FAVIPIRAVIR THERAPY FOR PATIENTS WITH COVID-19 PNEUMONIA: AN OBSERVATIONAL STUDY

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Abstract. Pneumonia in patients with COVID-19 is sometimes severe and life-threatening, and currently there is no specific effective drug approved for COVID-19 treatment. Favipiravir is a pyrazine analog inhibiting RNA virus RNA dependent RNA polymerase with antiviral activity against SARS-CoV-2. An observational study was conducted in confirmed COVID-19 pneumonia patients admitted to a university hospital in Thailand on effectiveness and safety of favipiravir prescribed on a compassionate-use basis. Among COVID-19 patients with pneumonia (n = 37), 54 and 46% had severe and non-severe pneumonia, respectively. Mean ± SD age was 48 ± 3 years, 62% were male and diabetes mellitus and hypertension were the most common comorbidities. Median period from initiation of favipiravir treatment to clinical improvement of patients with severe and non-severe pneumonia was 17 days (95% confidence interval (CI): 9-25) and 9 days (95% CI: 7-11) respectively. Ninety-five percent of patients completely recovered and were discharged within 39 days following admittance; unfortunately, the remaining patients succumbed to severe acute respiratory distress syndrome and multi-organ failure. In conclusion, favipiravir holds promise as a potential drug for treatment of COVID-19 pneumonia, but a larger randomized trial is warranted to confirm its efficacy.

Keywords: favipiravir, COVID-19, pneumonia, SARS-CoV-2, Thailand

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INTRODUCTION

A novel disease emerged in Wuhan, PR China, in late December 2019, with clinical characteristics of sudden acute pneumonia (WHO, 2020c). The syndrome was later named Coronavirus Disease 2019 (COVID-19), and the causative agent severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). The disease rapidly spread globally and the World Health Organization (WHO) declared COVID-19 a pandemic disease on 11 March 2020; as of 24 May 2020, COVID-19 has infected over 5.3 million people in 188 countries, causing more than 340,000 mortalities (WHO 2020b; Wu *et al*, 2020). Clinical manifestation of COVID-19 varies from asymptomatic to a life-threatening condition, with older age, obesity, immunocompromised status, and co-morbidity (*viz* diabetes, hypertension, cardiac conditions and renal disease) being risk factors associated with severe pneumonia (Chen *et al*, 2020b; Guan *et al*, 2020; Wang *et al*, 2020; Zhou *et al*, 2020).

To date, there is no specific effective antiviral drug approved for COVID-19 treatment, but guidelines mainly focusing on prevention and supportive treatment especially respiratory care (WHO, 2020c). Several drugs have been permitted for compassionate use in various clinical settings, such as antimalarials (chloroquine and hydroxychloroquine), antivirals (lopinavir/ritonavir, remdesivir and favipiravir) and anti-inflammatory agents (dexamethasone) (Cao *et al*, 2020; Cortegiani *et al*, 2020; Furuta *et al*, 2002; Shen *et al*, 2020). Benefits of adjunctive therapies such as convalescent plasma and immunomodulatory agents are under investigation (NIH, 2021).

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), a pyrazine analog initially developed as an antiviral agent against influenza virus by targeting RNA-dependent RNA polymerase (Furuta *et al*, 2002) also has antiviral activity against other RNA viruses *in vitro* and *in vivo* (Furuta *et al*, 2013; Furuta *et al*, 2017; Delang *et al*, 2018), and, in a few clinical trials, has demonstrated clinical benefits against Ebola (Bai *et al*, 2016; Sissoko *et al*, 2016; Kerber *et al*, 2019). Recently, favipiravir has shown antiviral activity on SARS-CoV-2, in the *in vivo* study (Cai *et al*, 2020; Dong *et al*, 2020). In PR China, favipiravir has been approved for of COVID-19 treatment since February 2020 (Dong *et al*, 2020) and in Thailand, favipiravir has recently been approved for compassionate use in COVID-19 pneumonia since March 2020 (MOPH, 2020b).

In order to provide preliminary data, an open-label study was carried out in a tertiary-care university hospital to determine safety and efficacy of favipiravir in Thailand in patients with COVID-19 pneumonia.

