 4 (second half).

A: Chest CT scans on the 62nd day in hospital showing improvement in both lungs.

B: Clinical and treatment course of the second half.

CRP:C-reactive protein, PE:plasma exchange, pO2/FiO2 ratio:partial pressure arterial oxygen and fraction of inspired oxygen

Fig6

Course of hospitalization and chest computed tomography(CT) findings in Case 5.

A: Chest CT scans at the time of admission showing slight ground glass opacities in both lungs.

B: Chest CT scans taken on the 7th day in hospital showing deterioration on both sides of the lung.

C: Chest CT scans taken on the 35th day in hospital showing improvement.

D: Clinical and treatment course.

CRP:C-reactive protein, mPSL:methylprednisolone, PE:plasma exchange, pO2/FiO2 ratio:partial pressure arterial oxygen and fraction of inspired oxygen