COVID-19 Ciclesonide Observational Study in Japan: Second Report

The Japanese Association for Infectious Diseases
Fujita Health University Antiviral Observational Study Group

Introduction

Ciclesonide (Alvesco®) is an inhaled corticosteroid indicated for the treatment of bronchial asthma. Since its *in vitro* activity against SARS-CoV-2 was demonstrated early in the pandemic,[1] its off-label use has become common in Japan. In response, the Japanese Association for Infectious Diseases initiated the Ciclesonide Observational Study to accumulate information on the safety and efficacy of ciclesonide given to COVID-19 patients, and released the first preliminary report in November 2020[2]. Here, we report data collected by this study through the end of February 2021.

Methods

Participating hospitals were asked to provide clinical characteristics of COVID-19 patients who were treated with ciclesonide. The information collected included patient demographics, comorbidities, severity of disease, clinical status 7 and 14 days from the start of the use of ciclesonide, clinical outcome approximately one month after admission to the hospital, dose and duration of ciclesonide, use of other medications to treat COVID-19, and adverse events associated with ciclesonide use. The data were collected using the survey function of REDCap, and limited data cleaning was conducted. The study was approved by the institutional review board of Fujita Health University and Toho University.

Results

【Overview】

Data on 6,480 COVID-19 patients who received ciclesonide at 549 hospitals across Japan by the end of February 2021 were included. Patient background was available in 6,442 cases, 7-day clinical status in 5,788 cases and 14-day clinical status in 4,351 cases. Clinical outcome at one month from admission was recorded in 6,207 cases.

Sixty-five percent of the patients in this cohort also received favipiravir. Since patients who received favipiravir and those who did not may have had different baseline risks, the analysis was conducted on the all-patient cohort (all patients who received ciclesonide) and the ciclesonide-only cohort (patients who received ciclesonide but not favipiravir) as in the previous report.

《All-patient cohort》

【Patient demographics and comorbidities】

The age distribution, sex, comorbidities, receipt of other agents intended for COVID-19 treatment are shown in Table 1. In this cohort, 47.1% were 60 years old or older, 40.0% were female, and 40.1% had at least one of the four comorbidities (diabetes, cardiovascular diseases, chronic lung diseases, immunosuppression). Favipiravir was also given in 65.0% of the patients. These percentages were largely unchanged from the previous report.

【Administration of ciclesonide】

Administration of ciclesonide is summarized in Table 2. The median duration of treatment was 11 days, 2 days shorter than at the time of the last report. The median time from report of a positive SARS-CoV-2 test result to the start of the drug was 2 days, and the median time from admission to the start of the drug was 0 days, both unchanged from previously.

【Severity of disease】

By the severity definition used in this study[2], 4,855 patients (74.9%) had mild disease, 1,506 patients (23.2%) had moderate disease and 119 patients (1.8%) had severe disease at the time of starting ciclesonide. The proportion of mild disease increased slightly from the previous report.

Table 1. Demographics of patients with COVID-19 who received ciclesonide (all patients)