MATERIALS AND METHODS

Patients' recruitment

An observational study was conducted among inpatients with COVID-19 pneumonia, ≥15 years of age, receiving favipiravir treatment at Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi

Hospital, Mahidol University, Samut Prakan, Thailand, between 12 March and 30 April 2020. Diagnosis of COVID-19 was established by detecting SARS-CoV-2 RNA in nasopharyngeal swabs using real-time RT-PCR assay of SARS-CoV-2 *ORF1ab* and *N* gene fragments (Novel Coronavirus (2019-nCoV) nucleic acid diagnostic kit; Sansure Biotech, Changsha, PR China). Baseline characteristics, medical history, risk exposures and clinical symptoms were collected. Risk exposures to SARS-CoV-2 were identified by contact tracing (MOPH, 2020a).

The study protocol was approved by the Institutional Review Board (IRB), Faculty of Medicine Ramathibodi Hospital, Mahidol University (no. MURA2020/968). The IRB waived the requirement to obtain informed consents, as the study presented no risk of harm, including a breach of confidentiality, to the patients.

Physical and clinical examinations

Physical examination, blood tests, and chest radiograph were performed on the day of admission. Data were collected of other treatments and medications [*viz* chloroquine/hydroxychloroquine, lopinavir/ritonavir, darunavir/ritonavir, azithromycin, oxygen therapy, mechanical ventilation, continuous veno-venous hemodialysis (CVVHD) and extracorporeal membrane oxygenation (ECMO)], and of any adverse events following favipiravir treatment until discharge. Definition of pneumonia is clinical symptoms of respiratory tract infection with abnormal lung imaging compatible with pneumonia, and severe pneumonia when respiratory rate >30 breath/minute, presence of severe respiratory distress, or peripheral oxygen saturation (SpO_2) ≤ 93% at room air (WHO, 2020a). Clinical improvement is defined by a reduction of at least 2 points from baseline on a modified six-point ordinal scale for clinical improvement, or being discharged from the hospital or both (Grein *et al*, 2020). The six-point scale is based on the following categories – 1: not hospitalized; 2: hospitalized and no oxygen therapy; 3: hospitalized and requirement of oxygen by nasal cannula or mask; 4: hospitalized and requirement of nasal high-flow oxygen, non-invasive mechanical ventilation, or both; 5: hospitalized and requirement of invasive mechanical ventilation, ECMO, or both; and 6, death (Grein *et al*, 2020).

Treatment regimen

Favipiravir was used on a compassionate-use basis in patients with confirmed SARS-CoV-2 infection with pneumonia: severe patients received favipiravir (Avigan®; FUJIFILM Toyama Chemical Co Ltd, Tokyo, Japan) 1,600 mg twice daily on Day 1 then 600 mg twice daily on Days 2-10 and non-severe patients 1,600 mg twice daily on Day 1 then 600 mg twice daily on Days 2-5, according to Thai national guidelines (MOPH, 2020b). Other prescribed medications included (i) chloroquine (Quinnel®) 250 mg twice daily or hydroxychloroquine (Nitaquine®) 400 mg twice daily for 1 day, then 200 mg twice daily, (ii) darunavir (Prezista®) 600 mg twice daily plus ritonavir (Norvir®) 100 mg twice daily, or lopinavir/ritonavir (Aluvia®) 400/100 mg twice daily, and

(iii) azythromycin (Azycin®) 500 mg once daily for 1 day, then 250 mg once daily. All medications were given for 5 and 10 days in patients with pneumonia and severe pneumonia, respectively (MOPH, 2020b).

Data analysis

Baseline characteristics of patients (demographic data, symptoms, physical examinations, and results of laboratory investigations) are reported as mean±SD for continuous variables and as frequency (%) for categorical variables. Proportion of patients with clinical improvement was analyzed using a Kaplan-Meier curve stratified according to severe and non-severe pneumonia. Period required for clinical improvement in all patients and in each group was recorded as median and 95% confidence interval (CI). Mann-Whitney U and Chi-square tests were performed for comparison of continuous and categorical variables, respectively. A p-value of <0.05 was considered significance. Statistical analysis was carried out employing IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY).

RESULTS

COVID-19 patients (n = 37) with pneumonia who had received favipiravir were 48 ± 13 years of age, 62% were males, 22% had diabetes mellitus, or hypertension or both, and 20 (54%) and 17 (46%) had severe and non-severe pneumonia respectively (Table 1). Prior to admission, patients had symptoms of respiratory tract infection (*viz* cough, shortness of breath, sputum production, sore throat, running nose, myalgia, headache, diarrhea, anosmia) for a duration of 6 ± 3 days. Mean body mass index of all patients was 26 ± 7 kg/m^2. Patients with severe pneumonia had significantly lower absolute lymphocyte counts/ml and serum albumin level, but higher lactate dehydrogenase, D-dimer and liver aminotransferase levels compared to non-severe pneumonia group (p-value <0.05).

