〈Case Report〉

Treatment of two cases of COVID-19 with ciclesonide resulted in amelioration of pneumonia symptoms

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We have observed two cases in which ciclesonide, an inhaled steroid drug for bronchial asthma, had a possibly useful effect on novel coronavirus disease (coronavirus disease 2019: COVID-19) pneumonia. Our observations suggest that ciclesonide treatment may ameliorate the clinical symptoms of COVID-19; however, further studies on a larger number of cases are required to confirm the therapeutic effects of ciclesonide.

Introduction

The novel coronavirus disease (coronavirus disease 2019: COVID-19), which originated in Wuhan City, Hubei Province, China in December 2019, is rapidly spreading worldwide[1)]. On the Diamond Princess ship (a cruise ship), which docked in Japan, 3,711 passengers and crew were tested for COVID-19 using the reverse transcription polymerase chain reaction (RT-PCR) test for severe acute respiratory syndrome coronavirus (SARS-CoV-2) and 712 tested positive[2)]. This infection is highly contagious and could be aggravated. Drugs used for treating cases of hepatitis B, human immunodeficiency virus (HIV), Ebola hemorrhagic fever, and malaria have been considered for treatment of COVID-19[3)]; however, their effectiveness remains unknown and no treat-

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ment methods have been established yet. Previously, ciclesonide was shown to inhibit the replication of Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 *in vitro*[4,5], and it exerted a similar effect on COVID-19 cases in Japan[6]. Although there is basic and effective data available for ciclesonide and some studies have reported its potential clinical effectiveness as a medicine, to date, only one study is available in Japanese on the effectiveness of the drug in treatment of COVID-19[6]. Here, we have detailed our observations of two patients admitted to our hospital with COVID-19 who showed improvement in their symptoms upon treatment with ciclesonide.

Case Studies

Case 1

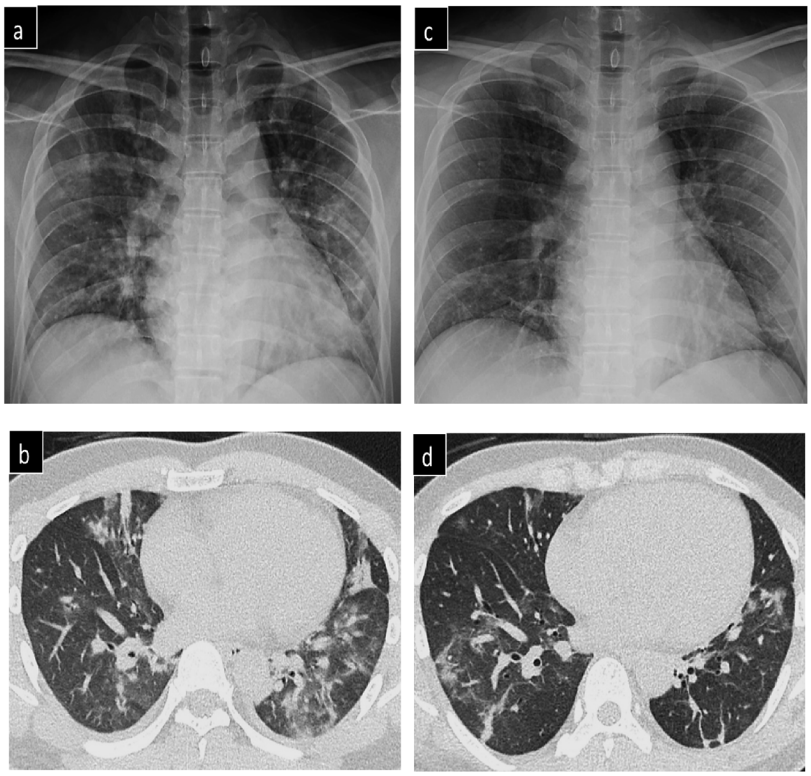
Case 1 is a 34-year-old Thai man without a preexisting disease or history of smoking. A waiter on the cruise ship had a fever of 39℃ four days before admission and a cough with dyspnea on exertion three days before admission. He complained of right lower quadrant abdominal pain two days before admission. His nasopharyngeal COVID-19 RT-PCR test was found to be positive, and he was transferred to our hospital. On admission, his vital signs were blood pressure (BP) 130/85 mmHg, pulse rate (PR) 96/min, respiratory rate (RR) 22/min, temperature (T) 38.6℃, and SPO_2 97% at rest on room air and 92% during exertion. Analysis of breath sound revealed crackles in the lower zones of both the lungs and tenderness in the right lower area of the abdomen. On the same day, oxygen treatment was started at a rate of 2 L/min. Blood testing results were: WBC, $4{,}900\times10^3/\mu$L (neutrophils, 70.9%; lymphocytes, 20.7%; monocytes, 7.8%; and eosinophils, 0.3%); Hb, 13.6 g/dL; platelets, $246\times10^3/\mu$L; LDH, 390 U/L; CRP, 5.33 mg/dL; procalcitonin, 0.21 ng/mL; and NT-proBNP, 23 pg/mL; no abnormalities in the liver or kidney function were observed (Table 1). Chest X-ray and computed tomography (CT) revealed infiltrative shadows and ground-glass opacities (GGOs) in the bilateral lung fields (Figures 1a, 1b). Further, moderate enlargement of the appendix was noted. After obtaining various culture specimens, we began to administer 500 mg azithromycin and 2 g ceftriaxone intravenously once daily. We began 500 mg metronidazole orally thrice daily in consideration of the risk of concomitant appendicitis, too. The tests for blood culture, *Streptococcus pneumoniae* and *Legionella* urinary antigens, *Mycoplasma pneumoniae* antibodies, *Chlamydia* IgA and *β*-D glucan, and other pneumonia-causing pathogens were negative, and no unusual bacteria were detected in the sputum culture. On day 2, the vital signs were BP 120/76 mmHg, PR 104/min, RR 25/min, and T 39.4℃, and oxygen treatment at the rate of 4 L/min was occasionally required. After obtaining consent, we administered ciclesonide at 200 μg per dose, with two inhalations daily. On day 5, his fever subsided, and on day 6, his SPO_2 on room air was found to be 97%. Chest X-ray and CT on day 6 showed remarkable improvement in the GGOs in the lung fields (Figures 1c, 1d). His abdominal

