Favipiravir Observational Study Interim Report 4
(as of July 1, 2021)

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Introduction

Since the SARS-CoV-2 pandemic started in early 2020, the virus has caused over 1.7 million cases of COVID-19 and over eighteen thousand deaths in Japan.

Under the circumstances, 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 fourth 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 July 1, 2021, a total of 15,245 patients who received favipiravir were registered from 869 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 15,091, 13,867, 11,186, and 15,001 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, 59.6% were age ≥60 years, and 62.3% were male. At least one of the four surveyed comorbidities (diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression) was present in 47.8% of the patients. The proportion of females increased by 1.1 percentage point, otherwise the demographics were similar from the last report.

【Administration of favipiravir】

Administration of favipiravir is shown in Table 2. In 94.4% 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, unchanged from the last report. The median days from the positive PCR test and hospital admission to the initiation of favipiravir therapy were 2 and 0 days, respectively, also unchanged from previously.

【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, 9,789 patients (64.2%) had mild disease, 4,901patients (32.1%) had moderate disease, and 555 patients (3.6%) had severe disease. Compared with the third report, the proportion of mild disease increased by 2.6 percentage points, whereas those of

moderate and severe diseases decreased by 1.5 and 1.1 percentage points, respectively.

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

Variables	Categories	n	(%)
Age group (n=15,244)	<20	58	(0.4%)
	20–29	489	(3.2%)
	30–39	801	(5.3%)
	40–49	1,888	(12.4%)
	50–59	2,922	(19.2%)
	60–69	2,847	(18.7%)
	70–79	3,289	(21.6%)
	80–89	2,316	(15.2%)
	≥90	634	(4.2%)
Sex (n=15,244)	Female	5,746	(37.7%)
	Male	9,498	(62.3%)
Diabetes (n=15,154)	Present	3,712	(24.5%)
	Absent	11,442	(75.5%)
Cardiovascular diseases (n=15,159)	Present	3,704	(24.4%)
	Absent	11,455	(75.6%)
Diabetes or cardiovascular diseases (n=15,176)	Present	6,085	(40.1%)
	Absent	9,091	(59.9%)
Chronic lung diseases (n=15,139)	Present	1,499	(9.9%)
	Absent	13,640	(90.1%)
Immunosuppression (n=15,133)	Present	809	(5.3%)
	Absent	14,324	(94.7%)
Any of the above comorbidities (n=15,173)	Present	7,259	(47.8%)
	Absent	7,914	(52.2%)
Ciclesonide (n=14,338)	Given	4,441	(31.0%)
	Not given	9,897	(69.0%)
Lopinavir–ritonavir (n=15,245)	Given	87	(0.6%)
	Not given	15,158	(99.4%)
Hydroxychloroquine (n=15,245)	Given	218	(1.4%)
	Not given	15,027	(98.6%)
Nafamostat (n=15,245)	Given	1,073	(7.0%)
	Not given	14,172	(93.0%)
Camostat (n=15,245)	Given	579	(3.8%)
	Not given	14,666	(96.2%)
Remdesivir (n=15,245)	Given	1,556	(10.2%)
	Not given	13,689	(89.8%)
Dexamethasone (n=15,245)	Given	5,738	(37.6%)
	Not given	9,507	(62.4%)
Methylprednisolone (n=15,245)	Given	1,638	(10.7%)
	Not given	13,607	(89.3%)
Outcome (n=15,001)	Died in hospital	1,012	(6.7%)
	Transferred for escalation of care	371	(2.5%)
	Still in hospital (alive)	1,288	(8.6%)
	Transferred for de-escalation of care	11,226	(74.4%)
	Discharged alive	1,012	(6.7%)

Table 2. Administration of favipiravir

(a) Dosing of favipiravir

n	Dosing	n(%)
15,183	2 doses of 1,600 mg followed by 600 mg twice a day	509 (3.4%)
	2 doses of 1,800 mg followed by 800 mg twice a day	14,340 (94.4%)
	Others	334 (2.2%)

(b) Duration of favipiravir

n	Median	Q1 (25%)	Q3 (75%)
14,487	9	6	12

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

n	Median	Q1 (25%)	Q3 (75%)
15,148	2	1	4

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

n	Median	Q1 (25%)	Q3 (75%)
15,158	0	0	1

【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 71.0% and 86.2%, 61.3% and 75.7%, and 46.1% and 59.3% for mild, moderate, and severe diseases, respectively (Table 3). The rates of clinical worsening at 7 and 14 days were 15.0% and 7.6%, 24.1% and 16.8%, and 27.2% and 25.7% 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 fatality rates within a month from hospitalization were 3.9%, 13.2%, and 27.6% for mild, moderate, and severe diseases, respectively. Overall, the fatality rates remained unchanged from the last 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 fatality rate was 1.5% in the 50–59 age group, whereas the rates were 4.4%, 9.8%, 21.1%, and 29.2% in the 60–69, 70–79, 80–89, and ≥90 age groups, respectively. These rates also remained unchanged from the last report.

