Original Article

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Inhaled ciclesonide does not affect production of antibodies or elimination of virus in patients with COVID-19: Subanalysis of a multicenter, open-label randomized trial

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SUMMARY During an earlier multicenter, open-label, randomized controlled trial designed to evaluate the effectiveness of high-dose inhaled ciclesonide in patients with asymptomatic or mild coronavirus disease 2019 (COVID-19), we observed that worsening of shadows on CT without worsening of clinical symptoms was more common with ciclesonide. The present study sought to determine if an association exists between worsening CT shadows and impaired antibody production in patients treated with inhaled ciclesonide. Eighty-nine of the 90 patients in the original study were prospectively enrolled. After exclusions, there were 36 patients each in the ciclesonide and control groups. We analyzed antibody titers against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleocapsid protein at various time points. Changes in viral load during treatment were compared. There was no significant difference in age, sex, body mass index, background clinical characteristics, or symptoms between the two groups. Although evaluation on day 8 suggested a greater tendency for worsening shadows on CT in the ciclesonide group ($p = 0.072$), there was no significant difference between them in the ability to produce antibodies ($p = 0.379$) or the maximum antibody titer during the clinical course. In both groups, worsening CT shadows and higher viral loads were observed on days 1-8, suggesting ciclesonide does not affect clearance of the virus ($p = 0.134$). High-dose inhaled ciclesonide did not impair production of antibodies against SARS-CoV-2 or affect elimination of the virus, suggesting that this treatment can be used safely in patients with COVID-19 patients who use inhaled steroids for asthma and other diseases.

Keywords SARS-CoV-2 nucleocapsid protein antibody, asymptomatic or mild COVID-19, randomized clinical trial, anti-viral effect, viral load

1. Introduction

In 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged and seriously threatened human health and socioeconomic activity worldwide. Clinical manifestations of SARS-CoV-2 infection vary depending on the presence of risk factors that include obesity, cardiovascular disease, diabetes, older age, and comorbidities (*1*). The rationale for using steroids in patients who are hospitalized with coronavirus disease 2019 (COVID-19) is based on the finding in a clinical trial that administration of dexamethasone reduced mortality in these patients, suggesting that the anti-inflammatory effects of the compound overcome its negative immunosuppression effects (*2*).

Interestingly, ciclesonide is thought to ameliorate inflammation by inhibiting the pathogenic kinase PAK1 (RAC/CDC42-activated kinase 1) (*3*). Basic research has suggested that ciclesonide may have potent antiviral activity against SARS-CoV-2 (*4*), and case reports have also shown the effectiveness of ciclesonide (*5*). Moreover, several lines of evidence suggest that inhaled ciclesonide has anti-viral activity (*6,7*). Although it is unclear whether asthma is a risk factor for severe SARS-CoV-2 infection (*8*), several clinical trials of ciclesonide have been conducted in outpatients or hospitalized

patients based on these results (*9-11*). However, it has not been confirmed that ciclesonide improves outcomes in patients with severe clinical symptoms. We performed a clinical trial to evaluate the effects of ciclesonide 400 μg inhaled three times daily for 7 consecutive days in patients with mild clinical signs of COVID-19 at the time of enrollment (*12*). Surprisingly, we found that worsening of shadows on CT was more common in patients treated with ciclesonide (39%, *n* = 16) than in those who received symptomatic treatment alone (18.8%, *n* = 9). Given that antibody production has been reported to be impaired after SARS-CoV-2 vaccination in patients on corticosteroids (*13*), it is necessary to clarify whether ciclesonide causes worsening of CT shadows and impairs antibody production.

The aim of this study was to determine if there is an association of worsening CT shadows with impaired antibody production in patients treated with inhaled ciclesonide.

2. Materials and Methods

2.1. Study population and protocol

This study is a subanalysis of a multicenter, open-labelled randomized trial (RACCO study). The complete study protocol has been described previously (*12*). This trial was approved by the Clinical Research Review Board at The University of Tokyo (protocol number: 2019017SP). Written informed consent was obtained from all patients before participation.

