



# Three coronavirus disease 2019 cases with acute progression of respiratory failure were improved after methylprednisolone therapy

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**Abstract:** The main target of anti-inflammatory drug therapies for coronavirus disease 2019 (COVID-19) is reducing the risk of acute respiratory distress syndrome (ARDS), an important risk factor for acute death. In the RECOVERY trial, 6 mg/day of dexamethasone for up to 10 days improved 28-day mortality compared with those who received usual care alone. Here, we present three COVID-19 cases who improved after treatment with methylprednisolone (MPSL) and/or following prednisolone (PSL) for acute progression of respiratory failure. Three male COVID-19 patients, aged 56, 84, and 49 years old, developed acute respiratory failure after admission. MPSL therapy (500 mg/day for 3 days) was started for these patients at 4, 4, and, 2 days after admission, respectively, when oxygen administration was required. Following this therapy, two of the three present cases received 30 or 40 mg/day of PSL for an additional 6 and 8 days, respectively. The remaining case discontinued corticosteroid after MPSL therapy. All three cases survived, had fever reduction at 6, 2, and 1 days after start of MPSL therapy, could discontinue oxygen therapy at 6, 6, and 11 days after start of MPSL therapy, and showed negative results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction at 8, 6, and 22 days after start of MPSL therapy, respectively. No serious side effects due to drug discontinuation of treatment for COVID-19 were observed. MPSL is a candidate drug for corticosteroid therapy for COVID-19. Corticosteroid therapy should be started in the early stage of respiratory failure. Optimal drug selection, timing of intervention, dose, and duration of corticosteroid therapy for COVID-19 should be analyzed in the further studies.

**Keywords:** Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); pneumonia; acute respiratory distress syndrome (ARDS); methylprednisolone (MPSL)

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## Introduction

An outbreak of viral pneumonia termed coronavirus disease 2019 (COVID-19), the causative agent of which is the novel pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China in December 2019. Following this, the illness rapidly spread globally (1). Development of acute respiratory distress syndrome (ARDS) is an important risk factor for acute death in patients with COVID-19 (1-3). Wu *et al.* found that 44 of 84 (52.4%) patients who developed ARDS attributable to COVID-19 died (2). SARS-CoV-2 infection is believed to dampen antiviral interferon responses via endosomal RNA receptors, such as Toll-like receptor 3 (TLR3), TLR7, and retinoic acid-inducible gene-1/melanoma differentiation-associated gene 5, resulting in uncontrolled viral replication and hyperproduction of pro-inflammatory cytokines (4). This insufficiency of the innate immune response may cause cytokine storms and promote the development of ARDS in patients with COVID-19. Recently, it was suggested that rare putative loss-of-function variants of X-chromosomal TLR7 that are associated with impairment of type I and II interferon responses were identified in severe COVID-19 patients (5). Immunosuppressive therapy had been considered to prevent cytokine storms and deterioration of COVID-19 (6), but treatment with corticosteroids (CS) against ARDS caused by SARS-CoV or Middle East respiratory syndrome (MERS-CoV) has not been recommended because of delayed clearance of virus RNA from respiratory tract secretions (7). A meta-analysis that was dominated by observational studies suggested that CS therapy for SARS-CoV-2, SARS-CoV, and MERS-CoV infections resulted in delayed virus clearance and did not improve survival, hospitalization duration, or the intensive care unit admission rate and/or mechanical ventilator use (8). However, some studies suggested that the time to SARS-CoV-2 RNA clearance was not different between patients treated with or without CS therapy (9,10). The RECOVERY trial, a controlled, open-label trial, compared mortality rates between patients with COVID-19 who received oral or intravenous dexamethasone (DEX, at a dose of 6 mg once daily) for up to 10 days or usual care alone. The primary outcome, the 28-day mortality rate, was lower among patients who received DEX compared with those who received usual care only (11). Treatment with anti-inflammatory drug candidates other than CS, including tocilizumab, hydroxychloroquine, and azithromycin has not improved mortality of COVID-19 cases in clinical trials

