COVID-19 Ciclesonide Observational Study in Japan: Preliminary Report

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

Introduction

Various approved drugs are being repurposed for the treatment of COVID-19. Ciclesonide (Alvesco®) is an inhaled corticosteroid indicated for the treatment of bronchial asthma. Its *in vitro* activity against SARS-CoV-2 was demonstrated by Matsuyama *et al.* early in the pandemic[1], and a case series suggesting its potential beneficial effect in patients with COVID-19 has been reported by Iwabuchi *et al*[2]. Given these developments, the Japanese Association for Infectious Diseases has issued a guidance on off-label use of ciclesonide for COVID-19[3], and has encouraged its members to participate in the Ciclesonide Observational Study[4]. This preliminary report summarizes the findings of the observational study for cases registered through the end of August 2020.

Methods

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 likely related to ciclesonide use. The data were collected using the survey function of REDCap, and limited data cleaning was conducted. This study was approved by the institutional review board of Fujita Health University and Toho University.

Results

【Overview】

Data on 2,728 COVID-19 patients who received ciclesonide by the end of August 2020 were included. Patient background was available in 2,710 cases, 7-day clinical status in 2,406 cases and 14-day clinical status in 1,891 cases. Clinical outcome at one month from admission was recorded in 2,632 cases.

Sixty-five percent of the patients in this cohort also received favipiravir. These patients who also received favipiravir on a compassionate use basis were likely considered by the providers to have unfavorable prognosis based on the overall clinical status at the time even with best supportive therapy[5]. Therefore, 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). Patients who received other medications intended as COVID-19 treatment (e.g., remdesivir, steroids) were included in both cohorts.

《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, 58.1% were under the age of 60, 38.4% were female, and 38.6% had at least one of the four comorbidities (diabetes, cardiovascular diseases, chronic lung diseases, immunosuppression). Favipiravir was also given in 64.6% of the patients.

【Administration of ciclesonide】

Administration of ciclesonide is summarized in Table 2. A majority of the patients received “other” doses. Since the options in the survey only included doses approved for bronchial asthma in adults, the patients in this study likely received higher than approved doses, for example, 400 mcg three times a day. The median duration of treatment was 13 days. 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.

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

Variables	Categories	n	(%)
Age group (n=2,726)	<10	6	(0.2%)
	10-19	32	(1.2%)
	20-29	222	(8.1%)
	30-39	287	(10.5%)
	40-49	462	(16.9%)
	50-59	576	(21.1%)
	60-69	470	(17.2%)
	70-79	420	(15.4%)
	80-89	211	(7.7%)
	≥90	40	(1.5%)
Sex(n=2,727)	Male	1,679	(61.6%)
	Female	1,048	(38.4%)
Diabetes (n=2,718)	Present	518	(19.1%)
	Absent	2,200	(80.9%)
Cardiovascular diseases (n=2,717)	Present	469	(17.3%)
	Absent	2,248	(82.7%)
Diabetes or cardiovascular diseases (n=2,720)	Present	811	(29.8%)
	Absent	1,909	(70.2%)
Chronic lung diseases (n=2,717)	Present	288	(10.6%)
	Absent	2,429	(89.4%)
Immunosuppression (n=2,716)	Present	121	(4.5%)
	Absent	2,595	(95.5%)
Any of the above comorbidities (n=2,718)	Present	1,048	(38.6%)
	Absent	1,670	(61.4%)
Favipiravir (n=2,728)	Given	1,762	(64.6%)
	Not given	966	(35.4%)
Lopinavir–ritonavir (n=2,728)	Given	79	(2.9%)
	Not given	2,649	(97.1%)
Nafamostat (n=2,970)	Given	153	(5.6%)
	Not given	2,575	(94.4%)
Methylprednisolone (n=2,728)	Given	32	(1.2%)
	Not given	2,696	(98.8%)
Dexamethasone (n=2,728)	Given	112	(4.1%)
	Not given	2,616	(95.9%)
Camostat (n=2,728)	Given	46	(1.7%)
	Not given	2,682	(98.3%)
Hydroxychloroquine (n=2,728)	Given	68	(2.5%)
	Not given	2,660	(97.5%)
Remdesivir (n=2,728)	Given	54	(2.0%)
	Not given	2,674	(98.0%)
Other therapy related to COVID-19 (n=2,728)	Given	746	(27.3%)
	Not given	1,982	(72.7%)
Outcome (n=2,632)	Died in hospital	141	(5.4%)
	Transferred for escalation of care	148	(5.6%)
	Still in hospital (alive)	99	(3.8%)
	Transferred for de-escalation of care	267	(10.1%)
	Discharged alive	1,977	(75.1%)

