Preliminary Report of the Favipiravir Observational Study in Japan (2020/5/15)

Favipiravir Observational Study Group

Introduction

The new coronavirus (SARS-CoV-2) was initially identified from patients with pneumonia of unknown cause in Hubei Province, People's Republic of China in December 2019. The virus has since spread globally and infected over four and a half million people as of May 15, 2020. In Japan, over 16,000 have been infected, and over 800 of them have died from the new coronavirus infection (COVID-19).

Favipiravir (brand name Avigan) was approved in 2014 in Japan for the treatment of new or re-emergent influenza against which conventional anti-influenza agents are ineffective, and its use has been strictly controlled by the government due to potential risk for teratogenicity. Favipiravir is an RNA-dependent RNA polymerase inhibitor which in its ribosyl triphosphate form inhibits replication of a broad range of RNA viruses. Favipiravir has been reported to be active against SARS-CoV-2 *in vitro* [1]. Clinically, a non-randomized study conducted in China reported faster achievement of SARS-CoV-2 PCR negativity and improvement of chest CT findings at 14 days when COVID-19 patients were given favipiravir in combination with interferon-alpha compared with lopinavir-ritonavir in combination with interferon-alpha, both for 14 days [2]. A randomized clinical study of COVID-19 patients, also conducted in China, compared clinical efficacy of favipiravir and umifenovir, an anti-influenza agent, both given for 10 days. While the primary endpoint of better clinical improvement at 7 days was not met, durations of fever and cough were significantly shorter among those who received favipiravir [3].

Based on these data, an observational study under which favipiravir is administered to hospitalized patients with COVID-19 on a compassionate use basis was started in February in Japan. To qualify for compassionate use, premenopausal women must document a negative pregnancy test, and all patients and their sexual partners must agree to effective contraception during and 10 days after administration of favipiravir in accordance with the government guidance on compassionate use of favipiravir [4]. Cases for which favipiravir was administered are enrolled to the case registry managed by the National Center for Global Health Medicine (COVID-19 Registry Japan) and the survey administered by Fujita Health University (Favipiravir Observational Study). This report describes cases that were deposited to the Favipiravir Observational Study as of May 15, 2020.

Method

Favipiravir is provided to hospitals admitting confirmed COVID-19 patients from FUJIFILM Toyama Chemical Co., Ltd. after a request for compassionate use is made to the Ministry of Health, Labour and Welfare. The hospitals are asked at the time to join the Favipiravir Observational Study and provide information regarding the patient demographics, comorbidities, severity of illness, dose and duration of favipiravir, use of other medications targeting SARS-CoV-2, adverse events likely related to favipiravir use, clinical status 7 and 14 days from the start of the use of favipiravir and clinical outcome approximately one month after admission to the hospital. The data were collected using the survey function of REDCap. The study was approved by the institutional review board of Fujita Health University.

Results

【Overview】

A total of 2,158 cases were registered from 407 hospitals as of 6 pm on May 15, 2020. Among them, patient demographics, clinical status at day 7, clinical status at day 14, clinical outcome at one month were available for 2,127, 1,713, 1,282 and 1,918 cases,

respectively. This study utilizes a survey function in an effort to prioritize timeliness of the data and ease of data entry at each hospital, and only limited data cleaning has been performed. Also, since information on patient transfer is not collected, the same patients may be registered more than once if they received favipiravir at multiple hospitals.

【Demographics】

The age distribution, sex, comorbidities, receipt of anti-viral agents other than favipiravir (ciclesonide, lopinavir-ritonavir and others), and overall clinical outcome at one month after hospital admission are shown in Table 1. In terms of demographics, 52.3% were age 60 years or older, and 67.1% were male. At least one of the four comorbidities surveyed (diabetes, cardiovascular diseases, chronic lung diseases, immunosuppression) was present in 49.2%. Ciclesonide, an inhaled steroid agent which is shown to possess activity against SARS-CoV-2 [5], was co-administered in 41.6% of the patients.

