Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Original Article

Favipiravir for symptomatic COVID-19: A nationwide observational cohort study

Yohei Doi a,b,* , Takuma Ishihara c , Sumi Banno d , Masahiko Ando e , Masashi Kondo d,f , on behalf of the Favipiravir Observational Study

ARTICLE INFO

Keywords:
Favipiravir
Drug therapy
COVID-19
Compassionate use

ABSTRACT

Introduction: Favipiravir, an antiviral agent with activity against SARS-CoV-2, was made available to hospitals in Japan for off-label use among COVID-19 patients between 2020 and 2021.

Methods: A nationwide observational cohort study was conducted on patients who received favipiravir as part of clinical care between February 2020 and December 2021. Information was collected on demographics, comorbidities, severity of illness, use of favipiravir and other medications targeting COVID-19, adverse events, clinical status at 7 and 14 days and clinical outcome one month after admission to the hospital.

Results: A total of 17,508 hospitalized patients who received favipiravir were registered from 884 hospitals. In terms of demographics, 55.9% were age ≥60 years, and 62.3% were male. At least one of the four surveyed comorbidities was present in 45.5% of the patients. The rates of clinical improvement at 7 and 14 days were 72.4%, 61.4% and 59.5% for mild, moderate, and severe diseases, respectively. The case fatality rates within a month from hospitalization were 3.3%, 12.6%, and 29.1% for mild, moderate, and severe diseases, respectively. Significant correlations were observed between death and advanced age, male sex, moderate or severe disease, diabetes, cardiovascular diseases, and immunosuppression. Commonly reported adverse events included uric acid level increase or hyperuricemia (16.8%), liver function abnormalities (6.9%), and rash (1.0%).

Conclusions: Favipiravir was well tolerated among COVID-19 patients. The study provides insights into the use of this agent at hospitals across Japan in the early phase of the pandemic.

1. Introduction

Favipiravir is a nucleoside analog antiviral agent that inhibits RNA-dependent RNA polymerase and demonstrates a wide spectrum of activity against RNA viruses. In Japan, favipiravir has been approved for the treatment of patients with novel or re-emerging pandemic influenza against which other treatments are ineffective, but the inventory is managed by the government and the drug is not routinely available for prescription. Given its in vitro activity against SARS-CoV-2, favipiravir was made available to hospitals for off-label use among patients with COVID-19 between February 2020 and December 2021, the period during which approved oral antiviral treatment options for COVID-19 were not yet available. Hospitals were asked to register the cases to this observational cohort study after it was administered to patients. This was the first occasion in which a large number of patients received favipiravir for the treatment of a viral infection in Japan. Here, we report the final dataset from the cohort, with a focus on demographics, disease course, and safety of favipiravir.

* Corresponding author. Departments of Microbiology and Infectious Diseases, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi, 470-1192, Japan.
E-mail address: yoheidoi@fujita-hu.ac.jp (Y. Doi).

https://doi.org/10.1016/j.jiac.2022.10.008
Received 22 August 2022; Received in revised form 12 October 2022; Accepted 14 October 2022
Available online 26 October 2022

© 2023 Japanese Society of Chemotherapy, Japanese Association for Infectious Diseases, and Japanese Society for Infection Prevention and Control.
Published by Elsevier Ltd. All rights reserved.
2. Methods

2.1. Off-label use of favipiravir

Favipiravir was made available to hospitals between February 2020 and December 2021 from FUJIFILM Toyama Chemical Co., Ltd., the manufacturer of favipiravir, after a request for off-label use of the agent was made by the hospitals to the Ministry of Health, Labour and Welfare and the requirements for close management of the medication were met, which practically restricted its use to hospitalized patients. The physicians prescribed favipiravir to patients with a confirmed diagnosis of COVID-19 upon consent in accordance with institutional regulations governing off-label use at each hospital.

2.2. Study design

This study was conducted as a retrospective study to collect clinical information after favipiravir was administered to patients as part of clinical care. Informed consent was on an opt-out basis given the non-interventional nature of the study. The hospitals were asked to provide anonymized information regarding the patient demographics, comorbidities, severity of illness, location of patient (inpatient or outpatient), dose and duration of favipiravir, use of other medications targeting COVID-19, 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. This study was approved by the Institutional Review Board of Fujita Health University.