Table 2. Administration of ciclesonide (all patients)

(a) Dosing of ciclesonide

n	Dosing	n	(%)
2,700	200 mcg daily	35	(1.3%)
	200 mcg twice a day	603	(22.3%)
	200 mcg three times a day	320	(11.9%)
	Others	1,742	(64.5%)

(b) Duration of ciclesonide

n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
2,356	12.4	7.3	13	8	14

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

n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
2,686	2.7	3.8	2	1	3

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

n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
2,685	4.4	141.1	0	0	1

【Severity of disease】

In this analysis, mild, moderate and severe diseases were defined as those not requiring supplemental oxygen, those requiring supplemental oxygen, and those requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), respectively. By this definition, 1,886 patients (69.1%) had mild disease, 738 patients (27.1%) had moderate disease and 104 patients (3.8%) had severe disease at the time of starting ciclesonide.

【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 73.3%, 65% and 43% for mild, moderate and severe disease, respectively. Rates of clinical improvement at 14 days were 85.6%, 81.4% and 57.3%, respectively. The rates of clinical worsening at 7 days were 10.5%, 20.6% and 31.2% for mild, moderate and severe disease, respectively. Rates of clinical worsening at 14 days were 4.2%, 11.8% and 27%, 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 1.8%, 11% and 26.9% 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=2,406)	Mild	1,228 (73.3%)	272 (16.2%)	176 (10.5%)
	Moderate	414 (65.0%)	92 (14.4%)	131 (20.6%)
	Severe	40 (43.0%)	24 (25.8%)	29 (31.2%)

(b) At 14 days after start of ciclesonide

		Improved	Unchanged	Worsened
Day 14 (n=1,891)	Mild	1,077 (85.6%)	128 (10.2%)	53 (4.2%)
	Moderate	443 (81.4%)	37 (6.8%)	64 (11.8%)
	Severe	51 (57.3%)	14 (15.7%)	24 (27.0%)

(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=2,632)	Mild	33 (1.8%)	70 (3.9%)	58 (3.2%)	151 (8.4%)	1,489 (82.7%)
	Moderate	80 (11.0%)	71 (9.8%)	34 (4.7%)	88 (12.1%)	454 (62.4%)
	Severe	28 (26.9%)	7 (6.7%)	7 (6.7%)	28 (26.9%)	34 (32.7%)

【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 in 6.5% of those in their sixties, 11.8% of those in their seventies, and 25.6% of those in their eighties, compared with 0.7% of those in their fifties.

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=2,406)	<10	6 (100%)	0 (0%)	0 (0%)
	10-19	18 (64.3%)	10 (35.7%)	0 (0%)
	20-29	164 (84.5%)	26 (13.4%)	4 (2.1%)
	30-39	217 (84.1%)	32 (12.4%)	9 (3.5%)
	40-49	313 (75.8%)	68 (16.5%)	32 (7.7%)
	50-59	402 (77.0%)	64 (12.3%)	56 (10.7%)
	60-69	258 (63.1%)	69 (16.9%)	82 (20.0%)
	70-79	204 (56.4%)	72 (19.9%)	86 (23.8%)
	80-89	81 (44.8%)	38 (21.0%)	62 (34.3%)
	≥90	19 (57.6%)	9 (27.3%)	5 (15.2%)

