Therapeutic strategy for severe COVID-19 pneumonia from clinical experience

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Abstract
Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019 in Wuhan, China, and has resulted in global pandemic. There is currently no effective therapeutic strategy for the management of mechanical ventilation or antiviral drugs for the treatment of this disease. As such, the development of a therapeutic strategy is urgently needed and should be established as soon as possible. In this case series, a therapeutic strategy was initially developed based on previous treatment methods used for the treatment of SARS and MERS in the absence of treatment options for COVID-19 due to a lack of information. During the search for a potential treatment, clinical findings were obtained from patients with severe COVID-19, and one therapeutic strategy was established. This therapeutic strategy was then applied to severe COVID-19 patients. In addition, we can require some interesting clinical features and characteristics of COVID-19 from blood analysis and physical findings. Here, we reported on the clinical features and characteristics of a therapeutic strategy for the treatment of severe COVID-19 pneumonia at our institution.

Keywords
ciclesonide, COVID-19, lopinavir/ritonavir, mechanical ventilation, therapeutic strategy

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Introduction
Coronavirus disease 2019 (COVID-19) named by the World Health Organization (WHO) on February 11, 2020 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1 It was first identified in December 2019 in Wuhan, China, and is causing great concern in the medical community due to the rate at which it is spreading around the world.2 Our understanding of the clinical and radiological features of COVID-19 is extensive,3,4 with many published reports on this disease within just 2 months of its spread outside of China. However, due to its ability to spread rapidly, there is an urgent need to consolidate any emerging insights into the clinical profile of this disease. At the time of writing, the outbreak of COVID-19 had spread both rapidly and widely, with cases confirmed in multiple countries.

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Severe COVID-19 is characterized by the development of acute respiratory distress syndrome (ARDS), for which the mainstay of treatment is mechanical ventilation. While the mortality associated with ARDS due to other causes ranges from 40% to 60%, there is not enough data available yet to draw safe conclusions on the prognosis of COVID-19 patients who require mechanical ventilation. Discussions regarding prognosis are central to obtaining informed consent for intubation. However, in the absence of definitive data, it is not yet clear what this discussion should entail. To our knowledge, no studies have investigated the long-term outcomes of intubation and mechanical ventilation in COVID-19 patients. A decrease in the number of patients in critical condition suggests that an increasing number of patients are being successfully extubated and discharged from hospitals. However, cohort studies with a longer follow-up period are needed to determine the efficacy and outcomes of this COVID-19 treatment. The treatment guidelines for COVID-19 vary between countries (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance). The WHO guidelines are very general, recommending management of symptoms and advising caution with pediatric patients, pregnant women, and patients with underlying comorbidities. There is currently no approved treatment for COVID-19; the recommendation is to provide supportive management according to each patient's needs (e.g. antipyretics for fever and oxygen therapy for respiratory distress). Moreover, the WHO’s recommendations indicate that severe cases should be administrated empiric antimicrobial therapy, with implementation of mechanical ventilation depending on the patient's clinical condition.

In this study, we describe a therapeutic strategy for the treatment of severe COVID-19 patients based on our own clinical experience with the aim to address the current lack of a standard therapeutic strategy for this disease.

Methods

Severe COVID-19 pneumonia patients were treated in our COVID-19 hospital. Since no official treatment exists, therapeutic strategies were based on the clinical course of individual patients. To establish a treatment strategy, our team reviewed and analyzed the currently available literature and researched the different types of treatments being used by medical specialists and infectious disease experts in emergency and intensive care units across the world.

Initially, patients with fever of 37.5°C or higher, general malaise, respiratory symptoms, and olfactory and taste disorders that persisted for 4 days or longer were suspected of being positive for COVID-19. Laryngeal swab and sputum samples of these patients were tested for COVID-19 via polymerase chain reaction (PCR). In addition, blood, sputum, and urine cultures, and Legionella pneumophila and Streptococcus antigens in urine were routinely monitored to confirm infection.

