Original Article

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Impact of inhaled ciclesonide on asymptomatic or mild COVID-19: A randomized trial

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SUMMARY The aim of this study was to determine the efficacy and safety of ciclesonide in the treatment of novel coronavirus disease 2019 (COVID-19) as gauged by pneumonia progression. This multi-center, open-label randomized trial was conducted with patients recruited from 22 hospitals across Japan. Participants were patients admitted with mild or asymptomatic COVID-19 without signs of pneumonia on chest X-rays. Asymptomatic participants were diagnosed after identification through contact tracing. Trial participants were randomized to either the ciclesonide or control arm. Participants in the treatment arm were administered 400 μg of ciclesonide three times a day over seven consecutive days. The primary endpoint was exacerbated pneumonia within seven days. Secondary outcomes were changes in clinical findings, laboratory findings, and changes over time in the amount of the viral genome. In the treatment group, 16 patients (39.0%) were classified as having exacerbated pneumonia compared to 9 (18.8%) in the control group. The risk ratio (RR) was 2.08 (95% confidence interval (CI): 1.15-3.75), indicating a worsening of pneumonia in the ciclesonide group. Significant differences were noted in participants with a fever on admission (RR: 2.62, 90% CI: 1.17-5.85, 95% CI: 1.00-6.82) and individuals 60 years of age or older (RR: 8.80, 90% CI: 1.76-44.06, 95% CI: 1.29-59.99). The current results indicated that ciclesonide exacerbates signs of pneumonia on images in individuals with mild or asymptomatic symptoms of COVID-19 without worsening clinical symptoms.

Keywords COVID-19, ciclesonide, randomized clinical trial, pneumonia

1. Introduction

Following initial reports of pneumonia related to novel coronavirus disease 2019 (COVID-19) from December 2019 onwards in Wuhan in Hubei Province, the People's Republic of China, similar reports were noted around the world, and the increasing number of reports signaled the advent of a pandemic. There are many patients with COVID-19 in Japan, but this is an emerging infectious disease, and there are limited treatments available for individuals with mild COVID-19. At the time of this research plan, standard treatment methods were limited

to symptomatic treatment (*1*).

Ciclesonide was first approved in Australia for indications of bronchial asthma in February 2004; as of March 2021, it was approved in 48 countries worldwide. In Japan, ciclesonide is manufactured and marketed by Teijin Pharma (Tokyo, Japan) under the trade name Alvesco, and it was first approved for indications of adult bronchial asthma in April 2007 and for children in January 2011. Ciclesonide's mechanism of action on asthma is through esterase activation in the lungs and alveoli, which then becomes the active metabolite desisobutrylciclesonide, which then binds to glucocorticoid receptors to control chronic inflammation in the alveoli.

In the wake of the COVID-19 pandemic, ciclesonide has been reported to possibly inhibit the Middle East respiratory syndrome coronavirus (MERS-CoV) in "Vero" cells (*2*). Basic research by the Coronavirus Laboratory at the National Institute for Infectious Diseases suggested that ciclesonide might have potent anti-viral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (*3*). Ciclesonide's effects on preventing viral proliferation were either equivalent to or exceeded those of lopinavir in *in vitro* tests. Case reports indicated that the ideal period of ciclesonide administration should be in the early to intermediate stage of infection or during the initial phase of pneumonia before symptoms worsen (*3-6*). Beyond these, there have been no further reports on ciclesonide administration in patients with COVID-19.

The current study conducted a prospective randomized controlled trial to analyze ciclesonide's efficacy and safety in patients with COVID-19 in the early stages of infection. Assembling findings related to COVID-19 through this study should help to develop future countermeasures against this disease.