Table 1. Vital sings and biochemistry date of a 34-year-old man and a 72-year-old man with pneumonia caused by COVID-19 on day of admission

	Case 1	Case 2
Systolic Blood Pressure	135 mmHg	125 mmHg
Diastolic Blood Pressure	85 mmHg	76 mmHg
Heart Rate	96/min	75/min
Respiratory Rate	22/min	22/min
Temperature	38.6°C	37.5°C
SPO_2	92%	99% (O2 of 4 L via face mask)
Baseline investigations		
WBC	4.900/μL	4,600/μL
neutro	3.474/μL	ND
lympho	1.014/μL	ND
Hb	13.6g/dL	14.7g/dL
Plat	246×10^3/μL	141×10^3/μL
Alb	3.8 g/dL	3.2 g/dL
T.Bil	0.5 mg/dL	1 mg/dL
AST	31 U/L	66 U/L
ALT	19 U/L	95 U/L
LDH	390 U/L	330 U/L
ALP	222 U/L	549 U/L
γGTP	76 U/L	370 U/L
BUN	11.5 mg/dL	20 mg/dL
Cr	0.99 mg/dL	0.84 mg/dL
Na	136 mEq/L	135 mEq/L
K	4.2 mEq/L	3.7 mEq/L
CL	100 mEq/L	100 mEq/L
Ca	8.6 mEq/dL	8.1 mEq/dL
CRP	5.33 mg/dL	5.28 mg/dL
PCT	0.21 ng/dL	0.1 ng/dL
NT-proBNP	23.1 pg/mL	21.1 pg/mL

pain was resolved. The nasopharyngeal RT-PCR test was negative on days 8 and 10 and he was discharged with full recovery on day 11. No side effects of ciclesonide were observed. Figure 2 shows the treatment response course of the patient after admission to the hospital.

