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Adjunctive favipiravir for severe COVID-19: a retrospective observational study of the first 41 patients in Thailand

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Abstract

Background: Favipiravir is a promising drug for COVID-19, but evidence from a robust clinical trial is limited.
Objective: To describe the demographics, clinical characteristics, and various antiviral treatment regimens (with and without favipiravir) of patients with severe and nonsevere COVID-19.
Method: We conducted a retrospective observational study in all COVID-19 patients admitted at Bamrasnaradura Infectious Diseases Institute (BIDI) from January 8 to March 30, 2020. We compared the demographics, clinical characteristics, and various antiviral treatment regimens of 12 severe and 29 nonsevere COVID-19 patients in Thailand.
Results: Adjunctive favipiravir was given to only severe cases. The median length of hospitalization of patients either receiving favipiravir or not receiving favipiravir was not significantly different ($P = 0.8549$), but those who received adjunctive favipiravir became reverse transcriptase–polymerase chain reaction negative 2 days sooner than the other group (median: 6 days vs. 8 days; $P = 0.1125$).
Conclusion: The findings suggested that adjunctive favipiravir might not be effective for patients with severe COVID-19, but further studies with larger sample sizes are needed.

Keywords: COVID-19; favipiravir; SARS-Cov-2

Favipiravir, an RNA-dependent RNA polymerase inhibitor, is one of the promising drugs investigated for the treatment of coronavirus disease 2019 (COVID-19) [1–3]. It was approved for the treatment of COVID-19 in China, and preliminary results from an ongoing open-label, nonrandomized controlled trial of nonsevere patients suggested that oral favipiravir 1,600 mg twice daily on Day 1, followed by 600 mg twice daily showed a superior antiviral action than that of oral lopinavir 400 mg and ritonavir 100 mg twice daily [4]. A randomized controlled trial recently published in a preprint found that compared to arbidol, favipiravir did not significantly improve clinical recovery at 1 week [5].

Given the present pandemic, evidence on the clinical effectiveness of each antiviral regimen in real-life settings,

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especially from less-developed countries, is essential yet limited. Various combinations of antivirals have been used simultaneously along with other supportive therapies, resulting in a more difficult context for evidence-based clinical decision-making. As potential drugs have joined the personal protective equipment to become scarce resources for fighting COVID-19, price and availability concerns are inevitable.

Thailand is one of the countries that have been affected by the novel coronavirus (severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2) [6, 7] but was fortunate enough to procure favipiravir, which is available only in Asia. Given its price and availability, the Thai Food and Drug Administration authorized the use of favipiravir as an adjunctive antiviral therapy to only severe COVID-19 patients under the clinical care system of the Department of Disease Control, Ministry of Public Health.

This report aims to describe the demographics, clinical characteristics, and various antiviral treatment regimens (with vs. without favipiravir) of patients with severe and nonsevere COVID-19 treated at the Bamrasnaradura Infectious Diseases Institute (BIDI), Thailand.

Methods

This study was approved by the Institutional Review Board of Bamrasnaradura Infectious Diseases Institute, Department of Disease Control, Ministry of Public Health (certificate of approval no. S012h_63_ExPD). We used the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" cohort checklist when writing our report [8].

In this retrospective observational study, we reviewed all 41 COVID-19 patients confirmed by a positive result on a reverse transcriptase–polymerase chain reaction (RT-PCR) assay of a nasopharyngeal swab specimen. They were admitted at Bamrasnaradura Infectious Diseases Institute (BIDI), Nonthaburi, Thailand, from January 8 to March 30, 2020. One major source of bias is that favipiravir was allowed only for severe COVID-19 cases. Various medication regimens were used based on the dosages summarized in **Table 1**. Disease severity was classified into three levels: 1 (Mild), 2 (Moderate; abnormal chest X-ray and respiratory rate ≤24 breaths per minute, and 3 (Severe; progressive chest X-ray or respiratory failure). Treatment efficacy was assessed by the time of viral clearance and length of hospital stay.

Descriptive statistics were used to summarize the data; results are reported as means and standard deviations, or medians and interquartile ranges, as appropriate. Categorical variables are presented as counts and percentages. Wilcoxon rank sum test was used to compare the length of stay and days from treatment initiation to negative RT-PCR result. The analysis was performed with Stata/MP 15.1 software (StataCorp LP, College Station, TX, USA).

Results

Forty-one COVID-19 patients were included in this study. Their mean age was 45 years, and 40% were female. Twenty-four patients (58.5%) had no pneumonia (disease severity level 1) whereas three patients (7.3%) were mechanically ventilated and dead (**Table 2**). Thirteen patients (31.7%) received at least LPV/r or DRV/r, whereas 12 patients (29.3%) also received CQ/HCQ. Ten patients (22.0%) received adjunctive favipiravir, one of whom also received remdesivir.