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=13,867)	Mild	6,420 (71.0%)	1,271 (14.1%)	1,355 (15.0%)
	Moderate	2,650 (61.3%)	632 (14.6%)	1,042 (24.1%)
	Severe	229 (46.1%)	133 (26.8%)	135 (27.2%)

(b) At 14 days after start of favipiravir

		Improved	Unchanged	Worsened
Day 14 (n=7,655)	Mild	6,156 (86.2%)	448 (6.3%)	540 (7.6%)
	Moderate	2,727 (75.7%)	269 (7.5%)	606 (16.8%)
	Severe	261 (59.3%)	66 (15.0%)	113 (25.7%)

(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	374 (3.9%)	490 (5.1%)	211 (2.2%)	606 (6.3%)	7,916 (82.5%)
	Moderate	639 (13.2%)	493 (10.1%)	133 (2.7%)	528 (10.9%)	3,066 (63.1%)
	Severe	151 (27.6%)	29 (5.3%)	27 (4.9%)	154 (28.1%)	187 (34.1%)

【Adverse events】

A total of 3,878 adverse events were reported in association with favipiravir use (Table 5). Adverse events reported in 1% or more of the patients were uric acid level increase or hyperuricemia in 2,628 patients (17.2%), liver disorder or liver function enzyme increase in 1,113 patients (7.3%), and skin eruption or toxicoderma in 150 patients (1.0%). 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, an observation that is unchanged from the third interim report.

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=13,867)	<20	48 (92.3%)	4 (7.8%)	0 (0%)
	20–29	401 (88.7%)	38 (8.4%)	13 (2.9%)
	30–39	627 (83.0%)	80 (10.6%)	48 (6.4%)
	40–49	1,396 (79.6%)	200 (11.4%)	157 (9%)
	50–59	2,019 (75.8%)	298 (11.2%)	348 (13.1%)
	60–69	1,775 (68.9%)	344 (13.3%)	458 (17.8%)
	70–79	1,737 (58.3%)	534 (17.9%)	707 (23.7%)
	80–89	1,048 (50.8%)	399 (19.3%)	616 (29.9%)
	≥90	248 (43.4%)	139 (24.3%)	185 (32.3%)

(b) At 14 days after start of favipiravir

		Improved	Unchanged	Worsened
Day 14 (n=11,186)	<20	29 (90.6%)	3 (9.4%)	0 (0%)
	20–29	316 (93.8%)	15 (4.5%)	6 (1.8%)
	30–39	549 (94.0%)	20 (3.4%)	15 (2.6%)
	40–49	1,247 (93.0%)	55 (4.1%)	39 (2.9%)
	50–59	1,948 (90.6%)	107 (5.0%)	94 (4.4%)
	60–69	1,745 (85.1%)	112 (5.5%)	193 (9.4%)
	70–79	1,864 (76.1%)	218 (8.9%)	369 (15.1%)
	80–89	1,174 (66.9%)	173 (9.9%)	409 (23.3%)
	≥90	272 (56.0%)	80 (16.5%)	134 (27.6%)