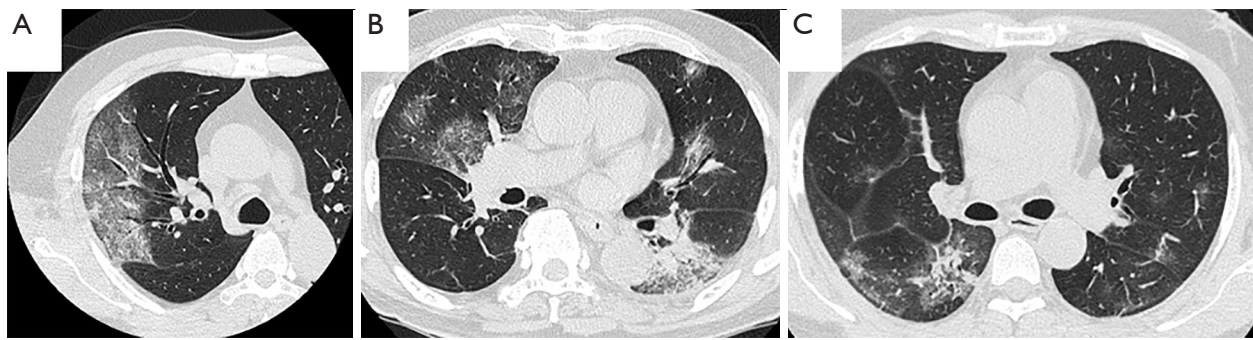
(12,13). To date, the only drugs with evidence of efficacy against COVID-19 are CS. This fact contrasts with the results of a meta-analysis among patients with influenza, showing that CS increased mortality (14). One of the conveniences of DEX therapy compared with other CS is its lower cost. However, the efficacy of CS therapy other than DEX for COVID-19 has not been sufficiently clarified by clinical trial. In addition, it is necessary to discuss the optimal drug selection, timing of intervention, dose, and duration of CS therapy for COVID-19. We present three cases who suffered rapid respiratory failure progression due to COVID-19 but improved after methylprednisolone (MPSL) and discuss these issues in the present case report.

We obtained written informed consent for publication from the patients and received specific approval for all procedures from the Institutional Review Board of our hospital, in accordance with the ethical standards of the Helsinki Declaration of 2013 for therapy without insurance. We present the following case in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/jxym-21-5>).

## Case presentation

### Case 1

A 56-year-old Japanese man visited our hospital with a cough and fever of over 38 °C over three days. He was suspected of having COVID-19 pneumonia and was admitted to our hospital. Chest high resolution computed tomography (HRCT) images at admission of this patient and the following two cases reported herein are shown in *Figure 1*. Chest HRCT images revealed ground-glass attenuation (GGA) in the right lung. At this time, we started treatment with hydroxychloroquine (400 mg/day) and azithromycin (500 mg/day) after admission. On day 3 after admission, he was officially diagnosed with COVID-19 pneumonia based on a positive result from the third of triplicate SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) assays. The patient's complications included hypertension and diabetes mellitus (DM), and those diseases activity were stabilized by receiving drug therapy or diet remedy. He had a smoking history of 16 packs/year. The characteristics and outcomes of this patient and the two following cases are shown in *Table 1*. This patient's vital signs on admission were as follows: respiratory rate, 18 breaths/min; SpO<sub>2</sub>, 98% (room air); heart rate, 90/min; blood pressure, 114/65 mmHg; and body temperature, 38.8 °C. Auscultation revealed no



**Figure 1** Chest high-resolution CT images of the patients at admission. (A) A high-resolution CT image at the pulmonary window on admission of Case 1 demonstrated coalescent ground-glass attenuation (GGA) with patchy consolidation in the middle to peripheral zone of the right upper lobe. (B) HRCT image of Case 2 showed GGA and consolidation in the bilateral lungs. (C) HRCT image of Case 3 demonstrated consolidation in the right lower lobe. Patchy GGA was also evident in the bilateral lungs.