2. Materials and Methods

2.1. Participants

This multi-center, open-label randomized trial was conducted in Japan with patients recruited from 22 hospitals across Japan (Figure 1) between April 3, 2020 and September 18, 2020. The efficacy and safety of ciclesonide was assessed in patients with COVID-19 in the early stages of infection. Patients who tested positive for SARS-CoV-2 based on a polymerase chain reaction (PCR) or according to loop-mediated isothermal amplification were identified for recruitment. Since this study was conducted on asymptomatic or mildly ill patients, many of them were tested as close contacts or individuals with mild symptoms who tested positive. Patients admitted with COVID-19 were screened, and those with no signs of pneumonia on chest X-rays (CXR) were deemed eligible. Additional inclusion criteria included: age ≥ 20 years, had no clear indications of COVID-19-induced pneumonia on plain CXRs, individuals who could be hospitalized to receive the trial drug (*i.e.*, one week), and individuals who could inhale ciclesonide using inhalation assistance. Exclusion criteria were: a history of ciclesonide hypersensitivity, an infectious disease or deep-seated mycosis other than COVID-19 for which there is no effective antibacterial, a chronic respiratory disease such as chronic bronchitis, current treatment with inhaled or oral steroids, a history of a persistent fever of ≥ 37.5°C that lasted for over seven days, or current treatment with agents that are potentially efficacious in treating COVID-19 and that may affect assessments of efficacy, including remdesivir, lopinavir/ritonavir compound drugs, favipiravir, interferon, and hydroxychloroquine. Patients were randomized using the stratified block randomization method.

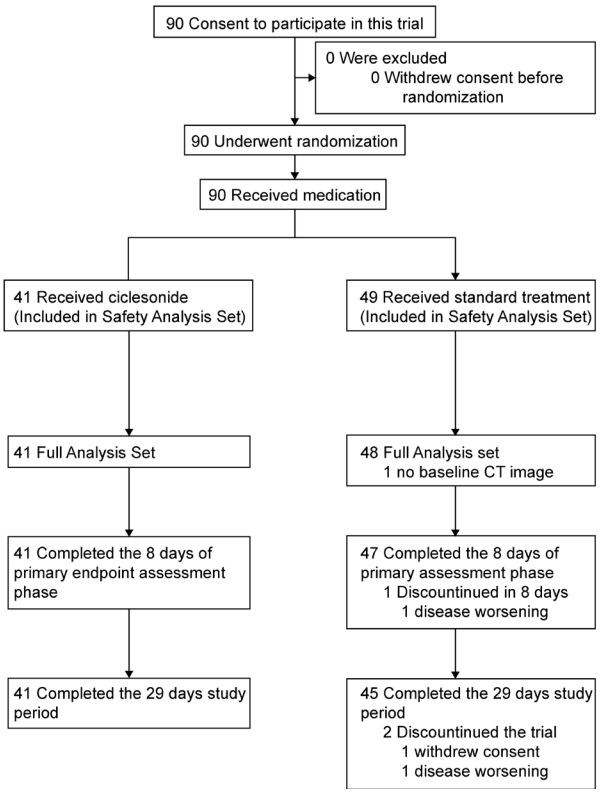

Figure 1. Flow diagram of participant recruitment and the phases of the RACCO randomized trial.

2.2. Protocol

Participants who were admitted to the hospital for 1-2 days of observation were identified prior to registration. Protocol details are provided in a previous paper (*6*). Demographic characteristics, vital signs, body mass index, samples and imaging, peak expiratory flow (PEF) measurements, and responses to a questionnaire were collected during the observation period.

Once enrolled, trial participants were randomized to either the ciclesonide group or a symptomatic treatment

group using the Electronic Data Capture (EDC) system. Participants in the ciclesonide group were administered 400 µg of ciclesonide in a pressurized metered-dose inhaler (pMDI) formulation three times a day with a spacer, over seven consecutive days. This dose was recommended for severe cases in a previous study, but this dose was chosen for the current study to avoid insufficient drug dosage to confirm antiviral activity (*2*). In contrast, the symptomatic treatment group received only symptomatic treatment for symptoms such as a fever and cough, *i.e.*, the study was open-label. The following information was obtained throughout the trial: demographic characteristics, a physical exam (including BMI), medical history (duration of hospitalization), hematological tests, blood chemistry, coagulation tests, infectious disease panel, and coronavirus tests (nasal and serum). A chest X-ray (CXR) was performed on days 1, 8, 15, 22, and 29, PEF was measured daily, and a questionnaire on appetite, fatigue, and coughing was administered on days 1-8, 15, 22, and 29. A complete listing of the study sites, data collected, and time points is shown in Supplemental Tables S1 and S2, and Supplemental Figure S1 (*http://www.ddtjournal.com/action/getSupplementalData.php?ID=123*).