Severe COVID-19 was characterized according to the following criteria:

1. SpO₂ <92% at 10 L/min, with the need for O₂ administration via a reservoir mask.
2. Shortness of breath, with a respiratory rate (RR) of >30 times per minute.
3. Severe dyspnea due to pneumonia, with the need to intubate using mechanical ventilation for oxygenation.

Potential treatments for severe COVID-19 patients from a clinical and physical perspective included:

1. Mechanical ventilation
2. Sedation during ventilator management
3. Treatment for community-acquired pneumonia
4. Antiviral therapy against COVID-19
5. Anti-inflammatory therapy for lung lesions with COVID-19
6. Nutrition therapy
7. Rehabilitation
8. Symptomatic treatment according to each condition
9. Other

Treatment strategies

Mechanical ventilation

The ventilation settings were selected in accordance with the settings for ARDS: mode pressure control assist control (PC-AC); FiO₂, 60%; high positive end-expiratory pressure (PEEP), 10 to 14 mmHg; driving pressure, 8 to 15 mmHg; respiratory rate (RR), 12 to 16/min (depending on the CO₂ storage). The control PaO₂/FiO₂ ratio (PFR) was used as an
index to reduce the latency setting and as an expulsion criterion. Finally, upon confirming that there was no oxygenation or CO₂ storage at mode continuous positive airway pressure (CPAP) with minimum support, the patients were extubated.

**Sedation during mechanical ventilation**

Pneumonia is an oxygenation disorder caused by lung lesions. Fentanyl, propofol, and dexmedetomidine were used to prevent the spread of infection and accidents, including extubation or accidents due to body movements in the range of the Richmond Agitation-Sedation Scale (RASS) –2 to –4. The use of muscle relaxants was avoided where possible. Spontaneous breathing was slowed down in the acute phase. After the acute phase, the respiratory condition tended to improve gradually, and daily interruption was performed during the daytime under RASS –2 to 0. The necessary adjustments were made to allow the rehabilitation described below to be performed.

**Primary antibiotics against community-acquired pneumonia**

It was not possible to rule out community-acquired pneumonia (CAP) based on imaging alone. Azithromycin (AZM) (500 mg) and ceftriaxone (CTXR) (2 g) were administered for 3 days and 7 days, respectively, as antibiotic treatments in a standard empiric treatment for CAP based on treatment of adults with CAP, as per the official clinical practice guideline.

**Lopinavir/ritonavir (LPVr) against COVID-19 as an antiviral drug**

For patients with confirmed diagnosis of COVID-19, LPVr (400 mg/100 mg) was administered twice a day for 7 days in patients who were strongly suspected of being infected or who showed pneumonia on computed tomography (CT) images. Thereafter, no additional administration of an antiviral drug was needed.

**Anti-inflammatory therapy for lung lesions with COVID-19**

Ciclesonide (400–1200 μg/day), a local anti-inflammatory agent, was administered via inhalation twice a day for the treatment of lung lesions caused by COVID-19. Inhalation was performed using a ventilator with a spacer.

**Nutrition**

One day after intubation, patients underwent continuous tube feeding (Plumocare®-Ex; Abbott, Japan). They were regularly monitored for diarrhea or dyspepsia. Thereafter, the intake was gradually increased to ensure the required caloric intake before switching to the intermittent administration of tube nutrients and nutritional management. Blood glucose levels were measured and insulin was administered if necessary. The patients’ blood glucose levels were maintained at 130 to 200 mg/dL. After extubation and checking for water withdrawal, patients were monitored while eating their first meal before being moved back onto a normal diet, according to their swallowing function.

**Rehabilitation**

Rehabilitation with nurses, physical therapists (PTs), and occupational therapists (OTs) was performed at the patient’s bedside from 1 day after intubation to prevent contracture, preserve muscle function, and ensure muscle recovery. The physical load was gradually increased based on the corresponding protocol. Rehabilitation was performed with the patients in half sitting, sitting, standing, or walking positions.