abnormal respiratory or heart sounds. Hematology and other laboratory examinations showed elevated levels of C-reactive protein (CRP; 15.4 mg/dL), lactate dehydrogenase (LDH; 226.0 IU/mL), ferritin (1,066.6 pg/mL), and interleukin (IL)-6 (41.5 pg/mL). Change of chest radiograph in Case 1 is shown in *Figure 2*. On post-admission day 4, his condition deteriorated; inflammatory markers were elevated, and HRCT images revealed progressed pulmonary infiltration. He required oxygen inhalation of 5 L/min via a reservoir mask and received 500 mg/day of MPSTL for 3 days followed by 30 mg/day of prednisolone (PSL) based on his diagnosis of COVID-19 with deterioration. After this therapy, his disease activity was improved, and both oxygen and CS therapy were discontinued on post-admission days 9 and 12, respectively. No serious side effects due to CS were observed. We confirmed that the results from RT-PCR assays for SARS-CoV-2 were negative on post-admission days 11 and 13. On day 14, we discontinued treatment with hydroxychloroquine, and the patient was discharged.

### Case 2

An 84-year-old Japanese man presented to his local hospital 13 days after his son's onset of COVID-19 with a fever of 38.3 °C and chills. Chest HRCT images showed GGA in the right lung, and laboratory findings showed elevated inflammation markers, so he was suspected of having COVID-19 and was admitted to our hospital. On post-admission day 2, he was officially diagnosed with COVID-19 pneumonia based on the SARS-CoV-2 RT-PCR results from a sputum sample. The patient's complications included hypertension and DM, and those

diseases activity were stabilized by receiving medical therapy or diet remedy. He had a smoking history of 36 packs/year. His vital signs on admission were as follows: respiratory rate, 16 breaths/min; SpO<sub>2</sub>, 98% (room air); heart rate, 64 beats/min; blood pressure, 144/79 mmHg; and body temperature, 38.3°C. Auscultation revealed no abnormal respiratory or heart sounds. Hematology and other laboratory examinations showed a slight increase in the levels of CRP (5.9 mg/dL), LDH (187.0 IU/mL), ferritin (371.8 pg/mL), and IL-6 (17.5 pg/mL). On day 2, we started treatment with hydroxychloroquine (400 mg/day) and azithromycin (500 mg/day). On day 4, the patient's oxygen saturation decreased to 91%, and pulmonary infiltration on HRCT progressed to consolidations in both lungs, so he was treated with 500 mg/day of MPSTL for 3 days. After this therapy, his disease activity was improved, and CS therapy and oxygen therapy were discontinued on post-admission days 6 and 9, respectively. No serious side effects due to CS were observed. After RT-PCR testing for SARS-CoV-2 produced negative results on days 9 and 10, we discontinued treatment with hydroxychloroquine, and the patient was discharged on post-admission day 10.

### Case 3

A 49-year-old Japanese man visited our hospital because of general fatigue, dyspnea, and a fever of over 38 °C that had lasted for 8 days. HRCT images showed patchy GGA with consolidation in the bilateral lungs. The patient's complications included DM, hypertension, chronic kidney disease, and an old cerebral infarction, and receiving medical therapy for DM and hypertension, and those diseases