(b) At 14 days after start of ciclesonide

	Age group	Improved	Unchanged	Worsened
Day 14 (n=1,891)	<10	6 (100%)	0 (0%)	0 (0%)
	10-19	9 (50.0%)	9 (50.0%)	0 (0%)
	20-29	113 (89.0%)	12 (9.4%)	2 (1.6%)
	30-39	154 (90.6%)	13 (7.6%)	3 (1.8%)
	40-49	261 (88.8%)	24 (8.2%)	9 (3.1%)
	50-59	396 (91.0%)	25 (5.7%)	14 (3.2%)
	60-69	266 (78.0%)	40 (11.7%)	35 (10.3%)
	70-79	237 (75.2%)	34 (10.8%)	44 (14.0%)
	80-89	105 (67.7%)	17 (11.0%)	33 (21.3%)
	≥90	24 (80.0%)	5 (16.7%)	1 (3.3%)

(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=2,632)	<10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (100%)
	10-19	0 (0%)	0 (0%)	0 (0%)	3 (9.7%)	28 (90.3%)
	20-29	1 (0.5%)	1 (0.5%)	3 (1.4%)	31 (14.5%)	178 (83.2%)
	30-39	1 (0.4%)	6 (2.1%)	4 (1.4%)	24 (8.6%)	245 (87.5%)
	40-49	0 (0%)	22 (5%)	8 (1.8%)	40 (9%)	372 (84.2%)
	50-59	4 (0.7%)	33 (5.9%)	10 (1.8%)	49 (8.7%)	467 (82.9%)
	60-69	29 (6.5%)	34 (7.6%)	21 (4.7%)	44 (9.8%)	319 (71.4%)
	70-79	48 (11.8%)	39 (9.6%)	27 (6.6%)	41 (10.1%)	252 (61.9%)
	80-89	52 (25.6%)	13 (6.4%)	22 (10.8%)	25 (12.3%)	91 (44.8%)
	≥90	6 (15.4%)	0 (0%)	4 (10.3%)	10 (25.6%)	19 (48.7%)

《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, 71.7% were under the age of 60, 44.4% were female, and 27.2% at least had one of the four comorbidities. Compared with the all-patient cohort, the cohort was younger, had more females and had less comorbidities.

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

Variables	Categories	n	(%)
Age group (n=965)	<10	6	(0.6%)
	10-19	26	(2.7%)
	20-29	144	(14.9%)
	30-39	166	(17.2%)
	40-49	189	(19.6%)
	50-59	161	(17.2%)
	60-69	127	(13.2%)
	70-79	88	(9.1%)
	80-89	47	(4.9%)
	≥90	11	(1.1%)
Sex (n=965)	Male	537	(55.6%)
	Female	428	(44.4%)
Diabetes (n=961)	Present	117	(12.2%)
	Absent	844	(87.8%)
Cardiovascular diseases (n=961)	Present	105	(10.9%)
	Absent	856	(89.1%)
Diabetes or cardiovascular diseases (n=961)	Present	185	(19.3%)
	Absent	776	(80.7%)
Chronic lung diseases (n=960)	Present	93	(9.7%)
	Absent	867	(90.3%)
Immunosuppression (n=960)	Present	17	(1.8%)
	Absent	943	(98.2%)
Any of the above comorbidities (n=960)	Present	261	(27.2%)
	Absent	699	(72.8%)
Lopinavir–ritonavir (n=966)	Given	30	(3.1%)
	Not given	936	(96.9%)
Nafamostat (n=966)	Given	15	(1.6%)
	Not given	951	(98.4%)
Methylprednisolone (n=966)	Given	2	(0.2%)
	Not given	964	(99.8%)
Dexamethasone (n=966)	Given	19	(2.0%)
	Not given	947	(98.0%)
Camostat (n=966)	Given	16	(1.7%)
	Not given	950	(98.3%)
Hydroxychloroquine (n=966)	Given	30	(3.1%)
	Not given	936	(96.9%)
Remdesivir (n=966)	Given	9	(0.9%)
	Not given	957	(99.1%)
Other therapy related to COVID-19 (n=966)	Given	139	(14.4%)
	Not given	827	(85.6%)
Outcome (n=922)	Given	13	(1.4%)
	Not given	31	(3.4%)
	Died in hospital	12	(1.3%)
	Transferred for escalation of care	87	(9.4%)
	Still in hospital (alive)	779	(84.5%)

【Administration of ciclesonide】

Administration of ciclesonide is summarized in Table 6. The results were similar to those in the all-patient cohort.