**Supportive therapies**

Regarding supportive therapies for pathological conditions, if ventilator-associated pneumonia (VAP) was suspected due to prolonged tracheal intubation, various samples (including blood, sputum, urine, and catheter) were obtained and analyzed, followed by the administration of the corresponding antibiotics. In the case of a drug allergy or hepatic/renal disorder, the suspected drugs were discontinued and an alternative drug was administered.

**Other**

In terms of the patient’s water balance, after the super-acute to acute phase, the dry balance was monitored.

These nine treatment strategies, in addition to the strict monitoring of patient vitals, daily blood analysis, blood gas analysis, and chest X-ray examination
were performed in an intensive care unit to evaluate the general condition of the severe COVID-19 patients.

Cases

Four cases of severe COVID-19 pneumonia and their characteristics are shown in Table 1. The patients’ ages ranged from 30 to 67 years (mean, 64 years). All patients were male. Their only symptoms were high fever and dyspnea. None of the patients were smokers. The patients’ comorbidities included diabetes mellitus in four patients, hypertension in two patients, and oral systemic steroid therapy for pemphigoid in one patient. The average number of days of illness before admission to our hospital and the start of our therapeutic strategy was 10 days. We assessed COVID-19 based on a positive reverse transcriptase–polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 in respiratory tract and laryngeal swab samples tested by a designated diagnostic laboratory.

Results

The CT scan images of all COVID-19 patients are provided in Figure 1(a) to (d). All of the patients showed the typical characteristics of COVID-19 pneumonia, laterality of some ground-glass opacities (GGOs), and consolidation in the whole lung. In particular, case 4 had more severe findings, high levels of consolidation, and darker GGOs. Three patients were successfully extubated. However, one patient unfortunately died of multiple organ failure (MOF) due to sepsis. The average number of days of illness to perform intubation was 10 days (range: 8–11 days), with an intubation period of 14 days (range: 12–15 days). Patients stayed in the intensive care unit (ICU) for 2 or 3 days after extubation for observation of respiratory symptoms before being moved to the general ward. The average ICU stay was 17 days (range: 15–20 days). No LPVr side effects were reported during this period.

The following vitals were monitored and directly linked to the pathological condition: (1) body temperature, (2) PFR, (3) C-reactive protein (CRP), and (4) serum amyloid A (SAA). Figure 2 shows the plots and clinical courses of these vitals with the corresponding ventilator settings and therapeutic strategies for 4 cases (Figure 2(a)–(d)).

In cases 1 and 4, there was no re-elevation of the inflammatory response during treatment, and there

| Table 1. Patient characteristics. |
|----------------------------------|
| | 1 | 2 | 3 | 4 |
| Gender | M | M | M | M |
| Age | 67 | 61 | 67 | 30 |
| Symptom | | | | |
| Fever | + | + | + | + |
| Dyspnea | + | + | + | + |
| Dysosmia | – | – | – | – |
| Dysgeusia | – | – | – | – |
| Smoking | Never | Never | Never | Never |
| Comorbidities | | | | |
| Hypertension | + | + | – | – |
| Diabetes | + | + | + | + |
| COPD | – | – | – | – |
| Asthma | – | – | – | – |
| Liver dysfunction | – | – | – | + |
| Renal dysfunction | – | – | – | – |
| Other | – | + | – | – |
| Day of illness at which treatment was started | 11 | 8 | 9 | 12 |