**Table 1** Patient characteristics and outcomes

	Case 1	Case 2	Case 3
Age, y	56	84	49
Gender	Male	Male	Male
Risk factor of aggravation of COVID-19	DM, Hypertension, Smoker	DM, Hypertension, Smoker	DM, Hypertension, Old cerebral infarction
Term of CS therapy*	Nine days, from day 4 to day 12 after admission	Three days from day 4 to 6 after admission	Eleven days from day 2 to 12 after admission
Initiation drug of CS therapy	Methylprednisolone of 500 mg for 3 days	Methylprednisolone of 500 mg for 3 days	Methylprednisolone of 500 mg for 3 days
Drug after MPSL	PSL of 30 mg/day	None	PSL of 40 mg/day
Pretreatment	HCQ of 400 mg/day AZM of 500 mg/day	HCQ of 400 mg/day AZM of 500 mg/day	HCQ of 400 mg/day AZM of 500 mg/day
Clinical data at admission			
Body temperature (°C)	38.8	38.3	38.6
O <sub>2</sub> saturation (%)	98	98	94
O <sub>2</sub> administration	Room air	Room air	5 L/min by cannula
CRP, mg/dL	15.4	5.9	10.7
LDH, IU/L	226.0	187.0	502.0
Ferritin, pg/mL	1,066.6	371.8	1,134.2
Interleukin-6, pg/mL	41.5	17.5	9.0
Clinical data at start of CS therapy			
Body temperature (°C)	38.7	39.6	39.9
O <sub>2</sub> saturation (%)	94	91	93
O <sub>2</sub> administration	5 L/min by reservoir mask	2 L/min by cannula	10 L/min by reservoir mask
CRP mg/dL	27.3	14.9	10.7
LDH IU/L	226.0	227.0	502.0
Ferritin pg/mL	1,066.6	927.3	1,134.2
Outcome			
Term from start of MPSL therapy, day			
Oxygen therapy	6	6	11
Fever ( $\geq 37.0$ °C)	6	2	1
To SARS-CoV2 PCR Conversion	8	6	22
Alive or died	Alive	Alive	Alive

\*, Day 0 was set. COVID-19, corona virus disease-2019; CS, corticosteroid; MPSL, methylprednisolone; PSL, prednisolone; DM, diabetes mellitus; HCQ, hydroxychloroquine; AZM, azithromycin.



**Figure 2** Change of chest radiograph of Case 1. (A) Chest radiograph in an anteroposterior sitting position at admission revealed infiltration in the outer zone of the right upper lung field. (B) On day 4, chest radiograph showed widespread infiltration in the right upper lobe. New infiltrations appeared on the periphery of the left lung. (C) On day 14, pulmonary infiltration was improved to focal wedge-shaped shadow.

activity were stabilized by receiving drug therapy or diet remedy. He reported that he had never smoked. His vital signs on admission were as follows: SpO<sub>2</sub>, 93% at 5 L/min of O<sub>2</sub> by nasal cannula; heart rate, 111 beats/min; blood pressure, 161/100 mmHg; and body temperature, 38.6 °C. Auscultation revealed no abnormal respiratory or heart sounds. Hematology and other laboratory examinations showed a slight increase in the levels of CRP (10.7 mg/dL), LDH (502.0 IU/mL), ferritin (1134.2 pg/mL), and IL-6 (9.0 pg/mL). COVID-19 was suspected, and we started treatment with hydroxychloroquine (400 mg/day) and azithromycin (500 mg/day). On day 2, his SARS-CoV-2 RT-PCR results were positive. The same day, the patient's oxygenation was further reduced, so he received 500 mg/day of MPSTL followed by 40 mg/day of PSTL with a subsequent taper. His oxygenation improved remarkably, and the oxygen and CS therapy were both discontinued on post-admission day 12. On post-admission day 19, we discontinued treatment with hydroxychloroquine, and the patient was relocated to another hospital to continue treatment. No serious side effects due to CS for COVID-19 were observed. After RT-PCR testing for SARS-CoV-2 produced negative results on post-admission days 23 and 25, the patient was discharged.