Variables	Categories	n	(%)
Age group(n=6,478)	<10	10	(0.2%)
	10-19	74	(1.1%)
	20-29	484	(7.5%)
	30-39	560	(8.6%)
	40-49	978	(15.1%)
	50-59	1,319	(20.4%)
	60-69	1,132	(17.5%)
	70-79	1,148	(17.7%)
	80-89	612	(9.4%)
	≥90	161	(2.5%)
Sex (n=6,478)	Female	2,593	(40.0%)
	Male	3,885	(60.0%)
Diabetes (n=6,462)	Present	1,298	(20.1%)
	Absent	5,164	(79.9%)
Cardiovascular diseases (n=6,455)	Present	1,177)	(18.2%
	Absent	5,278	(81.8%)
Diabetes or cardiovascular diseases (n=6,460)	Present	2,062	(31.9%)
	Absent	4,398	(68.1%)
Chronic lung diseases (n=6,460)	Present	656	(10.2%)
	Absent	5,804	(89.8%)
Immunosuppression (n=6,457)	Present	248	(3.8%)
	Absent	6,209	(96.2%)
Any of the above comorbidities (n=6,462)	Present	2,592	(40.1%)
	Absent	3,870	(59.9%)
Favipiravir (n=6,480)	Given	4,211	(65.0%)
	Not given	2,269	(35.0%)
Lopinavir–ritonavir (n=6,480)	Given	83	(1.3%)
	Not given	6,397	(98.7%)
Nafamostat (n=6,480)	Given	577	(8.9%)
	Not given	5,903	(91.1%)
Methylprednisolone (n=6,480)	Given	389	(6.0%)
	Not given	6,091	(94.0%)
Dexamethasone (n=6,480)	Given	1,548	(23.9%)
	Not given	4,932	(76.1%)
Camostat (n=6,480)	Given	224	(3.5%)
	Not given	6,256	(96.5%)
Hydroxychloroquine (n=6,480)	Given	160	(2.5%)
	Not given	6,320	(97.5%)
Remdesivir (n=6,480)	Given	563	(8.7%)
	Not given	5,917	(91.3%)
Outcome (n=6,207)	Died in hospital	274	(4.4%)
	Transferred for escalation of care	371	(6.0%)
	Still in hospital (alive)	125	(2.0%)
	Transferred for de-escalation of care	526	(8.5%)
	Discharged alive	4,911	(79.1%)

Table 2. Administration of ciclesonide (all patients)

(a) Dosing of ciclesonide

n	Dosing	n	(%)
6,402	200 mcg daily	64	(1.0%)
	200 mcg twice a day	1,071	(16.7%)
	200 mcg three times a day	1,014	(15.8%)
	Others	4,253	(66.4%)

(b) Duration of ciclesonide

n	Median	Q1 (25%)	Q3 (75%)
5,771	11	8	14

(c) Days from positive PCR to first dose of ciclesonide

n	Median	Q1 (25%)	Q3 (75%)
6,367	2	1	3

(d) Days from hospital admission to first dose of ciclesonide

n	Median	Q1 (25%)	Q3 (75%)
6,278	0	0	1

【Clinical status and outcome stratified by severity of disease】

Clinical status at 7 and 14 days from the start of ciclesonide was recorded as improved, worsened, unchanged compared with when therapy was started, based on the providers' clinical assessment (Table 3). The rates of clinical improvement at 7 days were 73.1%, 62.9% and 39.4% for mild, moderate and severe disease, respectively. Rates of clinical improvement at 14 days were 87.8%, 79.2% and 54.8%, respectively. The rates of clinical worsening at 7 days were 11.4%, 21.4% and 36.7% for mild, moderate and severe disease, respectively. Rates of clinical worsening at 14 days were 4.6%, 13.9% and 29.8%, respectively.

Clinical outcome was surveyed at approximately one month into hospitalization as discharged alive, died in hospital, transferred for de-escalation of care, transferred for escalation of care, and still in hospital (Table 3). The mortality rates at the time of survey were 2.1%, 9.8% and 27.7% for mild, moderate and severe disease, respectively.

Table 3. Clinical status and outcome stratified by severity of disease in patients who received ciclesonide (all patients)

(a) At 7 days after start of ciclesonide

		Improved	Unchanged	Worsened
Day 7 (n=5,778)	Mild	3,192 (73.1%)	676 (15.5%)	500 (11.4%)
	Moderate	825 (62.9%)	205 (15.6%)	281 (21.4%)
	Severe	43 (39.4%)	26 (23.9%)	40 (36.7%)

(b) At 14 days after start of ciclesonide

		Improved	Unchanged	Worsened
Day 14 (n=4,351)	Mild	2,806 (87.8%)	243 (7.6%)	148 (4.6%)
	Moderate	832 (79.2%)	72 (6.9%)	146 (13.9%)
	Severe	57 (54.8%)	16 (15.4%)	31 (29.8%)

(c) Clinical outcome one month from hospital admission

		Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
Outcome (n=6,207)	Mild	95 (2.1%)	190 (4.1%)	86 (1.9%)	339 (7.4%)	3,884 (84.5%)
	Moderate	146 (9.8%)	173 (11.6%)	35 (2.3%)	155 (10.4%)	985 (65.9%)
	Severe	33 (27.7%)	8 (6.7%)	4 (3.4%)	32 (26.9%)	42 (35.3%)

【Clinical status and outcome stratified by age groups】

Clinical status at 7 and 14 days from the start of ciclesonide and clinical outcome one month into hospitalization based on age groups is shown in Table 4. The outcomes were worse for higher age groups, with in-hospital death by one month occurring only in 0.8% of those in their fifties but in 3.4% of those in their sixties, 7.3% of those in their seventies and 19.0% of those in their eighties, but the mortality rates have declined overall compared with the previous report.