2.3. Outcomes

The primary endpoint was exacerbated pneumonia within seven days of inhalation of ciclesonide, based on computerized tomography (CT) scans before drug administration and one week following treatment. Chest CT images within seven days of administration were assessed in the three following stages: remission or stabilization compared to the status before administration, potential exacerbation compared to the status before administration, or obvious worsening compared to the status before administration. Two radiologists independently interpreted images, and worsening signs of pneumonia on images were determined. Instances where the two radiologists disagreed were resolved by a specialist in pulmonary medicine. Efficacy was confirmed by checking for the exacerbation of pneumonia. Secondary outcomes were changes in clinical findings, laboratory findings, and changes over time in the amount of the viral genome.

2.4. Safety

The safety of this therapy was evaluated and the number of adverse events (AEs) was determined. AEs were defined as abnormal variations in clinical values and physiological function. The following information on AE was collected: incident duration, time to resolution, extent, treatment, outcome, assessment of its severity, correlation with the study drug, and predictability. The extent of an AE was categorized as mild (continued administration is possible with no treatment), moderate (continued administration is likely with some form of treatment), or severe (administration was or should be suspended). A severe AE were defined as the following: death, life-threatening complications, hospitalization or an extended stay in the hospital or other care facility, permanent or significant disability or functional limitation, or congenital illness/abnormalities affecting subsequent generations.

2.5. Statistical analysis

Based on the experience of the Center Hospital, 35% of patients who were deemed positive for COVID-19 without symptoms of pneumonia developed pneumonia during the follow-up period. Assuming that the incidence of pneumonia in the standard treatment and trial treatment groups would hypothetically be 35% and 10%, respectively, then the required sample size of 84 patients was calculated for both a power of 10% and 80% with a two-tailed alpha. The planned sample size was set at 90 to account for several dropouts.

The primary population used for the efficacy analysis was the complete analysis set, including all patients who had undergone randomization, whose baseline CT image data were acquired, and who had no severe protocol violations. Primary efficacy, *i.e.*, the proportion of patients with exacerbated pneumonia within seven days of administration, was compared between the groups using Fisher's exact test. In addition, the risk ratio (RR) and risk difference (RD) and their 90% and 95% confidence intervals (CIs) were calculated.

Predefined subgroup analyses stratified by age (< 60 or ≥ 60), smoking (yes or no), a fever on admission (< 37.5°C or ≥ 37.5°C) were performed in the same manner as the primary analysis. Analysis using the secondary efficacy outcomes (changes in clinical findings, laboratory findings, and changes over time in the amount of the viral genome) were performed, and summary statistics (number of cases, average value, standard deviation, minimum value, median value, and maximum value) were calculated for each group. Missing data for the primary endpoint or secondary efficacy outcome were not input. Other statistical methods and details regarding statistical assumptions are described in the Supplemental Appendix. Since the widths of the confidence intervals have not been adjusted for multiple comparisons, the intervals should not be used to infer definitive therapeutic effects for the secondary efficacy outcomes or subgroup analyses. All statistical analyses were performed by Y.U. using the software SAS, version 9.4 (SAS Institute).

2.6. Research ethics and disclosure

This trial was approved by the Clinical Research Review Board at The University of Tokyo (Protocol Number: 2019017SP) and it has been registered with the Japan

Registry of Clinical Trials (jRCT No: jRCTs031190269). The data obtained in this study will be registered in the "Registry research relating to COVID-19 (COVIREGI) (NCGM Ethical Inspection Committee approval No. NCGM-G-003494-00)".

3. Results

3.1. Patient characteristics

Eighty-nine patients were randomized in this study, 41 in the ciclesonide group and 48 in the symptomatic treatment group, with a mean overall age of 23.17 ± 3.88 years (Table1). The sociodemographic and clinical characteristics of the sample are shown in Table 1. Forty-four (49.4%) patients were male, with 20 (48.8%) in the treatment group and 24 (50.5%) in the observation group. There were no statistical differences between the groups.

The median time from onset to hospitalization was 5.0 days in the ciclesonide group and 5.5 days in the symptomatic treatment group. Most of the participants were Japanese, but three in the ciclesonide group and one in the symptomatic treatment group were non-Japanese. The comorbidities in the ciclesonide group were congestive heart failure (2 patients), mild liver disease (2 patients), mild diabetes (2 patients), obesity (2 patients), a peptic ulcer (2 patients), dementia (1 patient), cerebrovascular disease (1 patient), and those in the symptomatic treatment group were mild diabetes (3 patients), obesity (3 patients), a solid tumor (3 patients), mild liver disease (1 patient), and HIV infection (1 patient).