Figure 1. Chest X-ray and computed tomography findings of Case 1

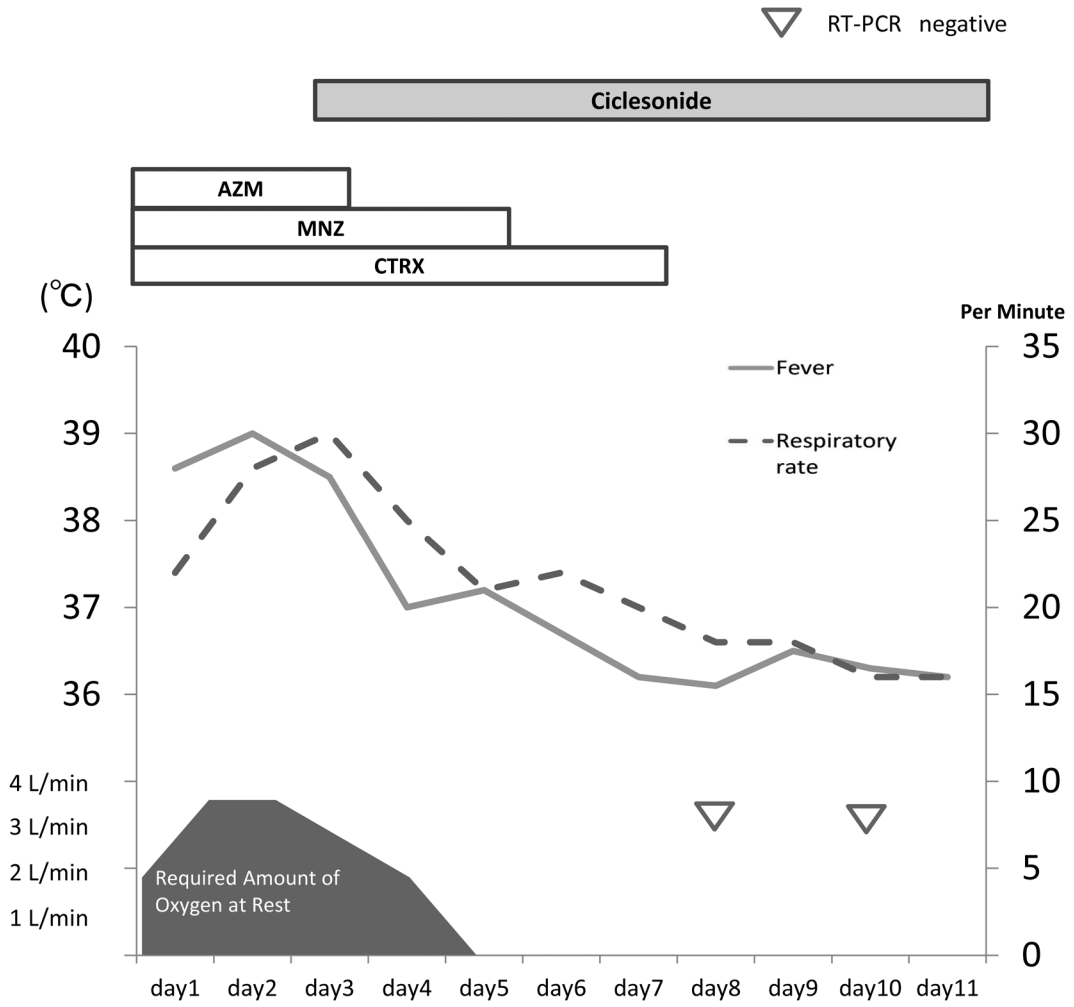


a. Upon admission of the patient, shadows accompanying changes due to shrinkage were confirmed over wide areas of the bilateral lung fields, with the overall lung volume being slightly reduced.
The heart shadow was also slightly enlarged.
b. High-density areas of ground-glass opacities and high-density areas accompanying changes due to shrinkage were confirmed across multiple lobes bilaterally.
The increase in heart size and a small amount of pleural effusion in bilateral lung fields were also confirmed.
c. On hospital day 6, improvements were observed in the overall shadows of the lung fields and in the lung volume and size of the heart shadow.
d. The confirmed shadows showed overall improvement, and lung volume was also improved. The bilateral pleural effusion was also reduced.