Table 4. Clinical status and outcome stratified by age group in patients who received ciclesonide (all patients)

(a) At 7 days after start of ciclesonide

	Age group	Improved	Unchanged	Worsened
Day 7 (n=5,788)	<10	8 (100%)	0 (0%)	0 (0%)
	10-19	53 (80.3%)	13 (19.7%)	0 (0%)
	20-29	351 (85.8%)	47 (11.5%)	11 (2.7%)
	30-39	419 (84.1%)	59 (11.8%)	20 (4.0%)
	40-49	695 (77.9%)	126 (14.1%)	71 (8.0%)
	50-59	917 (77.2%)	142 (12.0%)	129 (10.9%)
	60-69	677 (66.6%)	154 (15.2%)	185 (18.2%)
	70-79	602 (58.4%)	194 (18.8%)	234 (22.7%)
	80-89	262 (48.5%)	130 (24.1%)	148 (27.4%)
	≥90	76 (53.9%)	42 (29.8%)	23 (16.3%)

(b) At 14 days after start of ciclesonide

	Age group	Improved	Unchanged	Worsened
Day 14 (n=4,351)	<10	7 (100%)	0 (0%)	0 (0%)
	10-19	32 (76.2%)	10 (23.8%)	0 (0%)
	20-29	254 (92.0%)	18 (6.5%)	4 (1.4%)
	30-39	321 (92.8%)	19 (5.5%)	6 (1.7%)
	40-49	560 (90.8%)	40 (6.5%)	17 (2.8%)
	50-59	837 (91.0%)	48 (5.2%)	35 (3.8%)
	60-69	655 (84.5%)	61 (7.9%)	59 (7.6%)
	70-79	642 (78.4%)	75 (9.2%)	102 (12.5%)
	80-89	304 (70%)	43 (9.9%)	87 (20%)
	≥90	83 (72.2%)	17 (14.8%)	15 (13%)

(c) Clinical outcome one month from hospital admission

	Age group	Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
Outcome (n=6,207)	<10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (100%)
	10-19	0 (0%)	0 (0%)	0 (0%)	3 (4.3%)	67 (95.7%)
	20-29	1 (0.2%)	6 (1.3%)	3 (0.7%)	54 (11.9%)	388 (85.8%)
	30-39	2 (0.4%)	11 (2.1%)	5 (1%)	37 (7%)	470 (89.5%)
	40-49	1 (0.1%)	43 (4.6%)	6 (0.6%)	61 (6.5%)	824 (88.1%)
	50-59	10 (0.8%)	74 (5.9%)	13 (1%)	70 (5.5%)	1,095 (86.8%)
	60-69	37 (3.4%)	88 (8.1%)	20 (1.8%)	79 (7.3%)	860 (79.3%)
	70-79	82 (7.3%)	107 (9.6%)	37 (3.3%)	101 (9.1%)	789 (70.7%)
	80-89	114 (19.0%)	39 (6.5%)	28 (4.7%)	87 (14.5%)	332 (55.3%)
	≥90	27 (17.4%)	3 (1.9%)	13 (8.4%)	34 (21.9%)	78 (50.3%)

《Ciclesonide-only cohort》

【Patient demographics and comorbidities】

Table 5 shows the age distribution, sex, comorbidities, and receipt of other agents intended for COVID-19 treatment. In this cohort, 36.5% were age 60 or older, 45.8% were female, and 30.6% at least had one of the four comorbidities. Compared with the all-patient cohort, the cohort continued to be younger, have more females and have patients with less comorbidities, though the differences have narrowed slightly compared with the previous report.