3.2. Primary and secondary outcomes

Univariate analysis compared exacerbated pneumonia in the two groups. Figure 2A shows the RRs while Figure 2B shows the RDs. In the treatment group, 16 patients (39.0%) were classified as having exacerbated pneumonia compared to 9 (18.8%) in the control group. The RR was 2.08 (95% CI: 1.03-4.20, Figure 2A). In the stratified analysis, results differed little depending on whether a patient had a history of smoking or not. In contrast, RR tended to differ significantly among patients with a fever on admission (RR: 2.62, 95% CI: 1.00-6.82) and individuals 60 years of age or older (RR: 8.80, 95% CI: 1.29-59.99). These point estimates are based on small numbers.

The overall RD was not significant (RD: – 0.20, 95% CI: 0.02-0.39, Figure 2B). Fever was not significant at the 95% confidence level but was at the 90% confidence level. A significant difference was not noted for individuals 60 and older (RD: 0.71, 95% CI: 0.32-1.00). However, those numbers are very small.

3.3. Safety

Table 2 shows the number of AEs in each group. AEs,

Table 1. Demographic characteristics and select clinical variables

Background factors	Ciclesonide group, *n* (%)	Symptomatic treatment group, *n* (%)	Total, *n* (%)
Number of subjects	41	48	89
Sex			
Male	20 (48.8)	24 (50.0)	44 (49.4)
Female	21 (51.2)	24 (50.0)	45 (50.6)
Age			
< 60 years (≥20 years)	36 (87.8)	37 (77.1)	73 (82.0)
≥ 60 years	5 (12.2)	11 (22.9)	16 (18.0)
BMI			
N	40	45	85
Mean	22.53	23.74	23.17
SD	3.38	4.22	3.88
Smoking			
Current smoker	10 (24.4)	11 (22.9)	21 (23.6)
Former smoker	7 (17.1)	8 (16.7)	15 (16.9)
Non-smoker	23 (56.1)	27 (56.3)	50 (56.2)
Unknown	1 (2.4)	2 (4.2)	3 (3.4)
Presence of comorbidities			
Yes	8 (19.5)	10 (20.8)	18 (20.2)
No	33 (80.5)	38 (79.2)	71 (79.8)
Presence of immunosuppressive conditions			
Yes	0 (0)	0 (0)	0 (0)
No	41 (100)	48 (100)	89 (100)
Chest CT image			
Signs of pneumonia	18 (43.9)	24 (50)	42 (47.2)
No signs of pneumonia	23 (56.1)	24 (50)	47 (52.8)
Plain chest X-ray			
No abnormalities evident	41 (100)	46 (95.8)	87 (97.8)
Signs of pneumonia (including infiltrative opacities/interstitial opacities)	0 (0)	0 (0)	0 (0)
Abnormal opacities other than signs of pneumonia	0 (0)	1 (2.1)	1 (1.1)
No X-ray	0 (0)	1 (2.1)	1 (1.1)

with no deaths, were observed in 15 patients (36.6%) in the ciclesonide group and 18 patients (36.7%) in the symptomatic treatment group. There were no significant differences in the number of AEs between the two groups. There was one serious AE in the symptomatic treatment group, which was an exacerbation of COVID-19 pneumonia, and the patient recovered after stopping the study and receiving antiviral treatment. AEs that were observed in more than 5% of patients included liver disfunction, an elevated sedimentation rate, a decrease in creatine phosphokinase in the blood, and headaches, all of which were not causally related to the study drug.