2.2. Demographic characteristics

Eighty-nine of the 90 patients who participated in our previously reported trial (*12*) were enrolled in the present study (Table S1 in the Supplementary Data, *http://www.ddtjournal.com/action/getSupplementalData.php?ID=173*) and were divided into a ciclesonide group (*n* = 41, 20 men, mean age 38.7 ± 17.0 years) and a control group (*n* = 48, 24 men, mean age 42.7 ± 18.7 years). One patient was excluded from the analysis due to lack of baseline CT. There was no between-group difference in body mass index, mean age, or duration of hospitalization after onset of clinical signs of SARS-CoV-2 infection. After excluding 2 patients whose condition deteriorated and required additional medications, 3 who were discharged on day 7 (with a medication compliance rate of < 90%), and 12 who were negative on day 1 of the study but positive before hospitalization (ciclesonide group, *n* = 3; control group, *n* = 9), this left 72 patients for this study (ciclesonide group, *n* = 36; control group, *n* = 36) (Figure 1).

2.3. Exacerbation of pneumonia and production of antibodies against SARs-CoV-2 nucleocapsid protein

Antibody titers against SARS-CoV-2 nucleocapsid protein were measured by enzyme-linked immunosorbent assay on hospital days 1, 8, 15, and 22 and then compared between patients with exacerbation of pneumonia in the ciclesonide group and their counterparts in the control group. Exacerbation of pneumonia was judged on CT scans obtained on day 1 (pretreatment) and day 8 (*12*). The actual dates for antibody measurement were calculated from the date of onset of clinical signs of SARS-CoV-2 infection.

2.4. Measurement of antibody titers

A plate coated in recombinant nucleocapsid protein was incubated with a serum/plasma sample diluted to 1/800 for 1 h at 37ºC after blocking with 1% BlockAce (KAC, Kyoto, Japan). Following washing with phosphate-

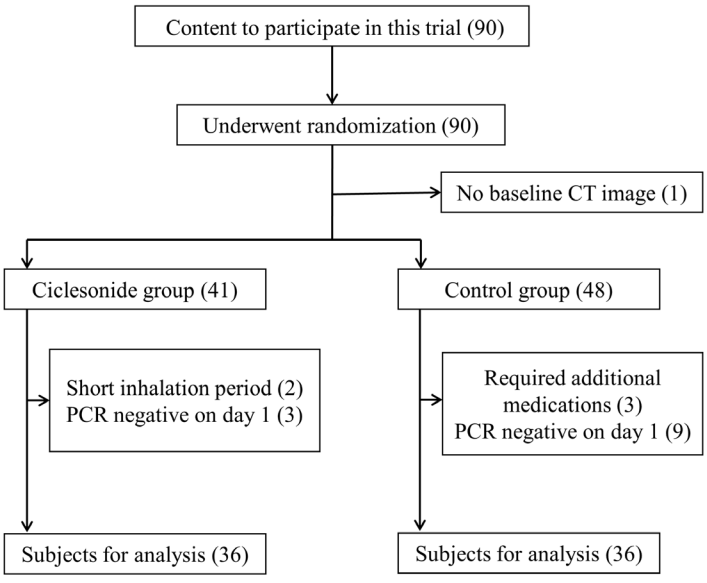

Figure 1. Flow diagram of participant recruitment in this study.

buffered saline containing 0.2% Tween 20, the plate was incubated with anti-human IgG conjugated with horseradish peroxidase (GeneTex, Irvine, CA) for 30 min at 37ºC. The captured antibodies were detected with 3,3',5,5'-tetramethylbenzidine substrate solution (Nacalai Tesque, Kyoto, Japan) and measured at a wavelength of 450 nm by a microplate reader (Bio-Rad, Irvine, CA, USA). Samples from a healthy volunteer without SARS-Cov-2 infection were used as a negative control. Anti-nucleocapsid human IgG (ACROBiosystems, Newark, DE) was used as a positive control and a standard curve was created. Each sample was assayed in triplicate, and all measurements were normalized to the value of the positive control. The positive and negative cut-off values for the antibody titer were set to a value of the mean plus three times the standard deviation of the negative control.

2.5. SARS-CoV-2 copy numbers

Nasopharyngeal swab fluid was collected on days 1 and 8. Nucleic acid RNA was extracted from the nasopharyngeal swab fluid using a QIAamp virus RNA mini kit. To determine the amount of SARS-CoV-2 per mL of universal transport medium (*14*), quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) was performed with QuantStudio 12K (Thermo Fisher Scientific, Waltham, MA) using primer/probe nucleocapsid protein set no. 2 (N2) (*15*). EDX SARS-CoV-2 standard (BR code: COV019, Bio-Rad Laboratories, Inc. Japan, 200,000 copies/mL of N-region RNA) was used as a quantitation standard to correct the calibration curve in real-time PCR quantification.