Table 5. Demographics of patients with COVID-19 who received ciclesonide (ciclesonide-only patients)

Variables	Categories	n	(%)
Age group (n=2,268)	<10	8	(0.4%)
	10-19	53	(2.3%)
	20-29	327	(14.4%)
	30-39	305	(13.4%)
	40-49	369	(16.3%)
	50-59	379	(16.7%)
	60-69	295	(13.0%)
	70-79	290	(12.8%)
	80-89	180	(7.9%)
	≥90	62	(2.7%)
Sex (n=2,268)	Female	1,038	(45.8%)
	Male	1,230	(54.2%)
Diabetes (n=2,258)	Present	307	(13.6%)
	Absent	1,951	(86.4%)
Cardiovascular diseases (n=2,255)	Present	298	(13.2%)
	Absent	1,957	(86.8%)
Diabetes or cardiovascular diseases (n=2,255)	Present	517	(22.9%)
	Absent	1,738	(77.1%)
Chronic lung diseases (n=2,257)	Present	210	(9.3%)
	Absent	2,047	(90.7%)
Immunosuppression (n=2,254)	Present	47	(2.1%)
	Absent	2,207	(97.9%)
Any of the above comorbidities (n=2,255)	Present	690	(30.6%)
	Absent	1,565	(69.4%)
Lopinavir–ritonavir (n=2,269)	Given	30	(1.3%)
	Not given	2,239	(98.7%)
Nafamostat (n=2,269)	Given	40	(1.8%)
	Not given	2,229	(98.2%)
Methylprednisolone (n=2,269)	Given	58	(2.6%)
	Not given	2,211	(97.4%)
Dexamethasone (n=2,269)	Given	302	(13.3%)
	Not given	1,967	(86.7%)
Camostat (n=2,269)	Given	67	(3.0%)
	Not given	2,202	(97.0%)
Hydroxychloroquine (n=2,269)	Given	65	(2.9%)
	Not given	2,204	(97.1%)
Remdesivir (n=2,269)	Given	232	(10.2%)
	Not given	2,037	(89.8%)
Outcome (n=2,127)	Given	36	(1.7%)
	Not given	90	(4.2%)
	Died in hospital	28	(1.3%)
	Transferred for escalation of care	194	(9.1%)
	Still in hospital (alive)	1,779	(83.6%)

【Administration of ciclesonide】

Administration of ciclesonide is summarized in Table 6. Dosing was similar with the all-patient cohort.

Table 6. Administration of ciclesonide (ciclesonide-only patients)

(a) Dosing of ciclesonide

n	Dosing	n	(%)
2,255	200 mcg daily	35	(1.6%)
	200 mcg twice a day	356	(15.8%)
	200 mcg three times a day	361	(16.0%)
	Others	1,503	(66.7%)

(b) Duration of ciclesonide

n	Median	Q1 (25%)	Q3 (75%)
1,990	12	8	14

(c) Days from positive PCR to first dose of ciclesonide

n	Median	Q1 (25%)	Q3 (75%)
2,232	2	1	3

(d) Days from hospital admission to first dose of ciclesonide

n	Median	Q1 (25%)	Q3 (75%)
2,161	0	0	1

【Severity of disease】

In this cohort, 1,900 patients (83.7%) had mild disease, 348 patients (15.3%) had moderate disease and 21 patients (0.9%) had severe disease at the time of starting ciclesonide. Thus, the overall severity of disease was lower in this cohort, similar to the previous report.

【Clinical status and outcome stratified by severity of disease】

The rates of clinical improvement at 7 days were 80.6%, 65.6% and 42.1% for mild, moderate and severe disease, respectively (Table 7). Rates of clinical improvement at 14 days were 88.8%, 80.9% and 76.5%, respectively. The rates of clinical worsening at 7 days were 4.8%, 17.2% and 15.8% for mild, moderate and severe disease, respectively. Rates of clinical worsening at 14 days were 2.0%, 9.8% and 17.6%, respectively. The mortality rates approximately one month into hospitalization were 0.7%, 6.1% and 9.5% for mild, moderate and severe disease, respectively. The rates of clinical improvement were lower than in the previous analysis, likely reflecting an increase in the elderly patients in the cohort, but the mortality rates remained unchanged.