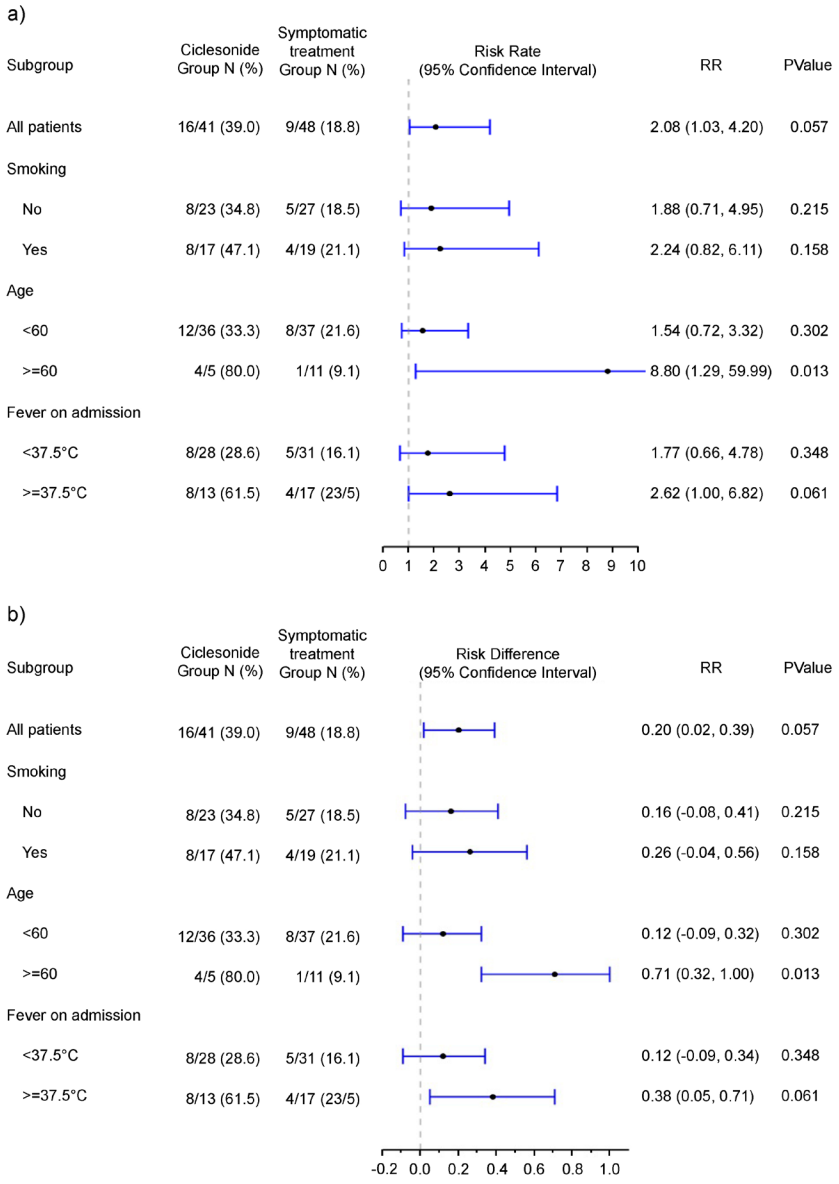

Figure 2. Primary outcomes and subgroup analysis. (**A**) shows the risk rate and (**B**) shows the risk difference. In both analyses, the ciclesonide group tended to have worsening opacities on CT images. Subgroup analysis revealed a similar trend regardless of smoking history or the presence or absence of a fever at admission. Elderly patients had particularly poor results in the ciclesonide group, but caution should be exercised in interpreting the results due to the small number of patients.

Table 2. The incidence of adverse events/side effects

Items	Ciclesonide group (n = 41)			Symptomatic treatment group (n = 49)		
	Number of events	Number of subjects (%)*	95% CI for incidence**	Number of events	Number of subjects (%)*	95% CI for incidence**
Adverse Events	26	15 (36.6)	0.22-0.53	34	18 (36.7)	0.23-0.52
Serious adverse event	0	0	0	1	1 (2.0)	0.00-0.11
Side effect	3	3 (7.3%)	0.02-0.20	0	0 (0.0%)	0.00-0.07
Any serious side effect	0	0 (0.0%)	0.00-0.09	0	0 (0.0%)	0.00-0.07

CI: confidence interval. *The sum of the number of subjects in whom a serious event occurred; if a corresponding event had occurred no less than once in the same subject, the event was counted as a single event. **The confidence intervals were calculated using the Clopper & Pearson method. ***Intergroup comparison was performed using Fisher's exact test.

3.4. Viral load

Figure 3 shows the viral load for each of the groups on Day 1 and within 8 days. There were no significant differences in the viral load between the two groups at either time. The distribution of the viral load from the nasopharyngeal swab on days 1 and 8 is shown in Table 3. Inhalation of steroids did not increase the viral load.