2.6. Statistical analysis

The anti-nucleocapsid IgG titer was compared between the placebo and ciclesonide groups using the nonparametric Mann-Whitney *U* test. For statistical analysis of the viral load, the value under the limit of quantification was set to 50 copy/mL and the value under the level detectable by qRT-PCR was set to 1 copy/mL. Categorical variables were compared between the groups using Fisher's exact test. A nonparametric Kruskal-Wallis test was performed to compare more than three groups followed by a post-hoc Dunn's multiple comparisons test to identify significant differences between specific groups. All statistical analyses were performed using Prism software (version 9; GraphPad Software, La Jolla, CA). A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The clinical characteristics of the ciclesonide group (n = 36) and the control group (n = 36) are shown in Table 1. Age tended to be younger in the ciclesonide group, with a median age of 44 years in the control group and 32.5 years in the ciclesonide group, but there were no significant differences. The control group consisted

Table 1. Clinical characteristics of the study participants

Items	Control group (n = 36)	Ciclesonide group (n = 36)	p-value
Age, years†	44.0 [25.3, 60.8]	32.5 [27.0, 46.3]	0.2284[a]
Sex			
Female	18	19	> 0.9999[b]
Male	18	17	
BMI†	22.0 [20.2, 25.7]	22.0 [19.7, 24.4]	0.448[a]
Days from symptom onset to day 1†	5.0 [3.0, 7.0]	5.0 [3.0, 6.0]	0.7977[a]
Clinical features on day 1††			
Body temperature (> 37.5°C)	13 (36.1) ††	14 (38.9)	> 0.9999[b]
Dry cough	16 (44.4)	22 (61.1)	0.2377[b]
Productive cough	5 (13.9)	6 (16.7)	> 0.9999[b]
Haemoptysis	0 (0.0)	0 (0.0)	> 0.9999[b]
Sore throat	6 (16.7)	11 (30.6)	0.2668[b]
Runny nose	7 (19.4)	5 (13.9)	0.7531[b]
Wheezing	0 (0.0)	0 (0.0)	> 0.9999[b]
Dyspnoea	9 (25.0)	6 (16.7)	0.5628[b]
Chest pain	3 (8.3)	3 (8.3)	> 0.9999[b]
Muscle pain	6 (16.7)	6 (16.7)	> 0.9999[b]
Joint pain	3 (8.3)	4 (11.1)	> 0.9999[b]
Headache	8 (22.2)	9 (25.0)	> 0.9999[b]
Altered consciousness	0 (0.0)	1 (2.8)	> 0.9999[b]
Fatigue	13 (36.1)	13 (36.1)	> 0.9999[b]
Abdominal pain	3 (8.3)	1 (2.8)	0.6142[b]
Vomiting/nausea	2 (5.6)	1 (2.8)	> 0.9999[b]
Diarrhoea	7 (19.4)	7 (19.4)	> 0.9999[b]

Data are presented as the †median [interquartile range] or ††number (percentage). [a]Mann-Whitney U test. [b]Fisher's exact test. BMI, body mass index.

of 18 males while the ciclesonide group consisted of 17 males. Both groups had a median body mass index (BMI) of 22.0, and the interval between symptom onset and hospitalization was 5 days for both groups, with no significant differences. Regarding clinical symptoms on the first day of admission, 13 (36.1%) patients in the control group and 14 (38.9%) in the ciclesonide group had fever. Dry cough was more common in the ciclesonide group, 16 (44.4%) in the control group and 22 (61.1%) in the ciclesonide group, but the difference between the two groups was not significant. Other respiratory symptoms such as sore throat, runny nose and dyspnoea were observed in 6 (16.7%), 7 (19.4%) and 9 (25.0%) patients in the control group respectively. In contrast, 11 (30.6%), 5 (13.9%) and 6 (16.7%) patients in the ciclesonide group showed no difference between the two groups. There were also no differences in systemic symptoms such as headache, muscle pain, joint pain and fatigue between the two groups: 8 (22.2%), 6 (16.7%), 3 (8.3%) and 13 (36.1%) patients in the control group and 9 (25.0%), 6 (16.7%), 4 (11.1%) and 13 (36.1%) patients in the ciclesonide group, respectively. In addition, gastrointestinal symptoms such as abdominal pain and diarrhoea occurred in 3 (8.3%) and 7 (19.4%) patients in the control group and 1 (2.8%) and 7 (19.4%) patients in the ciclesonide group, respectively, with no significant differences between the two groups.