2.3. Data collection and analysis

The data were collected using the survey function of REDCap. Query and data cleaning was conducted to address apparent errors such as duplicate record entry, missing values and outliers. Site monitoring was not conducted.

Continuous variables were described using median and interquartile range and categorical variables using frequencies. For the analysis of prognosis, the Kaplan-Meier estimate and Cox proportional hazards model were used. The date of the first dose of favipiravir was used as the baseline date, and a period up to the date of entry of clinical outcome was handled as the follow-up period. Only the clinical outcome recorded not conducted.

| Variables | Categories | n (%) |
|-----------|------------|-------|
| Demographics | Age group (n = 17,508) | <10 | 1 (0.0%) |
| | | 10–19 | 67 (0.4%) |
| | | 20–29 | 694 (4.0%) |
| | | 30–39 | 1074 (6.1%) |
| | | 40–49 | 2383 (13.6%) |
| | | 50–59 | 3501 (20.0%) |
| | | 60–69 | 3134 (17.9%) |
| | | 70–79 | 3499 |
| | | 80–89 | 2491 |
| | | ≥90 | 664 (3.8%) |
| | Sex (n = 17,508) | Female | 6597 (37.7%) |
| | | Male | 10,911 (62.3%) |
| | Diabetes (n = 17,429) | Present | 4070 |
| | | Absent | 13,359 (76.6%) |
| | Cardiovascular diseases (n = 17,440) | Present | 4034 |
| | | Absent | 13,406 (76.9%) |
| | Chronic lung diseases (n = 17,415) | Present | 1611 (9.3%) |
| | | Absent | 15,804 (90.7%) |
| | Immunosuppression (n = 17,410) | Present | 775 (4.5%) |
| | | Absent | 16,635 (95.5%) |
| | Any of the above comorbidities (n = 17,457) | Present | 7951 (45.5%) |
| | | Absent | 9506 (54.5%) |
| Concomitant COVID-19-related medications | Ciclosporine (n = 17,508) | Given | 4289 (24.5%) |
| | | Not given | 13,219 (75.5%) |
| | Lopinavir–ritonavir (n = 17,508) | Given | 72 (0.4%) |
| | | Not given | 17,436 (99.6%) |
| | Hydroxychloroquine (n = 17,508) | Given | 198 (1.1%) |
| | | Not given | 17,310 (98.9%) |
| | Nafamostat (n = 17,508) | Given | 1984 (6.2%) |
| | | Not given | 16,424 (93.8%) |
| | Camostat (n = 17,508) | Given | 702 (4.0%) |
| | | Not given | 16,806 (96.0%) |
| | Remdesivir (n = 17,508) | Given | 2312 (13.2%) |
| | | Not given | 15,196 (86.8%) |
| | Dexamethasone (n = 17,508) | Given | 7012 (40.1%) |
| | | Not given | 10,496 (59.9%) |
| | Methylprednisolone (n = 17,508) | Given | 2064 (11.8%) |
| | | Not given | 15,444 (88.2%) |
| Outcome (n = 17,461) | Died in hospital | 1203 (6.9%) |
| | Transferred for escalation of care | 934 (5.3%) |
| | Still in hospital (alive) | 179 (1.0%) |
| | Transferred for de-escalation of care | 1303 (7.5%) |
| | Discharged alive | 13,842 (79.3%) |
3. Results

3.1. Overview

A total of 17,508 hospitalized patients who received favipiravir were registered from 884 hospitals. Of these patients, the patient demographics, clinical status at Day 7, clinical status at Day 14, and clinical outcome at approximately one month after hospital admission were available for 17,366, 16,512, 13,425, and 17,461 patients, respectively. Fig. 1 shows the number of patients started on favipiravir by month. Over two thousand patients were treated with favipiravir in April 2020 at the height of the first surge. Its use then increased again in the summer and winter of 2020, corresponding to the second and third surges, respectively, then decreased in 2021 over the course of the summer and winter of 2020, and 2021.

3.2. 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, 55.9% 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 45.5% of the patients.

3.3. Administration of favipiravir

Administration of favipiravir is shown in Table 2. In 94.8% of the patients, favipiravir was dosed at two doses of 1800 mg followed by 800 mg twice a day. The median days from the first positive COVID-19 test and hospital admission to the initiation of favipiravir therapy were 2 and 0 days, respectively. The median duration of treatment was 8 days.