4. Discussion

This study evaluated the efficacy of inhaled ciclesonide in patients with COVID-19 by comparing the rate of exacerbated pneumonia in the inhaled ciclesonide

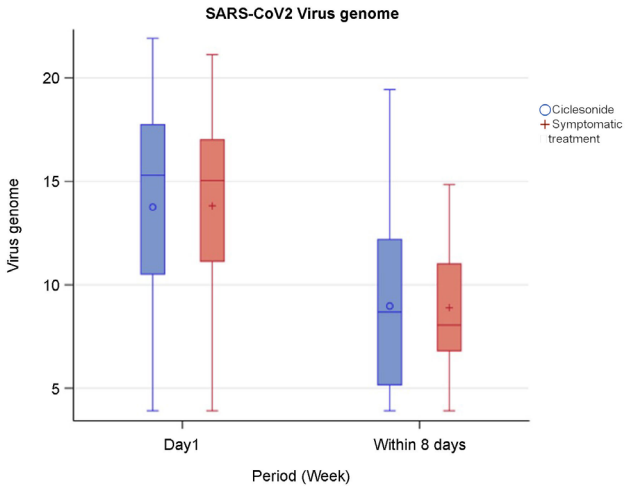

Figure 3. Viral load. Shown here is the amount of viral genome in nasopharyngeal swabs from Days 1 and 8. The amount of viral genome did not differ between the two groups.

Table 3. Nasopharyngeal viral load on days 1 and 8

Full Analysis Set

Treatment group	Summary statistics								*p*-value*
	Number	Average	Std Dev	Minimum	1st quartile	Median	3rd quartile	Maximum	
Ciclesonide group									
Day 1									
Viral load	37	13.76	4.96	3.9	10.5	15.29	17.7	21.9	0.983
Within 8 days									
Viral load	27	8.98	4.04	3.9	5.2	8.69	12.2	19.4	0.894
Variation	27	– 6.68	5.04	– 14.4	– 9.7	– 7.37	– 4.5	11.7	0.587
Rate of change	27	– 37.80	43.65	– 78.6	– 65.7	– 44.35	– 28.7	150.7	0.587
Symptomatic treatment group									
Day 1									
Viral load	39	13.82	4.79	3.9	11.1	15.04	17.0	21.1	
Within 8 days									
Viral load	26	8.90	3.09	3.9	6.8	8.05	11.0	14.8	
Variation	26	– 6.48	3.76	– 13.3	– 9.7	– 6.75	– 3.5	0.5	
Rate of change	26	– 40.20	21.52	– 70.5	– 57.4	– 44.76	– 27.1	7.5	

*Results were evaluating using the Wilcoxon rank-sum test.

Per-protocol Set

Treatment group	Summary statistics								*p*-value*
	Number	Average	Std Dev	Minimum	1st quartile	Median	3rd quartile	Maximum	
Ciclesonide group									
Day 1									
Viral load	36	13.61	4.95	3.9	10.0	15.04	17.6	21.9	0.841
Within 8 days									
Viral load	26	8.88	4.08	3.9	5.2	8.49	12.2	19.4	0.756
Variation	26	– 6.65	5.13	– 14.4	– 9.7	– 7.33	– 4.5	11.7	0.685
Rate of change	26	– 37.74	44.51	– 78.6	– 65.7	– 44.41	– 28.7	150.7	0.553
Symptomatic treatment group									
Day 1									
Viral load	38	13.87	4.84	3.9	11.1	15.24	17.0	21.1	
Within 8 days									
Viral load	25	8.95	3.14	3.9	6.8	8.09	11.0	14.8	
Variation	25	– 6.56	3.82	– 13.3	– 9.7	– 7.36	– 3.5	0.5	
Rate of change	25	– 40.32	21.96	– 70.5	– 57.4	– 45.25	– 27.1	7.5	

*Results were evaluating using the Wilcoxon rank-sum test.

group to that in the symptomatic treatment group. The primary outcome was the proportion of patients with worsening signs of pneumonia on CT images on day 7 in the ciclesonide inhalation group and in the conventional treatment group. Results indicated that the ciclesonide inhalation group had more exacerbated pneumonia than the symptomatic treatment group, even at the conservative two-sided significance level of 10%. Safety did not differ between the two groups, and there were no severe AEs. To the extent known, this is the first randomized clinical trial to yield these findings.

Previous studies have indicated that ciclesonide may be effective in inhibiting SARS-CoV-2 replication at the cellular level. Therefore, the current study hypothesized that inhibition of viral replication would directly inhibit the exacerbation of pneumonia and subsequent severe disease. As the results indicate, CT findings of pneumonia worsened in the ciclesonide group, but there were no instances of severe disease in either group, and clinical findings indicated that the incidence of fever tended to be higher in the ciclesonide group, but there was no exacerbation during the course of this study. There were no cases of severe illness requiring a ventilator and there was no relationship between the study drug and the exacerbation of pneumonia directly leading to severe illness, suggesting that ciclesonide administration temporarily aggravates pneumonia but does not affect the course of treatment.