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

Variables	Categories	n	(%)
Age group (n=2,158)	<10	0	(0%)
	10-19	2	(0.1%)
	20-29	71	(3.3%)
	30-39	133	(6.2%)
	40-49	313	(14.5%)
	50-59	511	(23.7%)
	60-69	437	(20.3%)
	70-79	380	(17.6%)
	80-89	249	(11.5%)
	≥90	62	(2.9%)
Sex (n=2,158)	Male	1,447	(67.1%)
	Female	711	(32.9%)
Diabetes (n=2,135)	Present	521	(24.4%)
	Absent	1,614	(75.6%)
Cardiovascular diseases (n=2,136)	Present	533	(25%)
	Absent	1,603	(75%)
Diabetes or cardiovascular diseases (n=2,139)	Present	855	(40%)
	Absent	1,284	(60%)
Chronic lung diseases (n=2,136)	Present	248	(11.6%)
	Absent	1,888	(88.4%)
Immunosuppression (n=2,134)	Present	156	(7.3%)
	Absent	1,978	(92.7%)
Any of the above comorbidities (n=2,140)	Present	1,053	(49.2%)
	Absent	1,087	(50.8%)
Ciclesonide (n=2,081)	Given	865	(41.6%)
	Not given	1,216	(58.4%)
Lopiniavir-ritonavir (n=2,017)	Given	69	(3.4%)
	Not given	1,948	(96.6%)
Other therapy related to COVID-19 (n=2,043)	Given	566	(27.7%)
	Not given	1,477	(72.3%)
Outcome a month after admission to hospital(n=1,918) (n=1,918)	Died in hospital	223	(11.6%)
	Transferred for escalation of care	111	(5.8%)
	Still in hospital	490	(25.5%)
	Transferred for de-escalation of care	180	(9.4%)
	Discharged alive	914	(47.7%)

【Administration of favipiravir】

In 92.8% of the patients, favipiravir was dosed at 2 doses of 1,800 mg orally on the first day followed by 800 mg orally twice a day on subsequent days (Table 2). The median duration was 11 days. The median days from the positive PCR test and hospital admission to the initiation of favipiravir therapy were 2 and 1 days, respectively.

Table 2 Administration of favipiravir

(a) Dosing of favipiravir

n	Dosing	n(%)
2,141	2 doses of 1,600 mg on first day followed by 600 mg twice a day on subsequent days	115 (5.4%)
	2 doses of 1,800 mg on first day followed by 800 mg twice a day on subsequent days	1,986 (92.8%)
	Others	40 (1.9%)

(b) Duration of favipiravir (Days)

n	Mean	SD	Median	Q1(25%)	Q3(75%)
1,672	10.4	5.6	11	7	13

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

n	Mean	SD	Median	Q1(25%)	Q3(75%)
2,114	3	3.4	2	1	4

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

n	Mean	SD	Median	Q1(25%)	Q3(75%)
2,134	2.9	8.2	1	0	3

【Severity of illness】

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, 976 patients (45.2%) had mild disease, 947 patients (43.9%) had moderate disease and 239 patients (10.9%) had severe disease.

【Clinical status and outcome stratified by severity of illness】

Clinical status at 7 and 14 days from the start of favipiravir therapy was recorded as improved, worsened, unchanged compared with when therapy was started, based on the providers' clinical assessment (Table 3). Rates of clinical improvement at 7 days were 73.8%, 66.6% and 40.1% for mild, moderate and severe disease, respectively. Rates of clinical improvement at 14 days were 87.8%, 84.5% and 60.3%, respectively. Rates of clinical worsening at 7 days were 13.1%, 21.3% and 28.3% for mild, moderate and severe disease, respectively. Rates of clinical worsening at 14 days were 5.9%, 8.8% and 25.2%, 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 5.1%, 12.7% and 31.7% for mild, moderate and severe disease, respectively.