3.4. Severity of illness

For this study, mild, moderate, and severe diseases at the start of favipiravir were defined as those not requiring supplemental oxygen, those breathing spontaneously but requiring supplemental oxygen, and those requiring mechanical ventilation or extracorporeal membrane oxygenation, respectively. By this definition, 11,680 patients (66.7%) had mild disease, 5303 patients (30.3%) had moderate disease, and 525 patients (3%) had severe disease.

3.5. 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 by the treating physicians. The rates of clinical improvement at 7 and 14 days were 72.4% and 87.5%, 61.4% and 76.6%, and 45.4% and 59.5% for mild, moderate, and severe diseases, respectively (Table 3). The rates of clinical worsening at 7 and 14 days were 14.5% and 6.8%, 24.4% and 16%, and 28% and 25.5% for mild, moderate, and severe diseases, respectively.

The clinical outcome was assessed at approximately one month from hospitalization as discharged alive, died in hospital, transferred for de-escalation of care, transferred for escalation of care, or still in hospital. The case fatality rates within a month from hospitalization were 3.3%, 12.6%, and 29.1% for mild, moderate, and severe diseases, respectively.

3.6. 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 worse in older patients. The case fatality rate was 1.2% in the 50–59 age group, whereas the rates were 3.7%, 9.4%, 21%, and 27.6% in the 60–69, 70–79, 80–89, and ≥90 age groups, respectively.

Table 2

| Administration of favipiravir |
|-----------------------------|
| (a) Dosing of favipiravir    |
| n  | Dosing                        |
|----|-------------------------------|
| 17,478 | 2 doses of 1600 mg followed by 600 mg twice a day |
| 17,508 | 2 doses of 1800 mg followed by 800 mg twice a day |
| Others | 16564 (94.8%) |
| 364 | 2.1% |

| (b) Duration of favipiravir |
|----------------------------|
| n  | Median | Q1 (25%) | Q3 (75%) |
|----|--------|----------|----------|
| 17,508 | 8 | 5 | 10 |

| (c) Days from first positive test to first dose of favipiravir |
|--------------------------------------------------------------|
| n  | Median | Q1 (25%) | Q3 (75%) |
|----|--------|----------|----------|
| 17,508 | 2 | 1 | 4 |

| (d) Days from hospital admission to first dose of favipiravir |
|-------------------------------------------------------------|
| n  | Median | Q1 (25%) | Q3 (75%) |
|----|--------|----------|----------|
| 17,508 | 0 | 0 | 1 |

Table 3

| Clinical status and outcome stratified by severity of illness in patients who received favipiravir |
|--------------------------------------------------------------------------------------------------|
| (a) At 7 days after start of favipiravir                                                        |
| Day 7 (n = 16,512)                                                                               |
| Mild | Improved | 8057 (72.4%) |
|      | Unchanged | 1449 (13%) |
|      | Worsened  | 1618 (14.5%) |
| Moderate | 3010 (61.4%) |
|          | 697 (14.2%) |
|          | 3585 (67.7%) |
| Severe  | 219 (45.4%) |
|          | 128 (26.6%) |
|          | 135 (28%) |

| Day 14 (n = 13,425)                                                                               |
| Mild   | Improved  | 7753 (87.5%) |
|        | Unchanged | 512 (5.8%) |
|        | Worsened  | 600 (6.8%) |
| Moderate | 3161 (76.6%) |
|          | 305 (7.4%) |
|          | 659 (16%) |
| Severe   | 259 (59.5%) |
|          | 65 (14.9%) |
|          | 111 (25.5%) |

| (c) Clinical outcome one month from hospital admission                                           |
| Outcome (n = 17,461)                                                                            |
| Died in hospital                                                                               |
| Mild   | 475 (4.1%) |
| Moderate | 438 (8.3%) |
| Severe  | 21 (4%) |
| Still in hospital (alive)                                                                      |
| Mild   | 86 (0.7%) |
| Moderate | 75 (1.4%) |
| Severe  | 18 (3.4%) |

| Transferred for de-escalation of care                                                          |
| Mild   | 621 (5.3%) |
| Moderate | 534 (10.1%) |
| Severe  | 148 (28.4%) |
| Discharged alive                                                                               |
| Mild   | 10,074 (86.5%) |
| Moderate | 3585 (67.7%) |
| Severe  | 183 (35.1%) |
3.7. Prognostic factors