The median lengths of hospitalization of patients either receiving favipiravir or not receiving favipiravir were not

Table 1. COVID-19 medication dosages at the Bamrasnaradura Infectious Diseases Institute (BIDI), Thailand

Medication	Day 1	Days 2–5	Days 6–10
Favipiravir (200 mg) PO	8 tablets twice a day	3 tablets twice a day	3 tablets twice a day
Lopinavir/ritonavir (LPV/r) (200 mg/50 mg) PO	2 tablets twice a day	2 tablets twice a day	2 tablets twice a day
Darunavir/ritonavir (DRV/r) (600 mg/100 mg) PO	1 tablet twice a day	1 tablet twice a day	1 tablet twice a day
Darunavir (DRV) (600 mg) PO	1.5 tablets daily or 1 tablet twice a day	1.5 tablets daily or 1 tablet twice a day	1.5 tablets daily or 1 tablet twice a day
Ritonavir (r) (100 mg) PO	1 tablet daily or 1 tablet twice a day	1 tablet daily or 1 tablet twice a day	1 tablet daily or 1 tablet twice a day
Chloroquine (CQ) (250 mg) PO	1–2 tablets twice a day	1–2 tablets twice a day	1–2 tablets twice a day
Hydroxychloroquine (HCQ) (200 mg) PO	1 tablet twice a day	1 tablet twice a day	1 tablet twice a day
Remdesivir IV	200 mg	100 mg	100 mg

IV, intravenously; PO, orally.

significantly different (P = 0.86), but those who received adjunctive favipiravir became RT-PCR negative 2 days sooner than the other group (median: 6 days vs. 8 days; P = 0.11) (**Table 3**). No major adverse drug reactions were observed.

Table 2. Characteristics of 41 patients with COVID-19 in the study

Characteristics	Mean/frequency
Age, years, n (SD)	45 (15.5)
Females, n (%)	17 (41.5)
Health workers, n (%)	1 (2.4)
Comorbidities, n (%)	
Hypertension	6 (14.6)
Dyslipidemia	2 (4.9)
Diabetes mellitus	2 (4.9)
Cardiac diseases	3 (7.3)
Chronic liver diseases	3 (7.3)
Chronic hematologic diseases	1 (2.4)
Rheumatologic diseases	1 (2.4)
Disease severity level, n (%)	
Mild	24 (58.5)
Moderate	5 (12.2)
Severe	12 (29.3)
On ventilator, n (%)	3 (7.3)
Deaths, n (%)	3 (7.3)
Medication profile, n (%)	
LPV/r or DRV/r	13 (31.7)
LPV/r or DRV/r + CQ or HCQ	12 (29.3)
LPV/r or DRV/r + CQ or HCQ + favipiravir	9 (22.0)
LPV/r or DRV/r + CQ or HCQ + favipiravir + remdesivir	1 (2.4)
Other or no specific medications	6 (14.6)

LPV/r, lopinavir/ritonavir; DRV/r, darunavir/ritonavir; CQ, chloroquine; HCQ, hydroxychloroquine.

Discussion

Findings from our experience suggest that adjunctive favipiravir might not be effective for patients with severe COVID-19. Given the lack of evidence on the clinical effectiveness of favipiravir on COVID-19 at the initial phase of our study, along with the limited availability of the medications as mentioned earlier, favipiravir was reserved for only severe patients in Thailand. We believe that the clinical outcomes could have been better had favipiravir been administered earlier, as suggested by the potential superior clinical efficacy of adding favipiravir to LPV/r (4).

Initially, we tried to administer favipiravir for only 5 days, which was extended to 10 days based mainly on clinical judgment and partly on the slightly improved chest X-ray findings. This is a good example of the real-life practices that were based mainly on clinical judgment because no standardized treatment protocols were available.

The major limitations of our observational study are as follows: (i) favipiravir was allowed only for severe COVID-19 cases, which is a potential source of bias; and (ii) the relatively small size of the sample, which limited generalization of the findings. This could have been improved by adopting a more robust design, such as a randomized controlled trial with larger sample size. Furthermore, we were not able to collect a comprehensive set of clinical outcomes, such as computed tomography of the chest, quantitative viral assessment, or other blood parameters. However, an early experience of a less-developed country might be beneficial for many other similar contexts.

Conclusion

Adjunctive favipiravir might not be effective for severe COVID-19 patients, but further studies with larger sample sizes are needed.

Table 3. Outcomes in COVID-19 patients treated with and without favipiravir

Outcomes	Overall (n = 41)	With favipiravir (n = 10)	Without favipiravir (n = 31)	*P*
Disease severity level, n (%)				
Mild	24 (58.5%)	0 (0.0%)	24 (77.4%)	
Moderate	5 (12.2%)	0 (0.0%)	5 (16.1%)	
Severe	12 (29.3%)	10 (100.0%)	2 (6.5%)	
Length of stay, median (IQR)	9.0 (7.0, 14.0)	8.0 (7.3, 13.0)	10.0 (7.0, 12.5)	0.86
Days from start of treatment to PCR-negative result, median (IQR)	7.0 (5.0, 10.0)	6.0 (4.3, 8.5)	8.00 (6.0, 10.0)	0.11

RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IQR, interquartile ranges.

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Author contributions. WP and KP contributed substantially to the conception and design of this study. WP, PS, CB, and WAP contributed substantially to the acquisition of data. KP, PS, and PP analyzed and interpreted the data. WP, KP, PS, PP drafted the manuscript. CB and WAP contributed substantially to its critical revision. All the authors approved the final version submitted for publication and take responsibility for the statements made in the published article.

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Data sharing statement. The data sets generated or analyzed during the current study are available from the corresponding author on reasonable request.

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