Table 3. Clinical status and outcome stratified by severity of illness

(a) Clinical status at 7 days after start of favipiravir therapy

n		Improved	Unchanged	Worsened
1,713	Mild	574 (73.8%)	102 (13.1%)	102 (13.1%)
	Moderate	498 (66.6%)	91 (12.2%)	159 (21.3%)
	Severe	75 (40.1%)	59 (31.6%)	53 (28.3%)

(b) Clinical status at 14 days after start of favipiravir therapy

n		Improved	Unchanged	Worsened
1,282	Mild	506 (87.8%)	36 (6.2%)	34 (5.9%)
	Moderate	469 (84.5%)	37 (6.7%)	49 (8.8%)
	Severe	91 (60.3%)	22 (14.6%)	38 (25.2%)

(c) Clinical outcome one month from hospital admission

n		Died in hospital	Transferred for escalation of care	Still in hospital	Transferred for de-escalation of care	Discharged alive
1,918	Mild	42 (5.1%)	35 (4.2%)	160 (19.3%)	81 (9.8%)	512 (61.7%)
	Moderate	110 (12.7%)	66 (7.6%)	248 (28.7%)	71 (8.2%)	369 (42.7%)
	Severe	71 (31.7%)	10 (4.5%)	82 (36.6%)	28 (12.5%)	33 (14.7%)

Table 4. Clinical status and outcome stratified by age group

(a) Clinical status at 7 days after start of favipiravir therapy

n		Improved	Unchanged	Worsened
1,713	<10	0	0	0
	10-19	0	0	0
	20-29	51 (86.4%)	4 (6.8%)	4 (6.8%)
	30-39	95 (84.1%)	15 (13.3%)	3 (2.7%)
	40-49	201 (77%)	38 (14.6%)	22 (8.4%)
	50-59	327 (77.9%)	47 (11.2%)	46 (11%)
	60-69	224 (64.7%)	50 (14.5%)	72 (20.8%)
	70-79	160 (56.1%)	52 (18.2%)	73 (25.6%)
	80-89	70 (38%)	39 (21.2%)	75 (40.8%)
	≥90	19 (42.2%)	7 (15.6%)	19 (42.2%)

(b) Clinical status at 14 days after start of favipiravir therapy

n		Improved	Unchanged	Worsened
1,282	<10	0	0	0
	10-19	0	0	0
	20-29	35 (94.6%)	1 (2.7%)	1 (2.7%)
	30-39	78 (95.1%)	4 (4.9%)	0 (0%)
	40-49	168 (89.4%)	15 (8%)	5 (2.7%)
	50-59	314 (93.2%)	16 (4.7%)	7 (2.1%)
	60-69	218 (83.8%)	19 (7.3%)	23 (8.8%)
	70-79	169 (74.4%)	22 (9.7%)	36 (15.9%)
	80-89	67 (54.5%)	13 (10.6%)	43 (35%)
	≥90	17 (60.7%)	5 (17.9%)	6 (21.4%)

(c) Clinical outcome one month from hospital admission

n		Died in hospital	Transferred for escalation of care	Still in hospital	Transferred for de-escalation of care	Discharged alive
1,918	<10	0	0	0	0	0
	10-19	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
	20-29	1 (1.4%)	0 (0%)	11 (15.9%)	10 (14.5%)	47 (68.1%)
	30-39	0 (0%)	2 (1.6%)	24 (19.7%)	16 (13.1%)	80 (65.6%)
	40-49	5 (1.8%)	16 (5.7%)	45 (16%)	34 (12.1%)	181 (64.4%)
	50-59	11 (2.4%)	25 (5.5%)	99 (21.8%)	42 (9.3%)	277 (61%)
	60-69	42 (10.7%)	31 (7.9%)	107 (27.3%)	37 (9.4%)	175 (44.6%)
	70-79	65 (19.8%)	24 (7.3%)	100 (30.5%)	26 (7.9%)	113 (34.5%)
	80-89	81 (36.7%)	13 (5.9%)	79 (35.7%)	11 (5%)	37 (16.7%)
	≥90	18 (36%)	0 (0%)	24 (48%)	4 (8%)	4 (8%)

