International Journal of Medicine, 10 (1) (2022) 7-11

International Journal of Medicine

Website: www.sciencepubco.com/index.php/IJM

Research paper

Coronavirus disease 2019 in an elderly patient who became severely ill despite antibody cocktail therapy but improved with lung-protective management: A case report

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Abstract

Casilivimab/imdevimab, called antibody cocktail therapy, is a treatment for mildly and moderately ill COVID-19 patients. In our care facility, we encountered an elderly patient treated with an antibody cocktail after being diagnosed with a moderate disease at the initial presentation that became severe. An 80-year-old man with a history of diabetes, hypertension, and cerebral infarction presented with a 5-day history of fever and was diagnosed with coronavirus disease 2019. He was diagnosed with moderate disease and immediately administered the antibody cocktail therapy. However, his respiratory status deteriorated rapidly, and mechanical ventilation was initiated. We performed lung-protective ventilation, centered on low tidal volume and prone position therapy, with good outcomes. Throughout the pandemic, his case, as well as others, highlighted that immediate intervention for mild and moderate cases and intensive treatment, such as lung-protective ventilation and prone position, for severe cases improved patient outcomes.

Keywords: *Antibody-Cocktail; Covid-19; Elderly; Lung Injury.*

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which started in Wuhan, China, in December 2019, is a pandemic (Huang et al. 2020). Vaccines and therapeutic agents are being developed; however, the disease continues to ravage the world even as of the summer of 2021, owing to the emergence of mutant strains. Currently, there are four drugs in Japan for the treatment of COVID-19: remdesivir, baricitinib, casilibimab/imdebimab, and sotrovimab; dexamethasone is indicated for severe infections. Among them, the SARS-CoV-2 monoclonal antibody, casilibimab/imdebimab, was approved as a special case in Japan on July 19, 2021, and became available in the market (Ministry of Health, Labour and Welfare. About special approval of novel coronavirus therapeutic agents [Press release: 2021.7.19]. Retrieved from: https://www.mhlw.go.jp/content/11123000/000807746.pdf [in Japanese]). It is also called antibody cocktail therapy because it uses two types of antibodies to bind to different sites of the SARS-CoV-2 spike protein, blocking its binding to human cells and suppressing the growth of the virus in the body. It is a treatment for mild and moderately ill patients and can be expected to reduce the risk of aggravation (Dougan et al. 2021, Chugai Pharmaceutical Co., Ltd. Casiribimab/Imdebimab intravenous Infusion Set, Package insert. July.2021 description [https://chugai-pharm.jp/content/dam/chugai/product/ron/div/pi/doc/ron_pi.pdf]).
At our care facility, we recorded good results during the fifth wave of the disease following the administration of casilibimab/imdebimab to 56 patients within 3 months. However, we encountered a case of an elderly patient treated with an antibody cocktail after being diagnosed with a moderate disease at the initial presentation that became severe. Following the good outcomes of respiratory management centered on lung-protective ventilation and prone position therapy, we herein report the treatment progress and recommendations.

2. Case presentation

2.1. History

Our patient is an unvaccinated 80-year-old male with a history of cerebral infarction, type 2 diabetes, and hypertension. He presented with a 5-day history of fever and was found to be SARS-CoV-2-positive using a polymerase chain reaction test. A positive result was observed on day X-1, and the patient visited our hospital on day X.

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2.2. Examination

His consciousness using the Glasgow coma scale was 15/15 (E4V5M6), body temperature 36.6 °C, pulse 78 beats/min, respiratory rate 18 breaths/min, and SpO_2 94% (room air), and subjective symptoms of cough and malaise were observed.

2.3. Blood test

The white blood cell count was 3440/μL, and the C-reactive protein level was 9.36 mg/dL (which pointed to increased inflammatory response); the platelet count was $10.0\times10^4/mm^3$, activated partial thromboplastin time was 47.3 s, fibrinogen 444 mg/dL, and D-dimer level was 1.2 μg/mL along with mild coagulation abnormalities. The results of the blood test are shown in Table 1.