Univariable analysis showed significant correlations between death and advanced age, moderate or severe disease, diabetes, cardiovascular diseases, chronic lung diseases, and immunosuppression (Table 5). A multivariable analysis showed significant correlations between death and advanced age, male sex, moderate or severe disease, diabetes, cardiovascular diseases, and immunosuppression (Table 6). Figs. 2–8 show survival curves stratified by each factor.
3.8. Adverse events

A total of 4312 (24.6%) patients had probable or possible adverse events in association with favipiravir use recorded based on the treating physicians’ assessment (Table 7). Commonly reported adverse events included uric acid level increase or hyperuricemia in 2934 patients, liver function abnormalities in 1205 patients, and rash in 170 patients. The adverse event rates by age groups are shown in Fig. 9. They were reported more commonly in younger age groups, and hyperuricemia or increase in serum uric acid level was reported most frequently in those between 30 and 39.

3.9. Outpatients

Separate from the data shown on hospitalized patients above, 219 patients from 19 hospitals were recorded as having been started on favipiravir in an outpatient setting. As information on location of care was not collected otherwise, they may have been hospitalized subsequently or followed up as outpatients. These patients were younger than inpatients with 71.7% less than 60 years of age. Males accounted for 53.9%, and at least one of the four surveyed comorbidities was present in 25.3%. The median day from the first positive COVID-19 test to the initiation of favipiravir was 1 day, and the median duration of treatment was 6 days. Among these patients, 216 patients (98.6%) had mild disease, 3 patients (1.4%) had moderate disease, and none had severe disease. The combined rates of clinical improvement at 7 and 14 days were 79.1% and 86.7%, respectively. At approximately one month, 89.0% of the patients had improved, 1.4% had not improved and the outcome was unknown for 2.7%. Adverse events reported were uric acid level increase or hyperuricemia (13 patients), liver function abnormalities (3 patients), and palpitation (1 patient).
4. Discussion

Favipiravir became available for off-label use in the treatment of COVID-19 in Japan beginning in February 2020 in response to the unprecedented pandemic which was quickly unfolding at the time. The off-label use program was coordinated through the Ministry of Health, Labour and Welfare, and the hospitals participating in this off-label use program were invited to register the cases to this observational cohort study in order to monitor its use, safety and patient outcomes. As the incidence of COVID-19 decreased and other oral antiviral treatment options became available, the off-label use program was concluded at the end of December 2021. Prior to this final report, four interim reports from this study have been published on the website of the Japanese Association of Infectious Diseases. In this final report, over seventeen thousand patients were registered, making it one of the largest cohorts of patients who received favipiravir.

Favipiravir shows variable degrees of in vitro activity against SARS-
CoV-2 depending on the cells and experimental conditions [1–3], and has demonstrated efficacy in hamster models [4,5]. A large number of clinical trials have also been conducted and reported. A recent meta-analysis suggested potential modest clinical benefit of favipiravir over standard of care in terms of faster viral clearance, defervescence, radiographic improvement, hospital discharge and clinical improvement among hospitalized patients, however no difference was observed on mortality [6]. Furthermore, clinical trials conducted among outpatients have not demonstrated clinical or virological benefit of favipiravir [7–9]. The present study was not designed to evaluate effectiveness, and the study covered periods with variable admission criteria, SARS-CoV-2 variants, vaccination rates and availability of additional treatment options, such as use of corticosteroids for patients requiring oxygen. It is also conceivable that the outcomes may have been confounded by indication in that those perceived to be at an elevated risk of suboptimal clinical outcomes were preferentially considered for treatment with favipiravir.

The common adverse events associated with favipiravir use were uric acid level increase and liver function test abnormalities. Elevation of uric acid levels, believed to be caused by its reduced excretion into the urine, have been observed among patients receiving favipiravir across clinical studies, and are known to normalize after discontinuation of the agent [10,11]. The reason for the higher frequencies of uric acid elevation in younger age groups was unclear. Importantly, there were no unanticipated safety signals in this large cohort of patients who received favipiravir.