(c) Clinical outcome 1 month from hospital admission

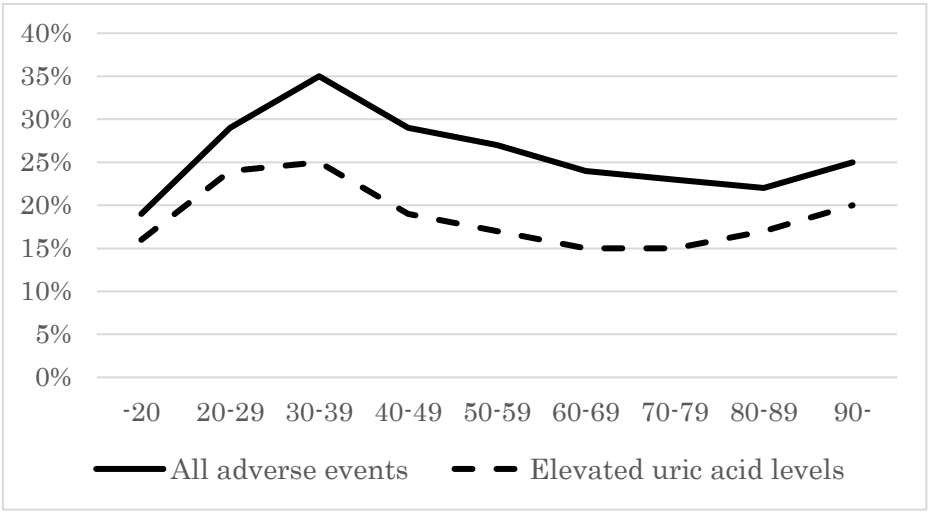
		Died in hospital	Transferred for escalation of care	Still in hospital (alive)	Transferred for de-escalation of care	Discharged alive
Outcome (n=15,001)	<20	0 (0%)	0 (0%)	2 (3.6%)	2 (3.6%)	52 (92.9%)
	20–29	1 (0.2%)	8 (1.6%)	6 (1.2%)	29 (6.2%)	441 (90.9%)
	30–39	3 (0.4%)	27 (3.4%)	14 (1.8%)	36 (4.6%)	710 (89.9%)
	40–49	10 (0.5%)	92 (4.9%)	11 (0.6%)	88 (4.7%)	1,652 (89.2%)
	50–59	44 (1.5%)	188 (6.5%)	32 (1.1%)	139 (4.8%)	2,475 (86.0%)
	60–69	124 (4.4%)	248 (8.9%)	48 (1.7%)	190 (6.8%)	2,190 (78.2%)
	70–79	319 (9.8%)	306 (9.4%)	114 (3.5%)	331 (10.2%)	2,173 (67.0%)
	80–89	480 (21.1%)	131 (5.7%)	99 (4.3%)	358 (15.7%)	1,211 (53.1%)
	≥90	180 (29.2%)	12 (1.9%)	45 (7.3%)	115 (18.6%)	265 (42.9%)

Table 5 Adverse events associated with favipiravir use

(showing those with two or more events)

Adverse events	n	(%)
Number of adverse events associated with favipiravir use	3,878	(25.4%)
Hyperuricemia/elevated uric acid levels	2,628	(17.2%)
Hepatic function disorder/elevated liver function enzyme levels	1,113	(7.3%)
Rash/toxicoderma/eczema/erythema	150	(1.0%)
Fever	135	(0.9%)
Renal impairment/elevated creatinine levels	58	(0.4%)
Diarrhea/soft stool	57	(0.4%)
Vomiting/nausea	51	(0.3%)
Bradycardia	37	(0.2%)
Worsening oxygenation	35	(0.2%)
Poor appetite	18	(0.1%)
Gout	16	(0.1%)
Leukocytopenia	16	(0.1%)
Worsening of COVID-19 symptoms	15	(<0.1%)
Abnormal coagulation test values	13	(<0.1%)
Abnormal lipid test values	12	(<0.1%)
Hyperkalemia	12	(<0.1%)
Rhabdomyolysis/elevated creatine kinase levels	10	(<0.1%)
Elevated CRP levels	8	(<0.1%)
Constipation	8	(<0.1%)
Elevated bilirubin levels	7	(<0.1%)
Fatigue	7	(<0.1%)
Thrombocytopenia	7	(<0.1%)
Hyperglycemia	6	(<0.1%)
Elevated amylase levels	6	(<0.1%)
Staggering	5	(<0.1%)
Gastric discomfort	5	(<0.1%)
Pruritus	5	(<0.1%)
Thrombocytosis	5	(<0.1%)
Elevated BUN levels	4	(<0.1%)
Dizziness	4	(<0.1%)
Neutropenia	4	(<0.1%)
Headache	4	(<0.1%)
Erythema	4	(<0.1%)
Lymphocytopenia	3	(<0.1%)
Stomatitis	3	(<0.1%)
Hypernatremia	3	(<0.1%)
Elevated LDH levels	3	(<0.1%)
Eosinophilia	3	(<0.1%)
Melena	2	(<0.1%)
Hiccup	2	(<0.1%)
Hypertension	2	(<0.1%)
Stroke	2	(<0.1%)
Restlessness	2	(<0.1%)
Abdominal pain	2	(<0.1%)
Seizure	2	(<0.1%)
Anemia	2	(<0.1%)
Altered mental status	2	(<0.1%)
Gastrointestinal symptoms	2	(<0.1%)
Thromboembolism	2	(<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. The number of registered cases have increased in accordance with the evolution of the pandemic, and has now exceeded fifteen thousand. Patient demographics, disease severity, clinical outcomes, adverse event rates and types have remained largely the same from the last interim report which included cases through the end of February, 2021[2].

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]. In particular, a patient who had a negative pregnancy test prior to starting favipiravir was found to have a positive pregnancy test after completion of the treatment, which prompted the manufacturer to issue an alert to all hospitals with access to favipiravir reiterating the importance of informing patients that a pregnancy test can be negative in early pregnancy when obtaining informed consent for the off-label use, in addition to confirming a negative pregnancy test.

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