Table 1: Blood Examination on Admission

Complete blood count			Biochemical test		
WBC	3440	/μL	TP	6.4	g/dl
Ne%	75.2	%	Alb	3.3	g/dl
RBC	484	$\times10^4$/μL	AST	36	IU/L
Hb	15.0	g/dl	ALT	19	IU/L
Hct	44.7	%	LDH	296	IU/L
PLT	10.0	$\times10^4/mm^3$	CK	79	IU/L
Coagulation test			BUN	9.4	mg/dl
PT	106	%	Cr	0.57	mg/dl
APTT	47.3	sec	Na	135	mEq/L
Fib	444	mg/dl	K	3.8	mEq/L
D-dimer	1.2	μg/ml	Cl	99	mEq/L
			CRP	9.36	mg/dl
			FBS	206	mg/dl
			HbA1c	7.3	%
			KL-6	451	U/ml

2.4. Imaging findings

Plain computed tomography (CT) (Fig. 1) showed ground-glass-like shadows just beneath the pleura, centered on the dorsal and bottom of lung fields.

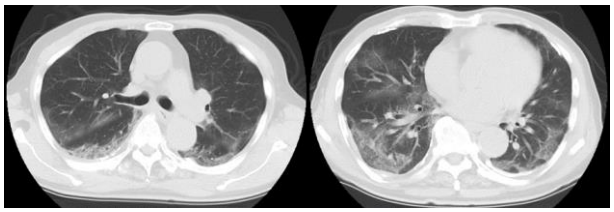


Fig. 1:

3. Clinical course

Although there were a few symptoms on arrival, including mild hypoxemia with a SpO_2 of 94%, this 80-year-old patient had risk factors for exacerbation, including type 2 diabetes, hypertension, and smoking. Since he was unvaccinated, we decided that he was at high risk of exacerbation and immediately hospitalized and commenced the antibody cocktail therapy (casilibimab/imdebimab). However, his respiratory condition deteriorated rapidly with a SpO_2 of < 90% and respiratory distress (tachypnea) 3 h after administering the antibody cocktail. Since oxygen administration alone did not improve the symptoms and reduce the respiratory effort, a high-flow nasal cannula (HFNC) was applied at an oxygen flow rate of 50 L/min and FiO_2 0.4. Considering the severity of the inflammatory reaction and the time course from the onset, we administered dexamethasone 8 mg. SpO_2 increased to 95%, and subjective symptoms temporarily improved. He was instructed on prone position therapy and continued respiratory management; however, it was difficult to maintain the prone position because of low back pain. Additionally, remdesivir 200 mg (100 mg from the next day) and baricitinib 4 mg were administered from the fourth day of hospitalization; however, it became difficult to maintain SpO_2 > 90% even with FiO_2 0.7. With further respiratory management, we judged that there was a high possibility of recovery—including the return to daily living activities before illness—despite him being elderly. After the patient and his family provided sufficient informed consent, ventilatory management was initiated on the same day under continuous administration of muscle relaxants for 24 h with sufficient analgesia and anesthesia. In addition, pulmonary protective ventilation centered on low tidal volume, high positive end-expiratory pressure (PEEP) management, and prone position therapy were performed. Anticoagulant management and enteral nutrition were also performed. Owing to the increased inflammatory response, azithromycin was added for its anti-inflammatory effects, and heparin was used to prevent deep vein thrombosis. Ventilatory management was completed in 4 days because of the risk of ventilator-related pneumonia and intensive care unit acquired weakness. Subsequently, the HFNC was applied again; however, at FiO_2 0.4 while maintaining the SpO_2 at approximately 90%, he gradually improved and actively commenced rehabilitation. The use of steroids was prolonged to 14 days to observe a reduction in inflammatory response; the inflammatory reaction peaked on the 17th day of hospitalization. On the 18th day of hospitalization, CT (Fig. 2) showed normal upper lobe lung fields, with emphysematous changes in the lower lung fields that remained unchanged. Oral intake gradually stabilized, and the HFNC was withdrawn on the 23rd day of hospitalization. Although SpO_2 sometimes decreased owing to exertion, O_2 at 2 L/min through the cannula improved to a state where activities of daily living could be performed with almost no assistance. On the 32nd day of hospitalization, CT (Fig. 3) still showed normal upper lobe lung fields and improved emphysematous changes in the fields of the lower lung, and on the 37th day of hospitalization, the patient was transferred to a recuperating hospital for rehabilitation (Table 2). After 35 days of rehabilitation, the patient was discharged.