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

(a) Dosing of ciclesonide

n	Dosing	n	(%)
962	200 mcg daily	19	(2.0%)
	200 mcg twice a day	228	(23.7%)
	200 mcg three times a day	93	(9.7%)
	Others	622	(64.7%)

(b) Duration of ciclesonide

n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
829	12.1	6.8	13	8	14

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

n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
952	3.1	4.7	2	1	3

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

n	Mean	SD	Median	Q1 (25%)	Q3 (75%)
950	1.4	5.1	0	0	1

【Severity of disease】

In this cohort, 820 patients (84.9%) had mild disease, 128 patients (13.3%) had moderate disease and 18 patients (1.9%) had severe disease at the time of starting ciclesonide. Thus, the overall severity of disease was lower in this cohort.

【Clinical status and outcome stratified by severity of disease】

The rates of clinical improvement at 7 days were 81%, 70.8% and 50% for mild, moderate and severe disease, respectively (Table 7). Rates of clinical improvement at 14 days were 85.9%, 83.3% and 86.7%, respectively. The rates of clinical worsening at 7 days were 2.9%, 14.2% and 12.5% for mild, moderate and severe disease, respectively. Rates of clinical worsening at 14 days were 1.2%, 9.5% and 13.3%, respectively. The mortality rates approximately one month into hospitalization were 0.4%, 6.6% and 11.1% for mild, moderate and severe disease, respectively.

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=850)	Mild	590 (81.0%)	117 (16.1%)	21 (2.9%)
	Moderate	75 (70.8%)	16 (15.1%)	15 (14.2%)
	Severe	8 (50.0%)	6 (37.5%)	2 (12.5%)

(b) At 14 days after start of ciclesonide

		Improved	Unchanged	Worsened
Day 14 (n=589)	Mild	421 (85.9%)	63 (12.9%)	6 (1.2%)
	Moderate	70 (83.3%)	6 (7.1%)	8 (9.5%)
	Severe	13 (86.7%)	0 (0%)	2 (13.3%)

(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=922)	Mild	3 (0.4%)	15 (1.9%)	10 (1.3%)	70 (9%)	684 (87.5%)
	Moderate	8 (6.6%)	14 (11.5%)	2 (1.6%)	17 (13.9%)	81 (66.4%)
	Severe	2 (11.1%)	2 (11.1%)	0 (0%)	0 (0%)	14 (77.8%)

【Clinical status and outcome stratified by age groups】

Clinical status and outcome stratified by age groups are shown in Table 8. While the clinical status and outcome were generally worse for higher age groups, the one-month mortality rates were lower those in the all-patient cohort between fifties and eighties, reflecting the preponderance of mild cases in this cohort.

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=850)	<10	6 (100%)	0 (0%)	0 (0%)
	10-19	15 (68.2%)	7 (31.8%)	0 (0%)
	20-29	103 (83.7%)	18 (14.6%)	2 (1.6%)
	30-39	129 (87.8%)	17 (11.6%)	1 (0.7%)
	40-49	142 (83.5%)	24 (14.1%)	4 (2.4%)
	50-59	125 (84.5%)	18 (12.2%)	5 (3.4%)
	60-69	74 (68.5%)	25 (23.1%)	9 (8.3%)
	70-79	52 (72.2%)	12 (16.7%)	8 (11.1%)
	80-89	23 (52.3%)	14 (31.8%)	7 (15.9%)
	≥90	4 (40.0%)	4 (40.0%)	2 (20.0%)

(b) At 14 days after start of ciclesonide

		Improved	Unchanged	Worsened
Day 14 (n=589)	<10	6 (100%)	0 (0%)	0 (0%)
	10-19	6 (50.0%)	6 (50.0%)	0 (0%)
	20-29	64 (87.7%)	8 (11.0%)	1 (1.4%)
	30-39	74 (89.2%)	8 (9.6%)	1 (1.2%)
	40-49	100 (87.0%)	13 (11.3%)	2 (1.7%)
	50-59	106 (93.0%)	7 (6.1%)	1 (0.9%)
	60-69	64 (80.0%)	13 (16.2%)	3 (3.8%)
	70-79	48 (84.2%)	6 (10.5%)	3 (5.3%)
	80-89	30 (71.4%)	7 (16.7%)	5 (11.9%)
	≥90	6 (85.7%)	1 (14.3%)	0 (0%)