Figure 1. Computed tomography (CT) scan images with typical COVID-19 pneumonia images, ground glass opacities (GGOs) and consolidation. (a) Case 1. (b) Case 2. (c) Case 3. (d) Case 4.
Figure 2. Time course of respiratory function, clinical features, changes in the levels of inflammation markers (SAA and CRP), and ventilator settings. (a) Case 1. (b) Case 2. (c) Case 3. (d) Case 4.
PFR: PaO₂/FiO₂ ratio; SAA: serum amyloid A; CRP: C-reacting protein; LPVr: lopinavir/ritonavir; AZM: azithromycin; CTRX: ceftriaxone; TAZ/PIPC: tazobactam/piperacillin; MEPM: meropenem; VCM: vancomycin; MCFG: micafungin; PC: pressure control; SIMV: synchronized intermittent mandatory ventilation; CPAP: continuous positive airway pressure; PEEP: positive end-expiratory pressure; RR: respiratory rate; ΔP: driving pressure; CRRT: continuous renal replacement therapy.
X-axis: day of illness (day). Y-axis: each parameter.
*intubation.
**extubation.
was no need for the use of additional antibiotics to prevent VAP. In case 2, pemphigus was administered orally as a systemic steroid. However, the patient was compromised because of long-term steroid treatment; therefore, broad-spectrum antibiotics were administered once the inflammatory reaction increased, resulting in the prevention of infection. In case 3, intubation was prolonged and methicillin-resistant Staphylococcus aureus (MRSA) was identified in the sputum culture. VAP was confirmed after an increase in the inflammatory reaction. This patient was administered with the antibiotics vancomycin for MRSA infection and micafungin for fungal infection caused due to elevated β-D-glucan levels, and was treated with continuous renal replacement therapy (CRRT) for acute kidney injury (AKI). Unfortunately, this patient died from MOF on day 29 of the illness.

The dynamic changes in the SAA and CRP levels reflected the change in the patients’ condition after 3 to 5 days of hospitalization. Patients with lower levels of SAA and CRP were more likely to improve. In all patients except case 3, BT and PFR did not improve for 5 to 7 days, but the SAA and CRP levels decreased gradually. Once BT began to normalize, PFR improved and became inversely correlated with BT. We were then able to gradually change the respiratory settings. According to our analysis of severe COVID-19 patients, the levels of SAA and CRP at admission were correlated with the dynamic changes in the patient’s condition, followed by improvements in the levels of BT and PFR, and an overall improvement in the systemic condition of the patients. Therefore, it is important to evaluate the relationship between SAA/CRP and BT/PFR in severe COVID-19 patients. All patients showed transient abnormally high levels of D-dimer in the super-acute phase. However, no signs of thrombosis were observed in any organs and the D-dimer levels gradually normalized. Although the prothrombin time (PT) and activated partial thromboplastin time (APTT) also increased slightly, no obvious coagulopathy was observed. In addition, procalcitonin was negative in all patients in all phases.

**Discussion**

There is currently no official therapeutic strategy for the treatment of patients with severe COVID-19 pneumonia caused by SARS-CoV-2. Therefore, many physicians are implementing supportive therapies to these patients based on their previous clinical experiences in treating bacterial or viral infections. It is therefore imperative that physicians establish an effective therapeutic strategy for the treatment of severe COVID-19. In response to increasing numbers of cases of severe COVID-19 pneumonia since the beginning of the COVID-19 outbreak, we have attempted to establish a therapeutic strategy for the treatment of severe COVID-19 pneumonia by consulting with medical specialists, pulmonologists, intensivists, and infection control physicians, among other clinical professionals. After testing a variety of therapies on COVID-19 patients, we have established an effective strategy for the treatment of severe COVID-19 pneumonia.

For the mechanical ventilation of severe COVID-19 pneumonia patients, we have selected to maintain the ventilation settings according to ARDS maintenance since the pathogenesis of COVID-19 pneumonia is similar to that of ARDS. The ARDS ventilation settings are as follows: (1) low tidal volume (<6mL/kg), (2) Pplat <30cmH2O, (3) permissive hypercapnia, and (4) high PEEP (8-14mmHg). Pulmonary compliance was good in all reported cases. As such, high PEEP should be used in the acute phase of COVID-19. Moreover, we considered the use of extracorporeal membrane oxygenation (ECMO) in COVID-19 cases experiencing a worsening of their respiratory conditions, according to the Extracorporeal Life Support Organization (ELSO) COVID-19 Interim criteria.12 Three of our cases were successfully treated using these mechanical ventilation management strategies. Unfortunately, one of our patients died because of MOF and sepsis caused by secondary infectious disease. Although ECMO improves respiratory status in the acute phase, our laboratory findings indicated that even if the criteria for introducing ECMO, which has a pulmonary protective effect, are satisfied, it should not be considered in cases with (1) gradually worsening respiratory condition after the onset of COVID-19 (not suddenly) and (2) a systemic condition that is irreversible, rather than the rapid deterioration of oxygenation after the onset of COVID-19, after consulting with an ECMO network member.