Ciclesonide is commonly used in respiratory medicine as a treatment for asthma. Experimental data from the National Institute of Infectious Diseases reported that ciclesonide has an antiviral effect against novel coronavirus (SARS-CoV-2) (*7*). In Japan, a case report noted alleviation of pneumonia following the use of inhaled ciclesonide in three patients with COVID-19 (*2*).

However, ciclesonide appeared to exacerbate pneumonia in the current study. Results suggest that mild or asymptomatic cases are likely to improve spontaneously with symptomatic treatment alone.

In SARS, MERS, and influenza, systemic steroid administration is known to delay viral elimination. In SARS, viral replication peaks in the second week, but in SARS-CoV-2 replication peaks early; after the first week, the immunological component becomes the main factor, and this immunological response leads to the development of pneumonia.

However, virologically and epidemiologically, the infectivity of SARS-CoV-2 is considered to be from 2-3 days before to 10 days after the onset of the disease, which means that the signs of pneumonia on images on Day 8 that were assumed to be an immune response were not directly caused by the virus. The current understanding is that ground-glass opacities (GGOs) appear on chest CT images within 3 to 5 days of onset. This is seen in approximately 90% of symptomatic cases (*8*). Even in asymptomatic patients with COVID-19, CT imaging findings of GGOs predominate over consolidation in many patients, but the severity score was higher in symptomatic patients, suggesting that imaging and symptoms may diverge in asymptomatic or mildly symptomatic patients. Therefore, pneumonia may have developed irrespective of antiviral therapy, suggesting that it may have had little impact on the course of treatment in mild cases. GGOs are consistent with type II alveolar epithelial cells infected with SARS-Cov-2, and the opacities may represent inflammation of the structures surrounding these cells. Accordingly, improvement in the pneumogram is not directly related to ciclesonide treatment.

No other studies have assessed imaging to evaluate the efficacy of ciclesonide on COVID-19. In a study of the effect of inhaled ciclesonide on reducing the risk of AEs in COVID-19 outpatients at risk of severe disease, there were no differences in COVID-19 exacerbation by day 14 in the ciclesonide and control groups, and secondary outcomes were similar in both groups (*9*). Blinded, randomized, controlled trials in non-hospitalized patients with symptomatic COVID-19 have indicated that ciclesonide did not achieve its primary endpoint of a reduction in the time to relief of all COVID-19-related symptoms (*10,11*). An open-label phase 2 study indicated that inhalation of ciclesonide accelerated viral elimination from nasopharyngeal swabs on day 14, but there was no difference in the duration of hospitalization or the rate of alleviation of symptoms (*12*). The current study noted no differences due to the intervention between swabs on day 1 and those on day 8. There might have been differences due to the intervention if the swabs on day 1 were compared to those on day 14, but the clinical significance of this difference is uncertain.

The current trial had several limitations. One limitation stems from not knowing the ciclesonide dosage needed to ensure that patients achieved a cellular ciclesonide concentration equal to that found to induce antiviral action in preclinical studies. However, this study used a high inhalation dose, and administering a higher inhalation dose was not possible. In addition, the average duration of administration was five days after the onset of illness, so administering an antiviral so early after the onset of the disease may have been inefficacious, as is true with influenza. Treatments need to be adapted to changes in viral replication. The second limitation is that this study had a small sample size. However, this study had a high level of internal validity because participants were randomized from 22 facilities across Japan. In addition, this study included patients with a confirmed diagnosis according to PCR or antigen testing, and CT images were evaluated blindly by a third party, so this study also had a high level of external validity. The third limitation is that the findings of this study were diminished by not including a placebo control group. However, a placebo could not be prepared as an inhalant because it is very time-consuming and the study needed to start as soon as possible in response to

the rapid spread of COVID-19. The primary endpoint was assessed in a blinded setting, and presumably there is no bias in the results because of the fact that this study was open-label. The use of CT imaging as an endpoint is also controversial, but this study was designed in the very early days of the COVID-19 epidemic, and whether use of imaging would be appropriate had yet to be determined. Several studies on ciclesonide have been conducted, but the endpoints have varied.

In conclusion, ciclesonide was found to exacerbate signs of pneumonia on CT images without worsening clinical symptoms in individuals with mild or asymptomatic symptoms of COVID-19.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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