Case 2

A 73-year-old Japanese man, also a passenger on the same cruise ship, had cough and fever of 37.5℃ four days before admission and his nasopharyngeal swabs were found to be positive for COVID-19 using RT-PCR two days before admission. One day prior to admission, he was transferred to a different hospital, where CT scan revealed GGOs and he required O_2 at 2 L/min. Later, he was transferred to our hospital. He had no history of smoking. His only known medical history was hypertension, for which he was taking amlodipine at 2.5 mg/day. On admission, his vital signs were BP 125/76 mmHg, PR 75/min, RR 22/min, T 37.5℃, and SPO_2 99% following O_2 treatment at a rate of 4 L, which was administered via a face mask. Blood testing results were: WBC, $4{,}600 \times 10^3/\mu L$; Hb, 14.7 g/dL; platelets, $141 \times 10^3/\mu L$; T bil, 1.0 mg/dL; AST 66 U/L; ALT 95 U/L; LDH 330 U/L; ALP 549 U/L; γ-GTP 370 U/L; CRP 5.33 mg/dL; and procalcitonin

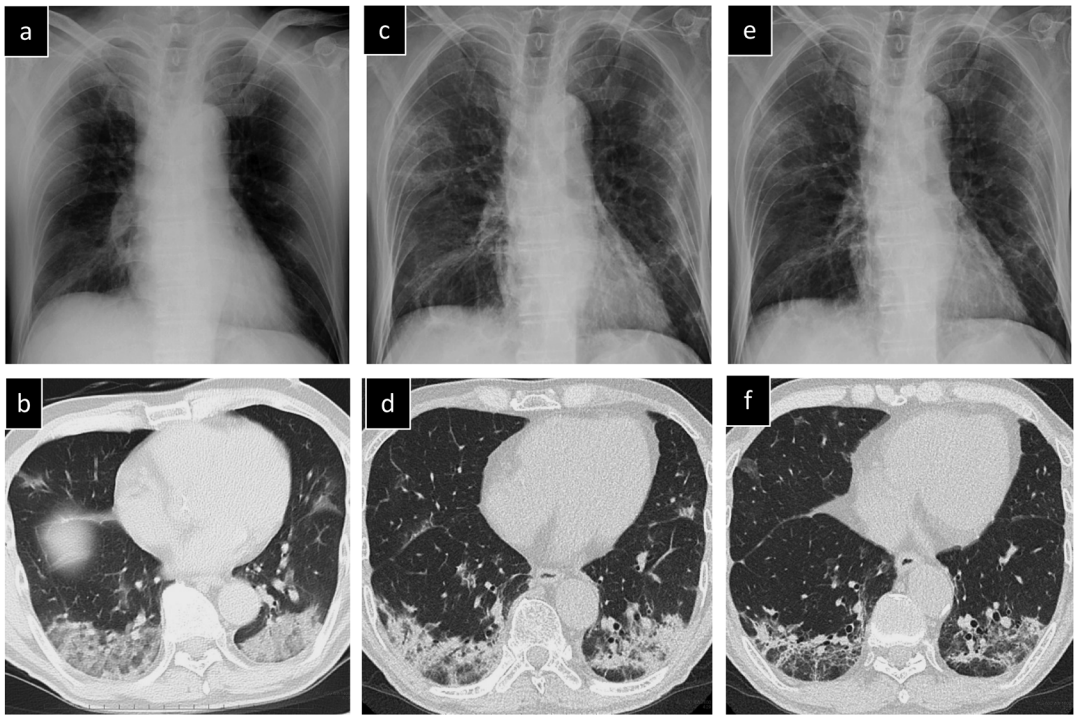
Figure 2. Hospital course of Case 1



AZM, azithromycin; CTRX, ceftriaxone; MNZ, metronidazole
The X-axis indicates the treatment period. The left Y-axis indicates body temperature and required amount of oxygen. The right Y-axis indicates respiratory rate.
Dotted lines and straight lines indicate respiratory rates and fever, respectively.
The rectangles indicate the administration period of drugs. Open triangles indicate the days on which the RT-PCR test was negative for COVID-19.