The study has several key limitations to be acknowledged. As this was an observational cohort study, not all patients who received favipiravir on an off-label basis were captured. Also, the study used the survey function of RedCap to minimize data entry effort on the part of the hospitals. This meant that the assessment of clinical improvement or worsening was delegated to the treating physicians, and data cleaning was also kept to a minimum. Underreporting of adverse events is another possibility. Despite these caveats, the study provides unique insights into how favipiravir was utilized in the management of COVID-19 at Japanese hospitals in the early phase of the pandemic.

Funding
This study was supported by Japan Agency for Medical Research and Development (AMED) under Grant Numbers JP19fk0108150, JP20fk0108150.

Availability of data and materials
The data will not be shared because of participant confidentiality.

Authors’ contributions
YD was the principal investigator and responsible for the data analysis. SB and MK contributed to the study design and ethical approval. TI conducted the statistical analysis. MA conducted quality control of the database. YD drafted the manuscript, and all authors contributed substantially to its revision.

Declaration of competing interest
YD has served on a scientific advisory board of Fujifilm, the manufacturer of favipiravir, for an unrelated study. All other authors declare no competing interests.

Acknowledgements
We thank all hospitals and healthcare providers across Japan that provided the clinical data for this study.

References
[1] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30(3):269–71.
[2] Shannon A, Selisko B, Le NT, Huchting J, Touret F, Piorkowski G, et al. Rapid incorporation of Favipiravir by the fast and permissive viral RNA polymerase complex results in SARS-CoV-2 lethal mutants. Nat Commun 2020;11(1):4682.
[3] Jeon S, Ko M, Lee J, Choi I, Ryu SY, Park S, et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. Antimicrob Agents Chemother 2020;64(7):e00819–20.
[4] Kaptein SJF, Jacobs S, Langendries L, Seldeslachts L, Ter Horst S, Liesenborghs L, et al. Favipiravir at high doses has potent antiviral activity in SARS-CoV-2-infected hamsters, whereas hydroxychloroquine lacks activity. Proc Natl Acad Sci U S A 2020;117(43):26955–65.
[5] Driouch JS, Cochin M, Lingas G, Mourera G, Touret F, Petit PR, et al. Favipiravir antiviral efficacy against SARS-CoV-2 in a hamster model. Nat Commun 2021;12(1):1735.
[6] Hung DT, Ghula S, Aziz JMA, Makram AM, Tawfik GM, Abuzaid AA, et al. The efficacy and adverse effects of favipiravir on patients with COVID-19: a systematic review and meta-analysis of published clinical trials and observational studies. Int J Infect Dis 2022;120:217–27.
[7] Bosaered M, Alharbi A, Mahmood F, Alrehily S, Bahlaq M, Gaiser Z, et al. Efficacy of favipiravir in adults with mild COVID-19: a randomized, double-blind, multicentre, placebo-controlled clinical trial. Clin Microbiol Infect 2022;28(4):602–8.
[8] Holubar M, Subramanian A, Purinton N, Hedlin H, Bunning B, Walter KS, et al. Favipiravir for treatment of outpatients with asymptomatic or uncomplicated COVID-19: a double-blind randomized, placebo-controlled, phase 2 trial. Clin Infect Dis 2022. https://doi.org/10.1093/cid/ciac312.
[9] Golan Y, Campos JAS, Wolfrom L, Cilla D, Hanahergh R, Gonzales-Rojas Y, et al. Favipiravir in patients with early mild-to-moderate COVID-19: a randomized controlled trial. Clin Infect Dis 2022. https://doi.org/10.1093/cid/ciac312.
[10] Mishima E, Anzai N, Miyazaki M, Abe T. Uric acid elevation by favipiravir, an antiviral drug. Tohoku J Exp Med 2020;251(2):87–90.
[11] Doi Y, Hihino M, Hane R, Yamanoto M, Kasamatu H, Hirose M, et al. A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. Antimicrob Agents Chemother 2020;64(12):e01897–20.

Table 7 (continued)

| Condition                  | Count |
|----------------------------|-------|
| Hyponatremia               | 1     |
| Diaphoresis                | 1     |
| Eye floater                | 1     |
| Dysgeusia                  | 1     |
| Drowsiness                 | 1     |
| Lacrimation                | 1     |
| Splenic infarction         | 1     |

Fig. 9. Adverse event rates by age group.