Favipiravir Observational Study Interim Report 3
(as of February 28, 2021)

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Introduction

Since the SARS-CoV-2 pandemic started a year ago, the virus has caused over four hundred thousand cases of COVID-19 and over nine thousand deaths in Japan. At the time of this writing, the antiviral agent favipiravir (brand name: Avigan) is undergoing clinical development as a potential treatment options for COVID-19.

In the meantime, compassionate use of favipiravir to hospitalized patients with COVID-19 is allowed at the discretion of the hospitals since February 2020. Hospitals are asked to register cases for which favipiravir was administered to the antiviral agent observational study conducted by Fujita Health University. This is the third report of COVID-19 cases treated with favipiravir and registered to this observational study.

Methods

Favipiravir is provided to medical institutions admitting patients who are eligible for the off-label use from the manufacturer and vendor FUJIFILM Toyama Chemical Co., Ltd., after a request for off-label use of favipiravir is made to the Ministry of Health, Labour and Welfare by medical institutions and the requirements are met[1]. This study is conducted as a retrospective study to collect clinical information when favipiravir is administered as part of clinical practice. The information collected on the case report form and approach to data analysis have been described in the previous report[2].

This study is approved by the Institutional Review Board of Fujita Health University.

Results

【Overview】

As of February 28 2021, a total of 10,986 patients who received favipiravir were registered from 765 hospitals. Of these patients, the patient demographics, clinical status at Day 7, clinical status at Day 14, and clinical outcome at approximately 1 month after hospital admission were available for 10,903, 9,782, 7,655, and 10,659 patients, respectively. This study utilizes a survey function, thus only limited data cleaning has been performed.

【Patient demographics】

The age distribution, sex, presence or absence of underlying disease (diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression), and use of other antiviral agents are shown in Table 1. In terms of demographics, 59.5% were age ≥60 years, and 63.4% were male. At least one of the four surveyed comorbidities (diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression) was present in 48.3% of the patients. These rates are similar from the previous report.

【Administration of favipiravir】

Administration of favipiravir is shown in Table 2. In 93.7% of the patients, favipiravir was dosed at two doses of 1,800 mg followed by 800 mg twice a day. The median duration of treatment was 9 days, compared with 12 days in the previous report. The difference likely reflected a change in the discharge criteria that occurred in the meantime, in which the requirement for two negative PCR test results was removed. The median days from the positive PCR test and hospital admission to the initiation of favipiravir therapy were 2 and 0 days, respectively.

【Severity of illness】

In this study, mild, moderate, and severe diseases at the start of favipiravir are defined as those not requiring supplemental oxygen, those with spontaneous respiration but requiring supplemental oxygen, and those requiring artificial respiration or extracorporeal membrane oxygenation, respectively.

By this definition, 6,772 patients (61.6%) had mild disease, 3,695 patients (33.6%) had moderate disease, and 519 patients (4.7%) had severe disease. The proportion of mild disease increased by 16.4 percentage points, whereas those of moderate and severe diseases decreased by 9.6 and 6.9 percentage points, respectively, suggesting that favipiravir is increasingly used for patients with mild disease.

Table 1. Demographics of patients with COVID-19 who received favipiravir

Variables	Categories	n	(%)
Age group (n=10,985)	<10	5	(0.0%)
	10–19	33	(0.3%)
	20–29	319	(2.9%)
	30–39	588	(5.4%)
	40–49	1,359	(12.4%)
	50–59	2,143	(19.5%)
	60–69	2,137	(19.5%)
	70–79	2,359	(21.5%)
	80–89	1,597	(14.5%)
	≥90	445	(4.1%)
Sex (n=10,984)	Male	4,017	(36.6%)
	Female	6,967	(63.4%)
Diabetes (n=10,944)	Present	2,747	(25.1%)
	Absent	8,197	(74.9%)
Cardiovascular diseases (n=10,937)	Present	2,587	(23.7%)
	Absent	8,350	(76.3%)
Diabetes or cardiovascular diseases (n=10,952)	Present	4,378	(40.0%)
	Absent	6,574	(60.0%)
Chronic lung diseases (n=10,942)	Present	1,134	(10.4%)
	Absent	9,808	(89.6%)
Immunosuppression (n=10,933)	Present	642	(5.9%)
	Absent	10,291	(94.1%)
Any of the above comorbidities (n=10,949)	Present	5,285	(48.3%)
	Absent	5,664	(51.7%)
Ciclesonide (n=10,645)	Given	4,211	(39.6%)
	Not given	6,434	(60.4%)
Lopinavir–ritonavir (n=10,986)	Given	89	(0.8%)
	Not given	10,897	(99.2%)
Hydroxychloroquine (n=10,986)	Given	222	(2.0%)
	Not given	10,764	(98.0%)
Nafamostat (n=10,986)	Given	960	(8.7%)
	Not given	10,026	(91.3%)
Camostat (n=10,986)	Given	389	(3.5%)
	Not given	10,597	(96.5%)
Remdesivir (n=10,986)	Given	855	(7.8%)
	Not given	10,131	(92.2%)
Dexamethasone (n=10,986)	Given	3,420	(31.1%)
	Not given	7,566	(68.9%)
Methylprednisolone (n=10,986)	Given	833	(7.6%)
	Not given	10,153	(92.4%)
Tocilizumab (n=10,986)	Given	444	(4.0%)
	Not given	10,542	(96.0%)
Outcome (n=10,659)	Died in hospital	852	(8.0%)
	Transferred for escalation of care	683	(6.4%)
	Still in hospital (alive)	449	(4.2%)
	Transferred for de-escalation of care	962	(9.0%)
	Discharged alive	7,713	(72.4%)