0.1 ng/mL; no abnormalities in kidney function were observed (Table 1). Chest X-ray and CT revealed infiltrative shadows and GGOs in bilateral lung fields (Figures 3a, 3b). After obtaining various culture specimens, we began to administer 500 mg azithromycin and 2 g ceftriaxone intravenously once daily and 400 mg/100 mg lopinavir/ritonavir orally twice daily. We performed an evaluation similar to that in Case 1 and observed that the test for pneumonia due to other pathogens was negative. On day 4, O_2 treatment at a rate of 6 L/min was necessary on exertion, but thereafter, the condition of the patient improved. On day 11, he required O_2 treatment at the rate

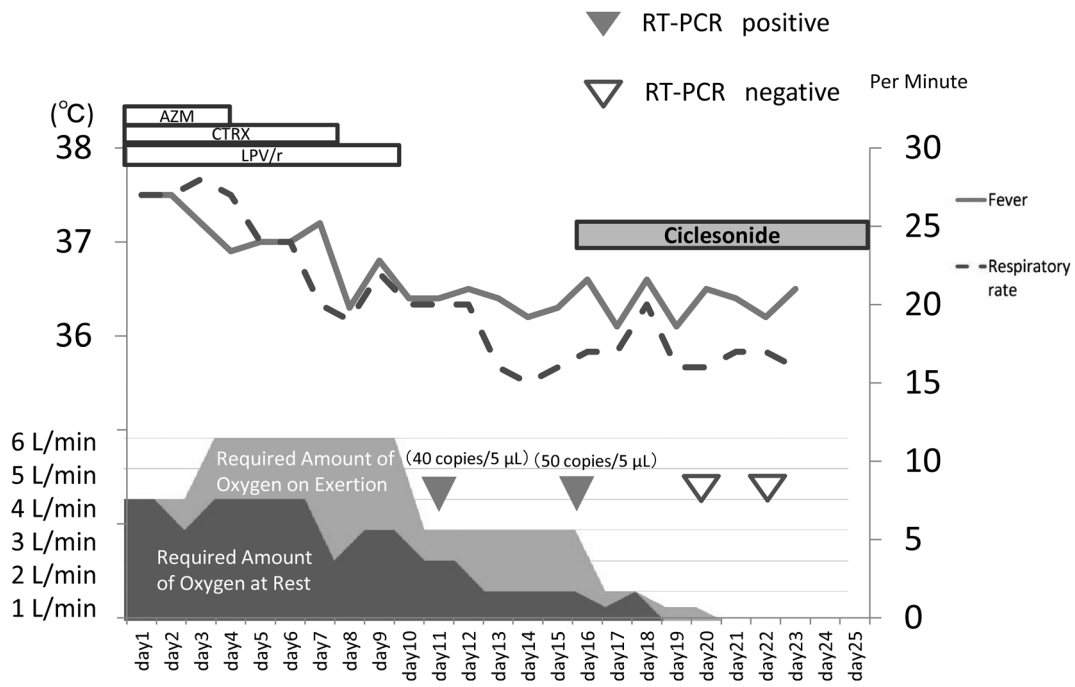
Figure 3. Chest X-ray and computed tomography findings of Case 2



a. On admission, light shadows were found in the bilateral lung fields, but they were primarily peripheral and more towards the right side.
b. High-density areas of ground-glass opacities and irregular high-density areas were confirmed, primarily peripherally, in the bilateral lung fields along with changes due to shrinkage.
c. On hospital day 16, the shadows were somewhat enlarged bilaterally, and changes due to shrinkage were also noticeable. The lung volume was slightly reduced overall.
d. Irregular high-density areas of the main body were apparent in the posterior region of the bilateral lower lobes, and the changes due to shrinkage had also increased and were accompanied by mildly dilated peripheral bronchi within the lesions.
e. On hospital day 23, both the shadows within the lung fields and the lung volume were improved.
f. Absorbance of the lesions in the lung fields was reduced overall, and the changes due to shrinkage were also improved. Fibrous network structures thought to represent fibrous changes and areas of bronchial dilation remained.

of 1 L/min at rest and 3 L/min on exertion, but the nasopharyngeal RT-PCR test remained positive (40 copies/5 μL). Chest X-ray and CT scan on day 16 showed partial reduction of the infiltrative shadows in his lungs (Figures 3c, 3d), and the nasopharyngeal RT-PCR test remained positive (50 copies/5 μL). After obtaining consent, we began to administer ciclesonide at 200 μg per dose, with two inhalations per day. On day 19, oxygenation at rest was deemed unnecessary, and on day 20, his nasopharyngeal RT-PCR test was found to be negative. The following day, oxygenation on exertion was also deemed unnecessary. On day 22, his nasopharyngeal RT-PCR test remained negative, and chest X-ray and CT on day 23 showed significant improvement in the shadows in both lung fields (Figures 3e, 3f). He was discharged with full recovery on hospital day 25. No side effects of ciclesonide were observed. Figure 4 shows the treatment response course of the