3.2. Induction of antibodies against SARS-CoV-2 nucleocapsid protein

Enzyme-linked immunosorbent assay data confirmed that seroconversion was induced in both groups (Figure 2A). The maximum antibody titer was reached in 2-3 weeks (Figure 2B). Although induction of antibodies tended to be weaker in the ciclesonide group (Figure 2A), there was no significant difference in the days taken to reach the maximum antibody titer and the amount of antibodies (Figure 2C left, $p = 0.187$; right, $p = 0.158$, respectively). Furthermore, there was no between-group difference in the fold increase of antibody titres on day 8 compared to those detected on day 1 (Figure 2D, $p = 0.379$). These data indicate that inhaled ciclesonide did not impair seroconversion against SARS-CoV-2.

3.3. Association between exacerbation of pneumonia and impaired antibody production

Worsening CT shadows on day 8 was observed in 15 patients (41.7%) in the ciclesonide group and 7 (19.4%) in the control group, indicating a greater likelihood of worsening CT shadows with ciclesonide (Figure 3A, $p = 0.072$). However, there was no between-group difference in antibody titers on day 8 among patients with worsening CT shadows (Figure 3B left, $p = 0.178$ for control; $p = 0.505$ for ciclesonide). Moreover, there was

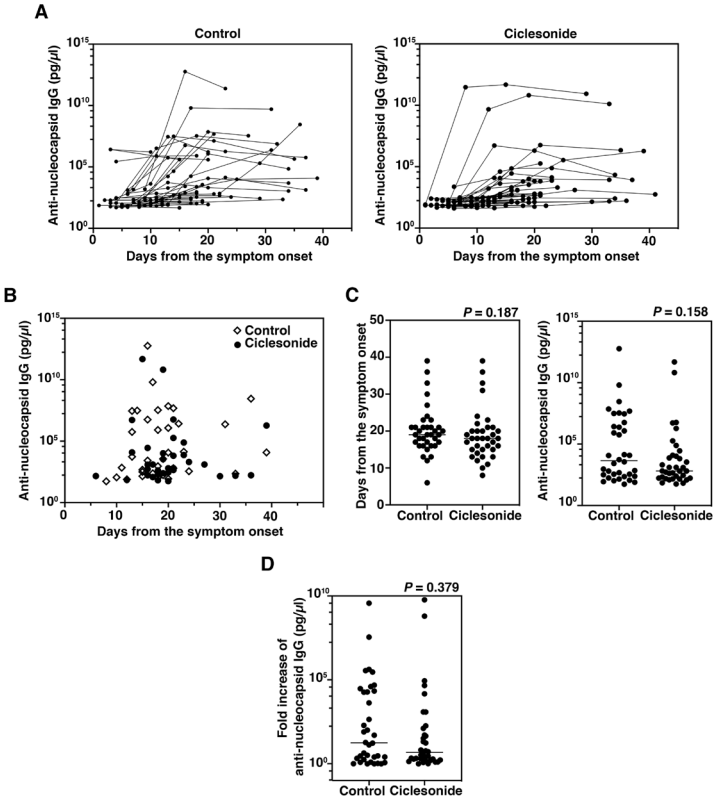

Figure 2 Comparison of anti-nucleocapside antibody acquisition and quantity change and comparison of maximum antibody titers between the control and ciclesonide groups. (A) Anti-nucleocapsid antibody titer over time starting at symptom onset. **(B)** Comparison of number of days from symptom onset to maximum antibody titer. **(C)** Days until maximum antibody value is reached. **(D)** Fold increase of antibody titers on day 8.

no significant between-group difference in the maximum antibody titer (Figure 3B right, $p = 0.388$ for control; $p = 0.102$ for ciclesonide). These data suggest that the worsening CT shadows observed in the ciclesonide group was not the result of impaired antibody production.