Table 2. Administration of favipiravir

(a) Dosing of favipiravir

n	Dosing	n(%)
10,918	2 doses of 1,600 mg followed by 600 mg twice a day	406 (3.7%)
	2 doses of 1,800 mg followed by 800 mg twice a day	10,235 (93.7%)
	Others	277 (2.5%)

(b) Duration of favipiravir

n	Median	Q1 (25%)	Q3 (75%)
10,210	9	6	13

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

n	Median	Q1 (25%)	Q3 (75%)
10,887	2	1	4

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

n	Median	Q1 (25%)	Q3 (75%)
10,877	0	0	2

【Clinical course and outcome by severity of disease】

The clinical course at 7 and 14 days after the start of favipiravir therapy was evaluated as improved, worsened, or unchanged. The rates of clinical improvement at 7 and 14 days were 72.6% and 86.5%, 63.4% and 77.2%, and 46.6% and 60.4% for mild, moderate, and severe diseases, respectively (Table 3). The rates of clinical worsening at 7 and 14 days were 13.8% and 7.0%, 23.1% and 16.1%, and 26.1% and 25.1% for mild, moderate, and severe diseases, respectively.

The clinical outcome was assessed at approximately 1 month into hospitalization as discharged alive, died in hospital, transferred for de-escalation of care, transferred for escalation of care, or still in hospital. The mortality rates within a month from hospitalization were 3.6%, 13.2%, and 27.6% for mild, moderate, and severe diseases, respectively. The mortality rates have decreased since the previous report.

【Clinical course and outcome by age group】

The clinical course and outcome based on age groups are shown in Table 4. Both the clinical course and outcome were poor in older patients. The mortality rate was 1.6% in the 50–59 age group, whereas the rates were 4.9%, 10.3%, 22.2%, and 28.9% in the 60–69, 70–79, 80–89, and ≥90 age groups, respectively. Thus, deaths continued to occur more commonly among those with advanced age, but the rates have declined across all these age groups.

Table 3. Clinical status and outcome stratified by severity of illness in patients who received favipiravir

(a) At 7 days after start of favipiravir

		Improved	Unchanged	Worsened
Day 7 (n=9,782)	Mild	4,436 (72.6%)	833 (13.6%)	841 (13.8%)
	Moderate	2,034 (63.4%)	433 (13.5%)	741 (23.1%)
	Severe	216 (46.6%)	127 (27.4%)	121 (26.1%)

(b) At 14 days after start of favipiravir

		Improved	Unchanged	Worsened
Day 14 (n=7,655)	Mild	4,010 (86.5%)	302 (6.5%)	325 (7.0%)
	Moderate	2,016 (77.2%)	175 (6.7%)	420 (16.1%)
	Severe	246 (60.4%)	59 (14.5%)	102 (25.1%)

(c) Clinical outcome 1 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=10,659)	Mild	233 (3.6%)	324 (5%)	246 (3.8%)	423 (6.5%)	5,290 (81.2%)
	Moderate	479 (13.2%)	335 (9.2%)	173 (4.8%)	396 (10.9%)	2,252 (62%)
	Severe	140 (27.6%)	24 (4.7%)	30 (5.9%)	143 (28.1%)	171 (33.7%)

【Adverse events】

A total of 3,324 adverse events were reported in association with favipiravir use in 2,841 of 10,986 patients (Table 5). Adverse events reported in >1% of the patients were uric acid level increase or hyperuricemia in 1,960 patients (17.8%), liver disorder or liver function enzyme increase in 834 patients (7.6%), and skin eruption or toxicoderma in 129 patients (1.2%). The adverse event rates by age groups are shown in Figure 1. They were reported more commonly in younger age groups, and hyperuricemia was reported most frequently in those between 20 and 39.