Table 7. Clinical status and outcome stratified by severity of disease in patients who received ciclesonide (ciclesonide-only patients)

(a) At 7 days after start of ciclesonide

		Improved	Unchanged	Worsened
Day 7 (n=1,962)	Mild	1,342 (80.6%)	242 (14.5%)	80 (4.8%)
	Moderate	183 (65.6%)	48 (17.2%)	48 (17.2%)
	Severe	8 (42.1%)	8 (42.1%)	3 (15.8%)

(b) At 14 days after start of ciclesonide

		Improved	Unchanged	Worsened
Day 14 (n=1,306)	Mild	964 (88.8%)	99 (9.1%)	22 (2.0%)
	Moderate	165 (80.9%)	19 (9.3%)	20 (9.8%)
	Severe	13 (76.5%)	1 (5.9%)	3 (17.6%)

(c) Clinical outcome one months from hospital admission

		Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
Outcome (n=2,127)	Mild	13 (0.7%)	35 (2.0%)	22 (1.2%)	157 (8.9%)	1,536 (87.1%)
	Moderate	21 (6.1%)	52 (15.2%)	6 (1.7%)	37 (10.8%)	227 (66.2%)
	Severe	2 (9.5%)	3 (14.3%)	0 (0%)	0 (0%)	16 (76.2%)

【Clinical status and outcome stratified by age groups】

Clinical status and outcome stratified by age groups are shown in Table 8. The clinical status and outcome were generally worse for higher age groups, with mortality rates at 0%, 0.7%, 2.9% and 10.1% of those in their fifties, sixties, seventies and eighties, respectively. The rates remained lower than in the all-patient cohort for all these age groups.

Table 8. Clinical status and outcome stratified by age group in patients who received ciclesonide (ciclesonide-only patients)

(a) At 7 days after start of ciclesonide

		Improved	Unchanged	Worsened
Day 7 (n=1,962)	<10	8 (100%)	0 (0%)	0 (0%)
	10-19	35 (77.8%)	10 (22.2%)	0 (0%)
	20-29	229 (85.8%)	33 (12.4%)	5 (1.9%)
	30-39	232 (87.2%)	30 (11.3%)	4 (1.5%)
	40-49	274 (84.6%)	41 (12.7%)	9 (2.8%)
	50-59	280 (84.6%)	34 (10.3%)	17 (5.1%)
	60-69	183 (71.5%)	46 (18.0%)	27 (10.5%)
	70-79	159 (63.9%)	46 (18.5%)	44 (17.7%)
	80-89	99 (61.5%)	43 (26.7%)	19 (11.8%)
	≥90	34 (61.8%)	15 (27.3%)	6 (10.9%)

(b) At 14 days after start of ciclesonide

		Improved	Unchanged	Worsened
Day 14 (n=1,306)	<10	7 (100%)	0 (0%)	0 (0%)
	10-19	23 (76.7%)	7 (23.3%)	0 (0%)
	20-29	160 (91.4%)	13 (7.4%)	2 (1.1%)
	30-39	155 (91.7%)	12 (7.1%)	2 (1.2%)
	40-49	176 (88.4%)	21 (10.6%)	2 (1.0%)
	50-59	213 (91.8%)	14 (6.0%)	5 (2.2%)
	60-69	140 (84.8%)	17 (10.3%)	8 (4.8%)
	70-79	145 (82.4%)	18 (10.2%)	13 (7.4%)
	80-89	91 (77.8%)	15 (12.8%)	11 (9.4%)
	≥90	32 (88.9%)	2 (5.6%)	2 (5.6%)