We also analyzed the viral load and frequency of detection of the virus on day 1 and 8. First, in the control group, we observed that the viral load was higher on both days 1 and 8 in cases with worsening CT shadows than in cases with amelioration (Figure 3C, $p = 0.007$ and $p = 0.022$, respectively). The frequency of detection on day 8 was significantly higher in cases with worsening CT shadows than in those with amelioration (Figure 3D left, $p = 0.034$). These data suggest that the worsening CT shadows in the control group were attributable to delayed elimination of the virus. In the ciclesonide group, we observed that the viral load was higher on day 1 in cases with worsening CT shadows than in cases with amelioration (Figure 3C left, $p = 0.046$), but there were no significant between-group differences on day 8 (Figure 3C, $p = 0.568$). There were also no between-group differences in the frequency of detection on day 8 (Figure 3D right, $p = 0.134$), and there was no significant difference in the time to discharge between cases with worsening CT shadows and those with amelioration in the control group or ciclesonide group (Figure 3E, $p = 0.482$ and $p = 0.118$, respectively). Furthermore, there were no significant between-group differences in clinical observations or laboratory findings on day 8 or at the time of discharge. Although there were more cases with worsening of CT shadows in the ciclesonide group, because there was no delay in viral clearance in the ciclesonide group compared with the control group, these data may indicate a therapeutic effect of ciclesonide.

4. Discussion

In this study, we prospectively compared the antibody production capacity between the ciclesonide group and control group in the RACCO study to determine whether administration of ciclesonide affects induction of antibodies against the SARS-CoV-2 nucleocapsid protein. We found that patients in both groups reached their peak antibody titers within 2-3 weeks, with no difference between them in peak values or number of days taken to reach them. There was also no significant difference in antibody production capacity, maximum antibody titer, or change in viral load between worsening

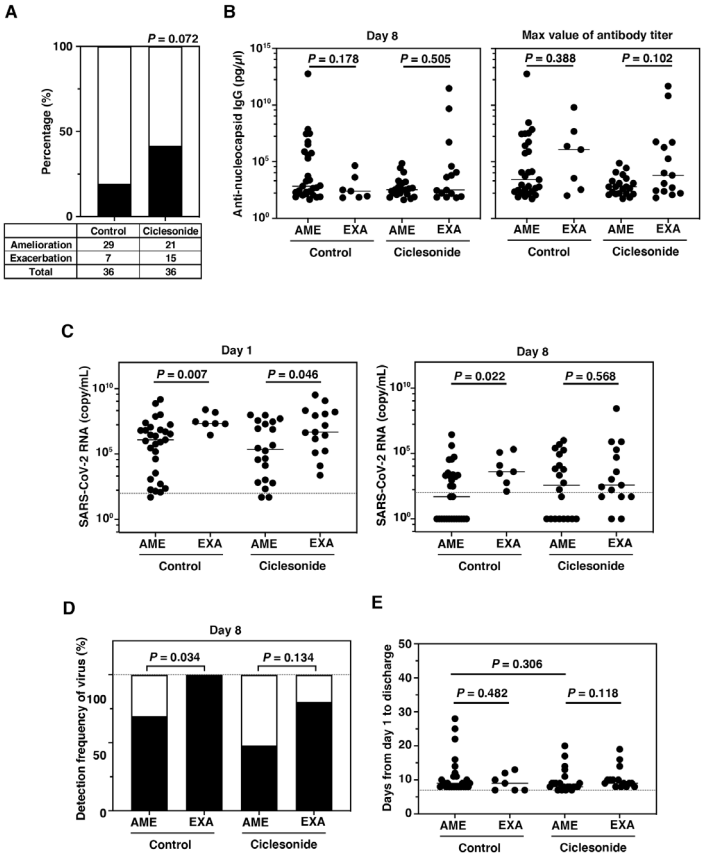

Figure 3 Comparison of the relationships between amelioration and exacerbation of CT images, viral antibody titers, and viral load between the control and ciclesonide groups. (A) Comparison of the amelioration and exacerbation groups: 15 of 46 patients (41.7%) in the ciclesonide group and 7 of 36 (19.4%) in the control group showed worsening CT shadows on day 8. **(B)** Comparison of antibody titers on day 8 and maximum antibody in the control and ciclesonide groups between the amelioration and exacerbation groups. **(C)** Viral load and detection frequency of SARS-CoV-2 in the nasopharyngeal swabs at days 1 and 8. **(D)** Detection frequency of the viruses. **(E)** Comparison of days from symptom onset to discharge.

CT shadows and improvement. These observations suggest that the influence of inhaled ciclesonide on antibody production capacity was neither statistically nor clinically significant.