Table 4. Clinical status and outcome stratified by age group in patients who received favipiravir

(a) At 7 days after start of favipiravir

		Improved	Unchanged	Worsened
Day 7 (n=9,782)	<10	2 (100%)	0 (0%)	0 (0%)
	10–19	25 (89.3%)	3 (10.7%)	0 (0%)
	20–29	255 (88.2%)	26 (9%)	8 (2.8%)
	30–39	450 (83.3%)	55 (10.2%)	35 (6.5%)
	40–49	980 (79%)	144 (11.6%)	117 (9.4%)
	50–59	1508 (77.5%)	201 (10.3%)	238 (12.2%)
	60–69	1324 (69.6%)	253 (13.3%)	324 (17%)
	70–79	1253 (60.5%)	354 (17.1%)	465 (22.4%)
	80–89	716 (52.1%)	261 (19%)	398 (28.9%)
	≥90	173 (44.7%)	96 (24.8%)	118 (30.5%)

(b) At 14 days after start of favipiravir

		Improved	Unchanged	Worsened
Day 14 (n=7,655)	<10	1 (100%)	0 (0%)	0 (0%)
	10–19	15 (83.3%)	3 (16.7%)	0 (0%)
	20–29	193 (91.9%)	12 (5.7%)	5 (2.4%)
	30–39	382 (93.6%)	15 (3.7%)	11 (2.7%)
	40–49	839 (91.8%)	45 (4.9%)	30 (3.3%)
	50–59	1394 (91.1%)	73 (4.8%)	63 (4.1%)
	60–69	1258 (84.8%)	88 (5.9%)	137 (9.2%)
	70–79	1261 (76.5%)	137 (8.3%)	251 (15.2%)
	80–89	755 (66.9%)	108 (9.6%)	265 (23.5%)
	≥90	174 (55.4%)	55 (17.5%)	85 (27.1%)

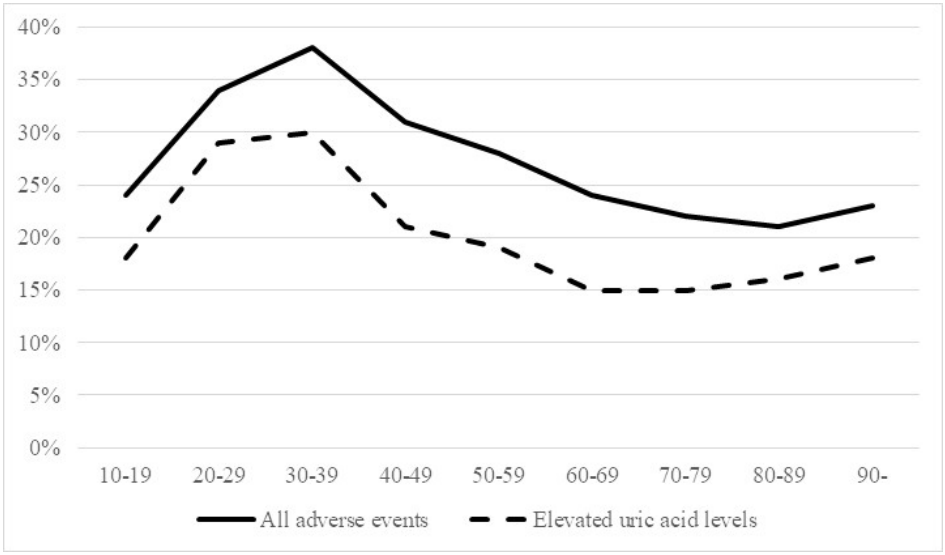
(c) Clinical outcome 1 month from hospital admission

		Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
Outcome (n=10,659)	<10	0 (0%)	0 (0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
	10–19	0 (0%)	0 (0%)	0 (0%)	1 (3.3%)	29 (96.7%)
	20–29	1 (0.3%)	5 (1.6%)	3 (1%)	28 (8.9%)	276 (88.2%)
	30–39	3 (0.5%)	19 (3.3%)	21 (3.7%)	31 (5.4%)	498 (87.1%)
	40–49	8 (0.6%)	67 (5.1%)	10 (0.8%)	83 (6.3%)	1,153 (87.3%)
	50–59	34 (1.6%)	124 (6%)	39 (1.9%)	113 (5.4%)	1,773 (85.1%)
	60–69	102 (4.9%)	164 (7.9%)	67 (3.2%)	163 (7.9%)	1,567 (76%)
	70–79	238 (10.3%)	203 (8.8%)	131 (5.7%)	247 (10.7%)	1,483 (64.4%)
	80–89	344 (22.2%)	93 (6%)	134 (8.6%)	221 (14.3%)	758 (48.9%)
	≥90	122 (28.9%)	8 (1.9%)	43 (10.2%)	74 (17.5%)	175 (41.5%)