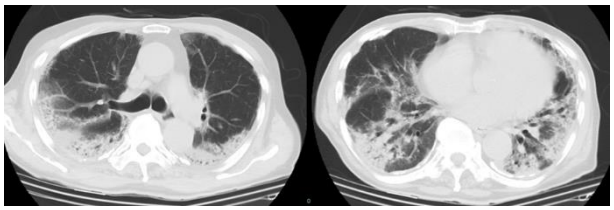


Fig. 2:

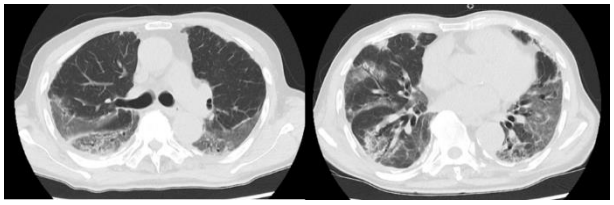
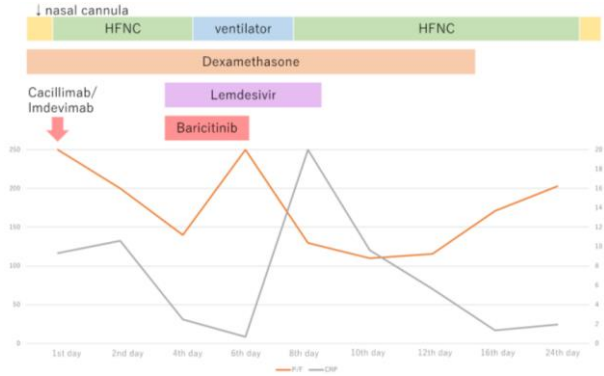


Fig. 3:

Table 2: Clinical Course



4. Discussion

Most patients with COVID-19 present with either asymptomatic or mild disease; however, some progress to severe disease and die. Many studies are still being conducted on the treatment and respiratory management of patients with severe diseases. Phase III trials of casilibimab/imdebimab, as a COVID-19 agent, recommended administration within 7 days of disease onset, with an oxygen saturation of 93% (room air) or higher in patients with at least one of the aggravation risk factors (such as being aged ≥50 years, obesity, heart disease, chronic lung disease, type 1 or 2 diabetes, chronic renal disorder, chronic liver disease, and immunosuppressive state). The number of hospitalization and death events occurring after 29 days was 7/736 (1.0%) in the riociguat-administered group and 24/748 (3.2%) in the placebo group; this indicated a reduction in the risk of adverse events occurring as large as 70.4% (Dougan et al. 2021, Chugai Pharmaceutical Co., Ltd. Casiribimab/Imdebimab intravenous Infusion Set, Package insert. July.2021 description [https://chugai-pharm.jp/content/dam/chugai/product/ron/div/pi/doc/ron_pi.pdf). In our hospital, as a result of the administration of casilibimab/imdebimab to 56 patients with at least one of the aggravation risk factors from July 2021, during the fifth wave, 55 cases were discharged without aggravation. In our case, the administration of casilibimab/imdebimab was performed immediately after admission; however, the timing of administration was 5 days after onset, which may have been delayed. Therefore, it is highly probable that the expected effect was not achieved because of delayed administration.

Today, it can be life-threatening when patients on these agents develop severe diseases. Therefore, we are focusing on thorough lung-protective ventilation and prone position therapy for the management of critically ill patients. Prone position therapy has been reported to improve oxygenation in approximately 70% of patients with acute respiratory distress syndrome (ARDS) in clinical trials spanning more than 40 years (Guérin et al. 2013). Several studies have shown that long prone position therapy can significantly reduce the mortality rate (Munshi et al. 2017, Gattinoni et al. 2013). Therefore, it is necessary to weigh the risks associated with the procedure against the possibility of saving lives (Scholten et al. 2017). Various complications of the prone position have been reported, such as airway obstruction due to increased oral and airway secretion, obstruction of intubation tubes and vascular catheters, increased intra-abdominal pressure, increased gastric residue, and facial pressure ulcer/edema (Gattinoni et al. 2013, Scholten et al. 2017). In our hospital, prone position therapy was safely introduced with the aid of a team of at least four people (such as doctors, nurses, and rehabilitation staff), who closely monitored these patients to tackle any possible complications that could arise. Various mechanisms have been considered to explain the oxygenation-improving effects of prone position therapy, one of which is the improvement of ventilation-perfusion mismatch. Normally, when ventilation disorders locally occur in the lungs—due to inflammation or pulmonary edema—a mechanism called hypoxic pulmonary vasoconstriction constricts pulmonary vessels in that area and reduces the amount of oxygenated blood. However, in patients with COVID-19, it is characterized by significant damage. Therefore, a large amount of blood continues to flow to the damaged alveolar region, which is hypoxic, causing severe ventilation and blood flow inequality and hypoxemia in these patients (Brocard et al. 2017). In severe cases, COVID-19 is classified into the L- and H-types. The L-type has a relatively maintained pulmonary compliance, while the H-type has a high possibility of developing ARDS at an early stage owing to decreased compliance. Prone position therapy is effective for both, and in cases where oxygenation improves in the prone position, the improvement in oxygenation often persists even after returning to the supine position (Coppo et al. 2020).