(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=922)	<10	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (100%)
	10-19	0 (0%)	0 (0%)	0 (0%)	3 (12.0%)	22 (88.0%)
	20-29	1 (0.7%)	1 (0.7%)	1 (0.7%)	15 (11.0%)	118 (86.8%)
	30-39	1 (0.6%)	3 (1.9%)	0 (0%)	13 (8.1%)	143 (89.4%)
	40-49	0 (0%)	5 (2.8%)	1 (0.6%)	16 (8.9%)	157 (87.7%)
	50-59	0 (0%)	5 (3.2%)	0 (0%)	10 (6.4%)	142 (90.4%)
	60-69	1 (0.9%)	6 (5.1%)	1 (1.9%)	9 (7.7%)	100 (85.5%)
	70-79	3 (3.5%)	9 (10.5%)	4 (4.7%)	13 (15.1%)	57 (66.3%)
	80-89	5 (10.9%)	2 (4.3%)	4 (8.7%)	6 (13.0%)	29 (63.0%)
	≥90	2 (22.0%)	0 (0%)	1 (10.0%)	2 (20.0%)	5 (50.0%)

【Adverse events】

A total of 41 events likely related to ciclesonide administration were reported in 40 patients (1.5%) (Table 9). They included hoarseness in 8 patients (0.3%), liver function test abnormalities in 7 patients (0.3%), and oral candidiasis in 5 patients (0.2%). The incidence of other adverse events was 0.1% or lower.

Table 9 Adverse events associated with ciclesonide use

n=2,728		
Number of patients with adverse events associated with ciclesonide use	40	(1.5%)
Number of adverse events associated with ciclesonide use	41	
（breakdown）		
Hoarseness	8	(0.3%)
Hepatic function disorder/elevated liver function enzyme levels	7	(0.3%)
Oral candidiasis	5	(0.2%)
Vomiting/nausea	4	(0.1%)
Diarrhea/soft stool	2	(0.1%)
Worsening of underlying disease	2	(0.1%)
Stomatitis	2	(0.1%)
Hyperuricemia/elevated uric acid levels	2	(0.1%)
Palpitation		
Pharyngeal discomfort	2	(0.1%)
Pharyngeal pain	2	(0.1%)
Ventilator-associated pneumonia	2	(0.1%)
Lymphocytopenia	1	(<0.1%)
Fatigue	1	(<0.1%)
Respiratory failure	1	
Angular cheilitis	1	(<0.1%)
Headache	1	(<0.1%)
Leukocytopenia	1	(<0.1%)
Rash/toxicoderma	1	(<0.1%)
	1	(<0.1%)
		(<0.1%)

Discussion

Ciclesonide, an inhaled steroid approved for the treatment of bronchial asthma, has been used for the treatment of COVID-19 in Japan from early in the pandemic based on the *in vitro* data demonstrating its robust anti-SARS-CoV-2 activity and potential anti-inflammatory effects as a steroid[2,6,7]. This is the first large-scale report on the clinical use of this agent against COVID-19 in Japan.

In reviewing the data, there appeared to be two groups of patients: those who received ciclesonide alone early in the disease course for mild disease, and those who received it along with favipiravir for more severe disease. For this reason, we summarized the data for all patients who received ciclesonide (“all-patient cohort”) and those who received ciclesonide but not favipiravir (“ciclesonide-only cohort”). The findings reflect the differences in the patient characteristics, clinical course and outcomes. However, the study did not include control patients who did not receive ciclesonide, which precludes assessment of efficacy of ciclesonide on the symptomatic relief and overall prognosis.

This study provides important information on the safety of administering ciclesonide to COVID-19 patients. There were only a total of 41 adverse events reported in 40 patients, including hoarsness and liver function test abnormalities in 0.3% each. Oral candidiasis, a concern with an inhaled steroid, was reported in 0.2%. There were no unexpected or serious adverse events reported. It is possible, however, that the incidence of adverse events was underreported since the study depended on voluntary reporting using a survey function.

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