Table 5 Adverse events associated with favipiravir use

n=10,986		
Number of patients with adverse events associated with favipiravir use	2,841	(25.9%)
Number of adverse events associated with favipiravir use	3,324	
(breakdown)		
Hyperuricemia/elevated uric acid levels	1,960	(17.8%)
Hepatic function disorder/elevated liver function enzyme levels	834	(7.6%)
Rash/toxicoderma/eczema/purpura/ erythema/skin damage	129	(1.2%)
Fever	67	(0.6%)
Renal impairment/elevated creatinine levels	46	(0.4%)
	43	(0.4%)
Diarrhea/soft stool	41	(0.4%)
Vomiting/nausea	17	(0.2%)
Bradycardia	14	(0.1%)
Gout	13	(0.1%)
Poor appetite	12	(0.1%)
Hyperkalemia	8	(0.1%)
Rhabdomyolysis/elevated creatine kinase levels	8	(0.1%)
Leukocytopenia	7	(0.1%)
Abnormal coagulation test values	7	(0.1%)
Constipation	6	(0.1%)
Pruritus	6	(0.1%)
Thrombocytopenia	4	(<0.1%)
Elevated BUN levels	4	(<0.1%)
Dizziness	4	(<0.1%)
Gastric discomfort	4	(<0.1%)
Thrombocytosis	4	(<0.1%)
Malaise	4	(<0.1%)
Headache	3	(<0.1%)
Lymphocytopenia	3	(<0.1%)
Hypernatremia	3	(<0.1%)
Convulsion	3	(<0.1%)
Eosinophilia	3	(<0.1%)
Elevated amylase levels	3	(<0.1%)
Hyperglycemia	3	(<0.1%)
Melena	2	(<0.1%)
Elevated LDH levels	2	(<0.1%)
Hiccup	2	(<0.1%)
Worsening of underlying disease	2	(<0.1%)
Stomatitis	2	(<0.1%)
Neutropenia	2	(<0.1%)
Stroke	2	(<0.1%)
Abdominal pain	2	(<0.1%)
Chest discomfort	2	(<0.1%)
Thromboembolism	2	(<0.1%)
Abnormal lipid values	2	(<0.1%)
Restlessness/psychotic symptoms	2	(<0.1%)
Worsening of pneumonia	2	(<0.1%)
Pancytopenia	2	(<0.1%)
Gastrointestinal symptoms	2	(<0.1%)
Elevated ALD values	1	(<0.1%)
Elevated D-dimer values	1	(<0.1%)
Elevated eGFR values	1	(<0.1%)
Elevated TLC values	1	(<0.1%)
Dizziness	1	(<0.1%)
Lymphadenitis	1	(<0.1%)
Altered mental status	1	(<0.1%)
Elevated inflammatory test levels	1	(<0.1%)
Jaundice	1	(<0.1%)
Lower extremity numbness	1	(<0.1%)
Arthritis	1	(<0.1%)
Arthralgia	1	(<0.1%)
Pseudomembranous colitis	1	(<0.1%)
Hypertension	1	(<0.1%)
Angina	1	(<0.1%)
Dyspnea	1	(<0.1%)
Worsening of respiratory failure	1	(<0.1%)
Oral candidiasis	1	(<0.1%)
Lip swelling	1	(<0.1%)
Visual field defect	1	(<0.1%)
Periodontal bleeding	1	(<0.1%)
Epigastric pain	1	(<0.1%)
Dehydration	1	(<0.1%)
Hypoxemia	1	(<0.1%)
Hyponatremia	1	(<0.1%)
Electrolyte abnormalities	1	(<0.1%)
Sepsis	1	(<0.1%)
Possible lung damage	1	(<0.1%)
Diaphoresis	1	(<0.1%)
Myodesopsia	1	(<0.1%)
Anemia	1	(<0.1%)
Congested heart failure	1	(<0.1%)
Drowsiness	1	(<0.1%)

Fig.1. Adverse event rates by age group



Discussion

The observational study is being conducted to overview the safety and efficacy of favipiravir against COVID-19 in patients who were administered the agent as off-label use since March 2020. With over ten thousand cases registered, this is one of the largest databases on the use of favpiravir for COVID-19.

A notable difference compared with the last interim report that included cases up to June 2020 is the higher proportion of patients with mild disease not requiring supplemental oxygen, now in excess of 60%. Furthermore, mortality rates have declined for each severity and age group, which may reflect advances in supportive therapy and other pharmacological interventions, as well as inclusion of more patients deemed to have better prognosis.

The common adverse events associated with favipiravir use continue to be uric acid level increase and liver function enzyme increase, and the incidence rates remain stable. Also, increase in the uric acid levels was more common in younger age groups.

Finally, early embryonic lethality and teratogenicity due to favipiravir have been observed in animal models. Pregnant women therefore must be excluded, and all patients and their sexual partners should practice effective contraception during and after the treatment period in reference to the "Guidelines for Drug Therapy for COVID-19."[3)]

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文　献

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