【Clinical status and outcome stratified by age groups】

Clinical status at 7 and 14 days from the start of favipiravir therapy and clinical outcome one month into hospitalization based on age groups is shown in Table 4. Clinical improvement rates were 79.0% at 7 days and 92.4% at 14 days for those 59 years old or younger, whereas they were 55.0% at 7 days and 73.8% at 14 days for those 60 years old or older. The mortality rates at the time of survey were 1.8% for those 59 years old or younger and 20.8% for those 60 years old or older.

Table 5 Adverse events possibly or likely related to favipiravir use

n=2,158		
Number of patients with adverse events	532	(24.65%)
Number of adverse events reported	626	
Hyperuricemia		
Liver function abnormalities	335	(15.52%)
Rash	159	(7.37%)
Diarrhea, loose stool	31	(1.44%)
Acute kidney injury, elevated creatinine levels	16	(0.74%)
Nausea, vomiting	16	(0.74%)
Fever	11	(0.51%)
Gout	9	(0.42%)
Hyperkalemia	8	(0.37%)
Rhabdomyolysis, elevated creatine kinase levels	7	(0.32%)
Thrombocytopenia	4	(0.19%)
Leukocytopenia	3	(0.14%)
Bradycardia	3	(0.14%)
Pruritus	2	(0.09%)
Worsening of pneumonia	2	(0.09%)
Coagulopathy	2	(0.09%)
Dizziness	2	(0.09%)
Poor appetite	1	(0.05%)
Agitation	1	(0.05%)
Jaundice	1	(0.05%)
Hypertension	1	(0.05%)
Hyponatremia	1	(0.05%)
Anemia	1	(0.05%)
Facial flushing	1	(0.05%)
hyperglycemia	1	(0.05%)
Swelling around mouth	1	(0.05%)
Fatigue	1	(0.05%)
Arthritis, enthesitis	1	(0.05%)
Thrombocytosis	1	(0.05%)
Stomatitis	1	(0.05%)
Abdominal pain	1	(0.05%)
Constipation	1	(0.05%)
Number of patients with adverse events	1	(0.05%)

【Adverse events】

Presence or absence of adverse events possibly or likely related to favipiravir use was recorded for 2,158 patients. A total of 626 events were reported for 532 patients (Table 5). The most common adverse events were hyperuricemia (335 patients; 15.52%) followed by liver injury or liver function test abnormalities (159 patients; 7.37%).

Discussion

Favipiravir Observational Study is being conducted in Japan to collect real-time data on the safety and efficacy of favipiravir that is being administered to COVID-19 patients as off-label, compassionate use. The data reported here suggest that the vast majority of patients with mild and moderate disease have recovered from the illness, whereas poor prognosis is not uncommon among those with severe disease. Furthermore, mortality rates are disproportionately higher among older patients, as has been reported in multiple other studies [6,7]. It should be noted, however, that this study only captures patients who received favipiravir, which precludes direct comparison of the clinical course with those who did not receive the agent. Given that over 80% of COVID-19 patients have mild disease which often improves by supportive therapy [6], caution is required in interpreting efficacy of favipiravir based on the data presented here.

Hyperuricemia and liver function abnormalities were the most commonly observed adverse events associated with favipiravir use, which was expected based on the known safety profile of the agent [8]. Nonetheless, the dose and duration of therapy are higher and longer, respectively, when used for COVID-19 compared with those approved for influenza (i.e. 2 doses of 1,600 mg orally on the first day followed by 600 mg orally twice a day on subsequent days for a total of 5 days), and close monitoring of these adverse events are recommend for this reason. Finally, early embryonic lethality and teratogenicity due to favipiravir have been observed in multiple animal models [8]. Pregnancy must therefore be excluded before dosing of favipiravir in premenopausal women, and all patients and their sexual partners should practice effective contraception during and 10 days after the end of favipiravir therapy.

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