Figure 4. Hospital course of Case 2



AZM, azithromycin; CTRX, ceftriaxone; LPV/r, lopinavir/ritonavir.
On the X-axis, treatment period is indicated. The left Y-axis indicates body temperature and required amount of oxygen. The right Y-axis indicates respiratory rate. Dotted lines and straight lines indicate respiratory rates and fever, respectively. Rectangles indicate the administration period of drugs. Filled triangles indicate days on which RT-PCR test was positive for COVID-19. Open triangles indicate days on which RT-PCR was negative for COVID-19.

patient after admission to the hospital.

Discussion

Various drugs have been considered for the treatment of COVID-19[3]. Some have not been effective, as reported in a randomized clinical trial of a drug used for treating HIV (lopinavir/ritonavir and arbidol) in China[7], while clinical trials for others are ongoing, e.g., remdesivir in the United States[8] and favipiravir in Japan. The US Center for Disease Control and Prevention currently does not recommend the use of steroids for treatment of COVID-19, except in case of acute exacerbation of chronic obstructive pulmonary disease and septic shock[9].

Ko *et al.* (2020) reported that ciclesonide suppresses the growth of a clinically isolated strain of the MERS-CoV[4] and Matsuyama *et al.* (2020) confirmed that ciclesonide blocks the replication of coronavirus RNA by targeting the viral NSP15[5]. Iwabuchi *et al.* (2020) reported to the Japanese Association for Infectious Diseases that they have obtained tentatively positive results after administering ciclesonide in patients with COVID-19[6]. After inhalation, esterases in the

lungs convert ciclesonide into active metabolites with strong glucocorticoid affinity that act locally within the lungs, resulting in reduced ciclesonide migration into the peripheral blood and fewer side effects[10]. In the attached document of their paper, side effects (including abnormal laboratory findings) were reported in 45 out of 588 (7.7%) ciclesonide-treated cases. The breakdown was 35 cases (6.0%) with subjective/objective side effects and 12 cases (2.0%) with abnormal laboratory findings. Main subjective/objective side effects included 5 cases of dyspnea (0.9%), 5 cases of hoarseness (0.9%), and 3 cases with skin rash (0.5%). According to them, abnormal laboratory findings as side effects included 4 cases with urine protein (0.7%), 3 cases with increased AST (GOT) (0.5%), and 3 cases with increased ALT (GPT)[11]. Ciclesonide has been available since 2007. In fact, it is a safe drug that is widely used in asthmatic patients, including the elderly.

As for Case 1, lopinavir/ritonavir were used previously for three other critically ill patients in our hospital. However, no effects were observed upon administration of the drugs, and thus, we had been considering the use of other effective agents. We then decided to use ciclesonide, whose effectiveness was reported in a crisis-response expansion meeting for measures against SARS-CoV-2, organized by the Novel Coronavirus Response Headquarters and held at the National Institute of Infectious Diseases on February 19.

The dosage recommended in this meeting was used. Ciclesonide was administered in response to progressive hypoxemia. As a result, oxygenation was deemed unnecessary, despite the need for O_2 administration at the rate of 4 L/min four days earlier. Although it is unclear whether this was the natural course of the disease, the improved treatment progress in this patient lends support to the efficacy of ciclesonide.

The effectiveness of lopinavir/ritonavir against severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) have been suggested in the past[12,13]. In Case 2, lopinavir/ritonavir were used since the admission of the patient to our hospital, but his nasopharyngeal swabs remained RT-PCR-positive. His samples continued to be RT-PCR-positive and no prospective treatment strategy was determined. The introduction of Home oxygen therapy (HOT) following hospital discharge was considered. Case 1 suggested the possible efficacy of ciclesonide, we started administering it for Case 2. As a result, three days after starting ciclesonide treatment, the nasopharyngeal swab samples of the patient were found to be RT-PCR-negative, and his lung shadows were improved. Oxygenation at the rate of 1 L/min at rest and 3 L/min on exertion became unnecessary 5 days after the initiation of ciclesonide treatment. In both cases, ciclesonide appeared not only to have an anti-inflammatory effect on COVID-19, but also an antiviral effect, and such an effect may be expected in both acute and sub-acute stages of COVID-19. After these cases, the Japanese Society of Infectious Diseases announced the concept of drug treatment for COVID-19[14]. It also mentioned ciclesonide.