## Discussion

In the present case series, patients were treated with MPSTL but not DEX, which improved mortality of COVID-19 patients in the RECOVERY trial. Most ongoing trials of CS therapies against COVID-19 suspended enrollment because

benefit of DEX therapy was clarified in the RECOVERY trial (15). A meta-analysis of seven randomized controlled trials (RCTs) of CS therapy for COVID-19 demonstrated that CS, including MPSTL, hydrocortisone (HC), and DEX, reduced mortality at 21, 28 or 30 days compared to usual care or placebo [odds ratio, 0.66; 95% confidence interval (CI), 0.53–0.82] (15). A phase IIIb RCT suggested that short course MPSTL therapy for COVID-19 patients reduced mortality in cases over 60 years of age but not in the overall population (10). In a retrospective study in Wuhan, MPSTL therapy decreased the risk of death among patients with COVID-19-associated ARDS (hazard ratio, 0.38; 95% CI, 0.20–0.72) (2). Among 11 Japanese cases with COVID-19 who required oxygen inhalation in a previous report, 10 (91%) cases responded well to treatment with MPSTL and favipiravir, requiring no further oxygen supplementation or ventilator management (16). Therefore, we believe that the efficacy of MPSTL therapy for COVID-19 is reproducible and can be generalized to other populations. MPSTL therapy has often been selected for severe respiratory failure empirically in clinical practice in Japan because of the reported therapeutic effects of 0.5–2.5 mg/kg of MPSTL for ARDS patients of various etiologies (17,18). The difference in efficacy of between MPSTL and other corticosteroids is unclear, as no prospective controlled studies compared efficacy of each corticosteroids. This issue should be analyzed in the further clinical trial.

The optimal timing of CS therapy intervention has not been established. In the RECOVERY trial, DEX therapy improved mortality among patients who received either invasive mechanical ventilation or oxygen alone

at randomization, but not among patients receiving no respiratory support (11). Conversely, the meta-analysis of CS therapy for COVID-19 showed that patients who received mechanical ventilation or vasoactive medication tended to have lower mortality than those who did not (15). In a previous report of Japanese COVID-19 cases, treatment with MPSL and favipiravir was started when patients had a blood oxygen saturation  $\leq 93\%$  on room air or required oxygen inhalation (16). All three present cases were also started on MPSL therapy immediately when oxygen administration was required. Thus, CS therapy should be started in the early stage of respiratory failure. In addition, early intervention with CS is required in cases with aggravating risk factors such as older age, complicating DM, hypertension, or malignant diseases (2,3).

The optimal dose and duration of CS therapy has not been assessed in previous studies and higher dose CS therapy had not been proven to be more beneficial than lower dose CS therapy (15). The present cases were treated with 500 mg/day of MPSL for 3 days followed by case-specific maintenance PSL therapy for 3–11 days and no serious side effects due to CS that cause drug discontinuation were observed. In previous studies, COVID-19 patients were treated with 500 mg/day of MPSL for 3 days or 80 mg/day for 3–5 days (10,15,16). High-dose and long-term administration of CS can cause side effects such as infections. Meta-analysis of COVID-19 patients showed that administration of CS did not increase risk of serious of adverse events (15).

The combination therapies of inhibitors of virus replication such as favipiravir, remdesivir and CS, which are anti-inflammatory drugs, may show an efficient therapeutic effect on COVID-19, but this has not yet been sufficiently analyzed (16,19,20). Efficacy of these combination therapies as well as the successful case report of treatment with MPSL and favipiravir in a Japanese COVID-19 patient (16), should be analyzed in greater detail.

The major limitation of the present case report is the small number of successful cases of MPSL therapy. Larger studies are needed to clarify the efficacy and tolerability of MPSL therapy for COVID-19.

## Conclusions

We report three cases who suffered rapid respiratory failure progression due to COVID-19 but were improved after MPSL treatment. MPSL is a candidate drug for CS therapy for COVID-19, which should be started in the

early stage of respiratory failure. Optimal drug selection, timing of intervention, dose, and duration of CS therapy for COVID-19 should be analyzed in the further studies.

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## Footnote

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jxym-21-5>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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