Several potential antiviral drugs for COVID-19 have been previously reported. However, there are currently no specific therapeutic agents available for the treatment of COVID-19. LPVR has been
used for the treatment of HIV and as an antiviral drug against SARS and MERS. The timing of administration, which is during the early peak of the viral replication phase (initial 7–10 days), is important since delayed therapy initiation with LPVr has no effect on the clinical outcome.\textsuperscript{13,14} Despite this, no published data on effect of LPVr on SARS-CoV-2 in vitro exist.\textsuperscript{15} Recently, Cao and colleagues found that there were no significant differences between a LPVr therapy group and supportive therapy group.\textsuperscript{16} The most commonly used and studied LPVr dosing regimen for COVID-19 treatment is 400 mg/100 mg twice daily for up to 14 days.\textsuperscript{16} However, due to the adverse effects of LPVr and the effect of SARS-CoV-2 itself, we chose to prescribe LPVr only for 7 days, a dose that was both feasible and available for the treatment of COVID-19. Alternative antiviral treatments that have been suggested by previous studies include chloroquine, redelivery, and favipiravir. However, a detailed analysis of these antiviral drugs and their effects on COVID-19 patients is still needed. Thus, the use of antiviral drugs for the suppression of SARS-CoV-2 activity requires further investigation, and there have been few clinical experiences thus far.

We previously reported on the effectiveness of ciclesonide, which is used to treat asthmatic attacks via suppression of increased airway responsiveness and immediate and delayed forms of pulmonary resistance induced by the inhalation of antigens, for the treatment of severe COVID-19 pneumonia.\textsuperscript{17} Ciclesonide exerts an anti-inflammatory effect by suppressing the production of tumor necrosis factor (TNF)-α and various inflammatory factors, as well as inhibiting eosinophil infiltration into the respiratory tract.\textsuperscript{18} Ciclesonide binds to the glucocorticoid receptor and produces a potent anti-inflammatory effect. In addition, as an aerosol, it has a high percentage of fine particles that are able to reach the peripheral airways, with a lung penetration rate of approximately 52%.\textsuperscript{19,20} It is also well-known for its low systemic side effects.\textsuperscript{19} These findings point to ciclesonide as a potential therapeutic option for use as a local anti-inflammatory inhaler in COVID-19 patients.

In terms of its clinical features, COVID-19 progresses rapidly, with patients developing severe symptoms, including ARDS, septic shock, uncompensated acidosis, and coagulation dysfunction, within a few days of infection. The severity of the prognosis is complicated by the diversity of symptoms, imaging manifestations, and the degree of disease progression.\textsuperscript{21–23} In severe cases, the deterioration of respiratory symptoms and an increase in oxygen demand can occur simultaneously, with patients requiring intubation and mechanical ventilation as a result of respiratory deterioration within 12 to 24 hours of hospital admission. This deterioration has been found to occur around 7 to 10 days from the onset of symptoms, affecting patients for a longer period than a typical viral infection. Inflammatory factors, such as SAA and CRP, are frequently used to predict, diagnose, and evaluate inflammatory diseases.\textsuperscript{22,24–26} In severe COVID-19 cases, patients’ CRP on admission tended to be higher than that of the mild cases, with a peak CRP that was very high.\textsuperscript{27} In our analysis, SAA was considered to be a prognostic biomarker for disease state, moving closely in parallel with CRP, as suggested in a previous report, where SAA was used as a prognostic biomarker to monitor the progression of respiratory diseases.\textsuperscript{22} SAA is able to promote inflammatory response by activating chemokines and inducing chemotaxis, even at very low concentrations.\textsuperscript{28,29} Previous studies have suggested that patients infected with COVID-19 exhibit high levels of IL-1 β, IFN-γ, IP-10, MCP-1, and other cytokines, leading to the activation of Th1 cells. Compared with patients with mild form of the disease, critically ill patients may have higher levels of IL-1 β, IL-6, MCP-1, MIP-1, and TNF-α, and other cytokines, boosting liver cells and producing SAA.\textsuperscript{30,31}