More COVID-19 cases must be studied to verify the efficacy of ciclesonide. Although the

harmful effects of long-term administration of inhaled corticosteroids must be considered, no proven effective treatments to curb this explosive expansion of the COVID-19 pandemic have been reported thus far. Thus, we have reported our findings observed in these two cases.

Conclusion

Ciclesonide appeared to be useful in the treatment of two cases of COVID-19. It may be a potential drug for the treatment of COVID-19 in the future; thus, its efficacy has to be ascertained through more studies.

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Conflict of interest

There is no conflict of interest.

References

1) World Health Organization: Novel coronavirus (2019-nCoV) situation report-1 [Internet]. Geneva: World Health Organization; 2020 January 21 [cited 2020 March 15]. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf.
2) Japanese Minister of Health, Labour and Welfare: About current situation of Coronavirus Disease 2019 (COVID-19) cases at the cruise ship [Internet]. 2020 May 6 [cited 2020 May 7]. Available at: https://www.mhlw.go.jp/stf/newpage_11178.html.
3) Lu H: Drug treatment options for the 2019-new coronavirus (2019-nCoV). BioSci Trends 2020; 14: 69–71.
4) Ko M, Chang SY, Byun SY, *et al.*: Screening of FDA-approved drugs using a MERS-CoV clinical isolate from South Korea identifies potential therapeutic options for COVID-19 [Preprint]. BioRxiv; 2020 March 02 [cited 2020 March 13]. Available from: https://www.biorxiv.org/content/10.1101/2020.02.25.965582v1.
5) Matsuyama S, Miyuki K, Naganori N, *et al.*: The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15 [Preprint]. BioRxiv; 2020, March 12 [cited 2020 March 25]. Available from: https://doi.org/10.1101/2020.03.11.987016.

6) Iwabuchi K, Yoshie K, Kurakami U, Takahashi K, Kato Y, Morishima T: Three cases of COVID-19 improved with ciclesonide inhalation in the early to middle stages of pneumonia [in Japanese]. The Japanese Association for Infectious Diseases; 2020 March 2 [cited 2020 March 5]. Available at: http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_200302_02.pdf.
7) Bin C, Yeming W, Danning W, *et al.*: A trial of Lopinavir–Ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020; DOI: 10.1056/NEJMoa2001282.
8) National Institute of Health: NIH clinical trial of remdesivir to treat COVID-19 begins [Internet]. Maryland (USA): National Institute of Allergy and Infectious Diseases; 2020 February 25 [cited 2020 March 13]. Available at: https://www.niaid.nih.gov/news-events/nih-clinical-trial-remdesivir-treat-covid-19-begins.
9) Centers for Disease Control and Prevention: Interim clinical guidance for management of patients with confirmed Coronavirus disease (COVID-19) [Internet]. Georgia (USA): Centers for Disease Control and Prevention; 2020 [updated 2020 April 3; cited 2020 March 15]. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html.
10) Nonaka T, Katsuura Y, Sugiyama H, Miyagi F: Pharmacological properties and clinical effects of the inhaled corticosteroid ciclesonide (Alvesco® inhaler) for treatment of asthma. Folia Pharmacologica Japonica 2008; 132: 237–43.
11) ALVESCO attached document (in Japanese). [cited 2020 April 22]. Available at: https://pins.japic.or.jp/pdf/newPINS/00059259.pdf.
12) Chu CM, Cheng VC, Hung IF, *et al.*: Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004; 59: 252–6.
13) Chong YP, Song JY, Seo YB, Choi JP, Shin HS: Antiviral treatment guidelines for Middle East respiratory syndrome. Infect Chemother. 2015; 47: 212–22.
14) Concept of drug treatment for COVID-19 Second Edition (in Japanese).The Japanese Association for Infectious Diseases [updated 2020 May 1; cited 2020 May 7]. Available at: http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_drug_200430.pdf.