Representative CT shadows in each group are compared in Figure 4. Both groups showed worsening CT shadows on day 8, suggesting a possible exacerbation of COVID-19 pneumonia. However, the shadows had disappeared at the 3-month follow-up. Although worsening CT shadows on day 8 were more common in the ciclesonide group, exacerbation of COVID-19 pneumonia during the clinical course was not observed in the ciclesonide group but was observed in 3 controls (Table 2). This discrepancy was addressed in a subsequent study by Inui *et al*., who found lung abnormalities even in asymptomatic cases, with 54% having pneumonia-like changes (*16*), suggesting a significant discrepancy between initial CT findings and subjective symptoms. Such imaging changes are reported to be distinct from changes indicative of the progression of severe pneumonia. Therefore, it is hypothesized that the changes induced by ciclesonide might be different from these imaging-related changes.

Ciclesonide has been demonstrated to inhibit the intracellular enzyme PAK1, which is implicated in the pathogenesis of COVID-19 associated with angiotensin-converting enzyme 2. By inhibiting PAK1, ciclesonide is reported to alleviate immune suppression and reduce

Table 2. Comparison of exacerbations of COVID-19 pneumonia between the ciclesonide group and the control group

Adverse event	Control group (n = 48)	Ciclesonide group (n = 41)
COVID-19 pneumonia	3	0
Mild	0	0
Moderate	2	0
Severe	1	0

Exacerbations were more common on computed tomography scans on day 8 in the ciclesonide group. However, exacerbation of COVID-19 pneumonia was not clinically diagnosed in any patients in the ciclesonide group but was diagnosed in 3 patients in the control group. COVID-19, coronavirus disease 2019.

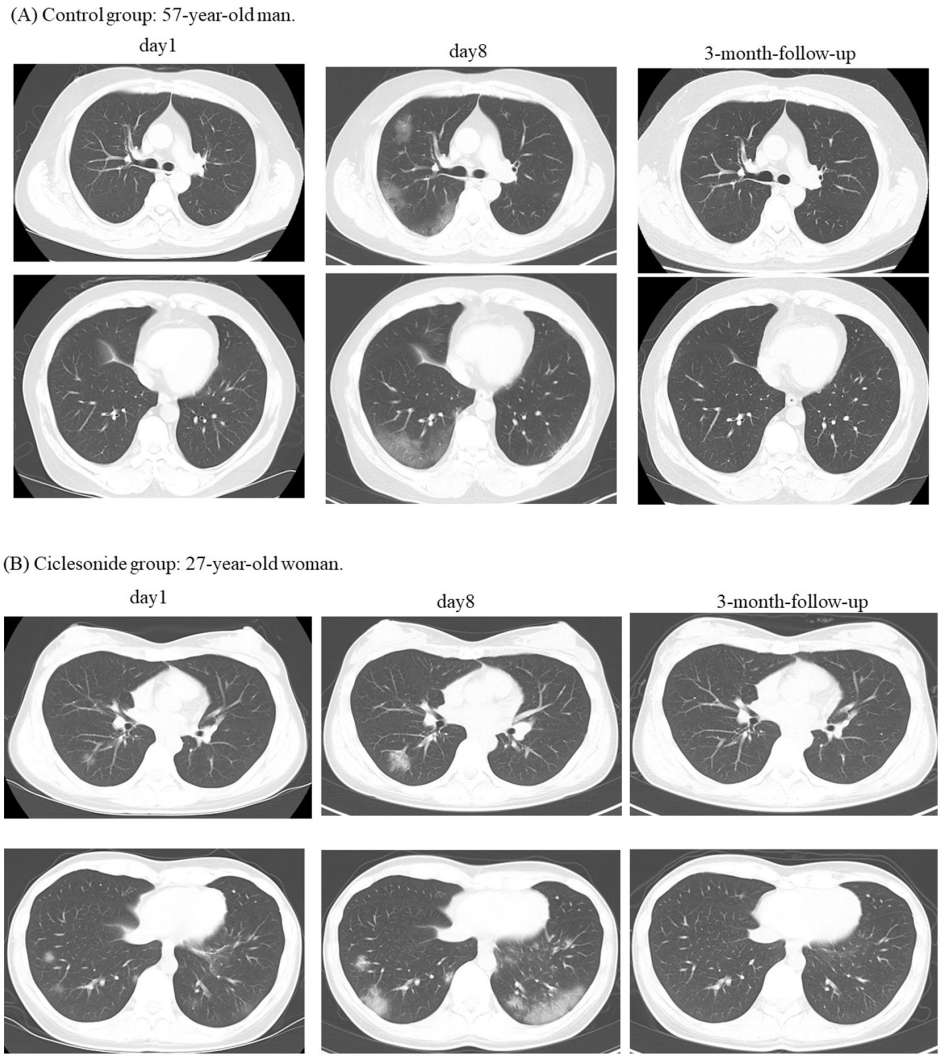

Figure 4. Representative cases of changes in CT image findings in the control and ciclesonide groups. (A) Control group: 57-year-old man. **(B)** Ciclesonide group: 27-year-old woman. Worsening CT shadows at day 8 in both cases are no longer evident at the 3-month follow-up.