(c) Clinical outcome one month from hospital admission

	Age group	Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
Outcome (n=2,127)	<10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (100%)
	10-19	0 (0%)	0 (0%)	0 (0%)	2 (4.1%)	47 (95.9%)
	20-29	1 (0.3%)	2 (0.7%)	1 (0.3%)	36 (12.1%)	257 (86.5%)
	30-39	1 (0.4%)	4 (1.4%)	0 (0%)	23 (8.2%)	251 (90.0%)
	40-49	0 (0%)	11 (3.2%)	0 (0%)	25 (7.2%)	311 (89.6%)
	50-59	0 (0%)	16 (4.5%)	1 (0.3%)	21 (5.9%)	317 (89.3%)
	60-69	2 (0.7%)	19 (6.8%)	4 (1.4%)	20 (7.2%)	233 (83.8%)
	70-79	8 (2.9%)	29 (10.5%)	6 (2.2%)	23 (8.3%)	211 (76.2%)
	80-89	18 (10.1%)	9 (5.1%)	10 (5.6%)	32 (18.0%)	109 (61.2%)
	≥90	6 (10.2%)	0 (0%)	6 (10.2%)	12 (20.3%)	35 (59.3%)

【Adverse events】

A total of 81 events associated with ciclesonide administration were reported in 80 patients (1.2%) (Table 9). They included liver function test abnormalities in 13 patients (0.2%), hoarseness in 12 patients (0.2%), and oral candidiasis in 9 patients (0.1%). The incidence of other adverse events was 0.1% or lower. Liver function test abnormalities are known to commonly accompany COVID-19[3].

Table 9 Adverse events associated with ciclesonide use

n=2,728		
Number of patients with adverse events associated with ciclesonide use	80	(1.2%)
Number of adverse events associated with ciclesonide use	81	
（breakdown）		
Hepatic function disorder/elevated liver function enzyme levels	13	(0.2%)
Hoarseness	12	(0.2%)
Oral candidiasis	9	(0.1%)
Vomiting/nausea	6	(0.1%)
Rash/toxicoderma	5	(0.1%)
Pharyngeal discomfort/pain	5	(0.1%)
Cough	4	(0.1%)
Diarrhea/soft stool	3	(<0.1%)
Stomatitis	3	(<0.1%)
Hyperuricemia/elevated uric acid levels	3	(<0.1%)
Bacterial pneumonia	3	(<0.1%)
Worsening of underlying condition	2	(<0.1%)
Low oxygenation/respiratory failure	2	(<0.1%)
Palpitation	2	(<0.1%)
Leucopenia/lymphopenia	2	(<0.1%)
Discomfort, not otherwise specified	1	(<0.1%)
Angina	1	(<0.1%)
Fatigue	1	(<0.1%)
Angular cheilitis	1	(<0.1%)
Esophageal obstruction	1	(<0.1%)
Tongue discomfort	1	(<0.1%)
Headache	1	(<0.1%)

Discussion

Over six thousand COVID-19 patients who were administered ciclesonide have been registered in this observational study. Off-label use of ciclesonide for COVID-19 has been widely adopted in Japan, given its potent anti-SARS-CoV-2 activity demonstrated in vitro as well as its anti-inflammatory properties as a steroid.

The study did not include control patients who did not receive ciclesonide, therefore the potential efficacy of ciclesonide on the symptomatic relief and overall prognosis for COVID-19 patients cannot be determined with certainty, but the data demonstrate an overall favorable prognosis for patients with mild disease, with the exception of those in the highest age groups. In addition, adverse events potentially related to ciclesonide use remained rare and non-serious.

Notably, the top-line results of the randomized controlled study to evaluate the efficacy and safety of inhaled ciclesonide for asymptomatic and mild patients with COVID-19 (RACCO trial) were released in December 2020. The study enrolled 90 patients with asymptomatic or mild disease without pneumonia and found that the rate of new pneumonia or exacerbation was higher in the ciclesonide group compared with no therapy group (press release in Japanese only)[4]. Though other clinical studies of ciclesonide continue in other countries, its use has declined significantly in Japan since this press release. Accordingly, the Ciclesonide Observational Study will be closed for enrollment after March 31.

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Antiviral Observational Study Group、Fujita Health University

Yohei Doi and Masashi Kondo (Faculty of Medicine, Fujita Health University)

Masahiko Ando and Yachiyo Kuwatsuka (Department of Advanced Medicine, Nagoya University Hospital)

Takuma Ishihara (Innovative and Clinical Research Promotion Center, Gifu University Hospital)

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