CRP and SAA were found to peak within 3 to 4 days of patients being under intensive care. Although these levels declined steadily thereafter, a high fever persisted and PFR did not show any improvement. As such, patients were maintained on ventilators for around 1 week.

In a previous study, the levels of SAA were found to continuously decrease at a rate faster than CRP during the recovery phase.\textsuperscript{32} Patients with decreased SAA showed an improved clinical condition, which was complemented by changes in the CRP levels. A subsequent rise in CRP and SAA during this period was indicative of infection. In these cases, culture samples were immediately collected and analyzed to identify the source of infection, followed by the administration of the corresponding antibacterial
agents for empiric therapy. As such, patients with low levels of SAA were more likely to have a better prognosis than patients with consistently high levels of SAA, suggesting a significant correlation between the dynamic changes in SAA levels and prognosis. Therefore, we suggest that SAA is a sensitive indicator of the severity of COVID-19. After 1 week, the levels of BT suddenly decreased, with PFR improving thereafter. In cases without secondary infection, the patients did not develop high levels of BT and the ventilator could be slowly withdrawn, followed by extubation. BT and PFR were inversely correlated in all cases. Although chest X-rays were obtained every day during this period to confirm the state of COVID-19 pneumonia, no significant improvements in GGOs were observed. This indicates that it is difficult to assess the state of the disease using only chest X-rays. However, cardiac function and water balance can be evaluated using chest X-rays, as well as ultrasonography, to prevent respiratory deterioration due to an excessive water load. These clinical findings suggest that there are limits to drug treatment and ample room for the study of the actual clinical effects. Although many questions remain about the effects of treatment, the levels of both CRP and SAA, which are associated with a poor patient status, peaked. The clinical data suggest that patients were admitted to intensive care units about 1 week from the start of illness. This was followed by approximately 2 weeks of mechanical ventilation and intensive care. Since an official strategy for the treatment of COVID-19 remains to be established, we believe that the therapeutic strategy presented in this study could be of interest for the treatment of critically ill COVID-19 patients.

This study has some limitations. Firstly, this study was performed in a single hospital with a small study population since there are currently few confirmed and recovered cases of COVID-19 in Japan. Second, no alternative treatment was available for use in a parallel, control group. However, we believe that the credibility of the therapeutic effect is high, as our study provides a comprehensive examination, including clinical features, laboratory findings, and physical findings, at a single institution. In the future, we hope to collaborate with other medical institutes in our area to design a control group that will allow us to improve the reliability of our study.

**Conclusion**

Severe COVID-19 patients require constant monitoring and ventilator management after admission to intensive care units. There is currently an urgent need for the development of a vaccine for the prevention of COVID-19 and therapeutic strategies for the treatment of severe COVID-19. However, the analysis of patient vitals and blood samples and the application of symptomatic treatment strategies play a key role in the treatment of severe COVID-19 patients and should be conducted periodically for the detection and monitoring of infection.

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**Authors’ contributions**

FO prepared the manuscript and collected the references. IT coordinated the authors. FO, HK, KN, TN, RM, YO, KS, MU, and YO provided clinical support. HK and TA helped to draft the manuscript. All authors have read and approved the final manuscript.

**Availability of data and materials**

Data requests should be made to the corresponding authors.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval**

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**Consent for publication**

Written consent was obtained from patients for the publication of this case report and the relevant images. A copy of the written consent is available for review by the Editor-in-Chief of European Journal of Inflammation.
Informed Consent
Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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