lung inflammation (*3*). Furthermore, it is believed that ciclesonide targets the non-structural proteins of this novel coronavirus. This target has been shown to hinder viral replication *in vitro* (*4,6,7*).

Song *et al.* performed a randomized non-blinded multicenter phase II clinical trial of inhaled ciclesonide in patients with mild-to-moderate COVID-19 and found a significantly higher SARS-CoV-2 clearance rate on day 14 in their ciclesonide group ($p = 0.021$). Inhaled ciclesonide was found to shorten the SARS-CoV-2 shedding period and demonstrated the potential to inhibit progression to acute respiratory failure in patients with mild-to-moderate COVID-19 (*17*).

Ciclesonide has been identified as a potential treatment for COVID-19 in several studies, including ours. However, there is still no clear research demonstrating its efficacy. Indeed, Clemency *et al.* reported that the median time to relief of all COVID-19-related symptoms in outpatients with symptomatic COVID-19 was 19.0 days in both a ciclesonide group and a placebo group. Although there was no significant difference in symptom improvement, patients in the ciclesonide group were less likely to make subsequent visits to the emergency room or be hospitalized for COVID-19-related reasons by day 30 than those in the placebo group (1.0% *vs.* 5.4%; $p = 0.03$) (*10*). Furthermore, in the COVERAGE study, which evaluated ciclesonide in adults at risk of severe progression of COVID-19, there was no significant difference in the primary endpoint of worsening COVID-19 (hospitalization, home oxygen therapy, or death) up to day 14 (*9*). Studies targeting hospitalized patients have also been conducted, but there was also no reduction in the duration of oxygen administration in patients hospitalized with COVID-19 receiving oxygen therapy (*11*).

In terms of safety, a study by Lee *et al.* in South Korea indicated that prior use of ICS did not increase the likelihood of SARS-CoV-2 positivity. Moreover, the dosage and type of ICS did not impact the positivity rate (*18*). Meta-analyses have also found that use of ICS, either as monotherapy or in combination with bronchodilators, does not influence the risk of SARS-CoV-2 infection (*19*). Therefore, antibodies are produced in patients with asymptomatic to mild COVID-19, even those on high-dose ICS, with no significant difference in antibody titers according to whether or not these agents are used. This finding suggests that patients with asthma can safely use high-dose ICS containing ciclesonide if they contract COVID-19.

The study has several limitations. The first is its small sample size. When planning the RACCO study, the number of infected individuals in Japan was not particularly high, so the study focused on a smaller number of cases that allowed the results to be delivered more rapidly. The present analysis is based on sera samples that were carefully selected in that study because we believed that there was an association between inhaled ciclesonide and antibody titers. The second limitation is the uncertainty regarding the dosage of ciclesonide needed for patients to achieve intracellular concentrations equal to the concentrations found to induce antiviral effects in previous studies. In basic research, ciclesonide powder is directly dispersed onto infected cells. However, we used inhaled ciclesonide, and there have been no definitive experiments to confirm how much of the drug is absorbed through the respiratory mucosa after inhalation and whether an adequate amount reaches the infected cells. Therefore, in this study, we used high-dose ciclesonide to ensure an adequate dosage. The third limitation is the choice of the primary endpoint. The RACCO study focused on CT images obtained at day 8 rather than clinical symptoms. A relationship between worsening on imaging and progression to severe disease has not been clearly established, making this assessment complex. There have been several studies of ciclesonide but the endpoints have varied.

It is reasonable to conclude that high doses of inhaled ciclesonide do not affect antibody production even in patients with asymptomatic to mild COVID-19. Furthermore, we found no significant difference in antibody titers according to whether or not ciclesonide was inhaled. Therefore, in the event of COVID-19 infection in patients with asthma, it can be inferred that high-dose ICS are safe to use.

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

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