In our case, the patient was elderly and at a high risk of aggravation. However, 5 days after the onset, casilibimab/imdebimab was administered to prevent aggravation, and prone position therapy was initially performed on awakening, with the patient's cooperation. After applying the HFNC, prone position therapy was continued as much as possible. Although SpO_2 temporarily increased to 95% and more, it

was difficult to continue for a long time because of preexisting back and shoulder pain. The patient was repositioned in the lateral or supine position as appropriate; however, oxygenation could not be maintained, and the oxygen concentration had to be increased. Although a slight decrease in SpO_2 was already observed at admission, 94% of SpO_2 was judged to be moderate; however, without complaints of respiratory distress, the patient's respiratory state suddenly worsened. The time from disease onset to casilibimab/imdebimab administration may have contributed to this deterioration. Dexamethasone was also administered at the same time as the initiation of oxygen administration, in consideration of the increased inflammatory response and the time course from the onset. Subsequently, from the 4th day of hospitalization, remdesivir administered to prevent aggravation was also ineffective. Regarding remdesivir, its effectiveness has been questioned by a report (Wang et al. 2020), and it is possible that its administration was delayed. In our case, we overestimated the side effects of remdesivir because of the patient's age.

In severe respiratory distress, the local force generated from excessive respiratory effort causes damage to the lungs. Vascular permeability enhanced by inflammation is further enhanced by breathing efforts, causing a vicious cycle. Therefore, suppressing patient self-inflicted lung injury is also a major management point (Brocard et al. 2017), and it is necessary to administer muscle relaxants as needed under mechanical ventilation for pulmonary protective ventilation, in addition to sufficient analgesics and sedatives. Considering the above points, in the management of patients with severe COVID-19 in our hospital, muscle relaxants are continuously administered immediately after the initiation of the mechanical ventilation while the patient is managed in the prone position for 48 h. Repositioning was performed during the day shift when many personnel could be available, and the muscle relaxant was administered with sufficient analgesics and sedatives to maintain the prone position. The fixation position, depth, and obstruction of the intubation tube were carefully observed in case the fixation tape peeled off. After extubation, the prone position was continued as appropriate; however, low back pain remained severe and made it difficult to be performed for a long time. It was considered that position therapy was important for this patient. As the general condition gradually stabilized, the subjective symptoms improved, the prone position was actively performed, and the respiratory condition improved until HFNC withdrawal.

In our case, the risk of aggravation was judged to be extremely high because he was an older man with comorbidities. Casilibimab/imdebimab administered on the 6th day following onset did not directly prevent aggravation; however, it is unclear how these agents affected the course after aggravation. Many studies on antibody cocktail treatment have reported the effect of preventing aggravation; however, no case report of aggravation after antibody cocktail could be found in Japan.

In treating patients with COVID-19, it is necessary to prevent aggravation in patients with some risks by the early administration of casilibimab/imdebimab.

Finally, it is believed that full recovery is possible for severely ill patients with the aid of pulmonary protective ventilation centered on low tidal volume and high PEEP and thorough systemic management, such as prone position therapy.

5. Conclusion

Casilibimab and imdebimab are significant therapeutic agents for preventing COVID-19 aggravation, and the earliest possible administration maximizes their effects after disease onset. For severe COVID-19 pneumonia, a good prognosis is possible when using lung-protective management and prone position therapy in addition to drugs. However, careful preparation should be considered for the implementation and continuation of prone position therapy. Therefore, it is important to secure sufficient medical resources.

Acknowledgment

We want to thank Editage (www.editage.com) for English language editing.

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