All COVID-19 pneumonia patients received both favipiravir and an anti-malarial drug, chloroquine or hydroxychloroquine, and in addition, a majority also received darunavir/ritonavir or lopinavir/ritonavir and over half azithromycin (Table 1). Other supportive treatments, in particular for patients with severe pneumonia, were oxygen therapy, mechanical ventilation, CVVHD, and ECMO. Median time from initiation of favipiravir treatment to clinical improvement for patients with severe and non-severe pneumonia was 17 days (95% CI: 9-25) and 9 days (95% CI: 7-11), respectively (Fig 1). Thirty-five (95%) patients had complete recovery and were discharged from the hospital within 39 days after clinical improvement, but two (5%) patients succumbed to severe acute respiratory distress syndrome (ARDS) and multi-organ failure.

A majority of patients reported adverse events, most common (except diarrhea) being among patients with severe pneumonia (Table 1). Serious adverse events (acute kidney injury (stage 3), hypotension, elevated liver enzymes (grades 3-4) and multi-organ failure) were present in one-fifth of severe pneumonia patients. No patient was discontinued from favipiravir treatment.

Table 1

Baseline characteristics, treatment and adverse events of COVID-19 patients with pneumonia, Chakri Naruebodindra Medical Institute,
Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (12 March - 30 April 2020)

Characteristic	Number (%)	With severe pneumonia Number (%)	With non-severe pneumonia Number (%)
	(*n* =37)	(*n* = 20)	(*n* = 17)
Age, years, mean ± SD	48 ± 13	53 ± 12	41 ± 11
Male	23 (62)	14 (70)	9 (53)
Underlying condition			
Diabetes	8 (22)	6 (30)	2 (12)
Hypertension	8 (22)	7 (35)	1 (6)
Dyslipidemia	6 (16)	5 (25)	1 (6)
Coronary heart diseases	3 (8)	3 (15)	0 (0)
Current smoker	6 (16)	4 (20)	16 (23)
Current alcohol drinker	17 (46)	10 (50)	41 (58)
Days of illness at admission, days, mean ± SD	6 ± 3	7 ± 4	6 ± 3
Body weight at admission, kg, mean ± SD	72 ± 17	76 ± 16	68 ± 17
BMI at admission, kg/m^2, mean ± SD	26 ± 7	25 ± 8	26 ± 6
Oxygen saturation RA at admission, %, mean ± SD	96 ± 2	94 ± 3	97 ± 1

Table 1 (cont)

Characteristic	Number (%) (n =37)	With severe pneumonia Number (%) (n = 20)	With non-severe pneumonia Number (%) (n = 17)
Laboratory finding (mean ± SD)			
Hemoglobin, g/dl	14 ± 2	14 ± 2	14 ± 1
White blood cells/mm^3	5,913 ± 1,796	6,038 ± 1,796	5,867 ± 1,810
Absolute neutrophil counts/mm^3	3,577 ± 1,357	4,346 ± 1,654	3,293 ± 1,118
Absolute lymphocyte counts/mm^3	1,780 ± 811	1,215 ± 448	1,989 ± 818
Platelets/mm^3	243,351 ± 75,334	214,900 ± 56,643	253,889 ± 79,045
Lactate dehydrogenase, U/l	238 ± 98	347 ± 118	201 ± 54*
D-Dimer, ng/ml	541 ± 592	722 ± 622	491 ± 309*
Creatinine, mg/dl	0.9 ± 0.3	1 ± 0.3	0.8 ± 0.2
Aspartate aminotransferase, U/l	40 ± 25	62 ± 37	32 ± 13*
Alanine aminotransferase, U/l	37 ± 27	50 ± 38	32 ± 21*
Alkaline phosphatase, U/l	72 ± 49	86 ± 82	67 ± 23
Total bilirubin, mg/dl	0.5 ± 0.3	0.6 ± 0.2	0.5 ± 0.3
Direct bilirubin, mg/dl	0.2 ± 0.1	0.3 ± 0.2	0.2 ± 0.1
Total serum protein, g/l	78 ± 6	73 ± 8	80 ± 5
Albumin, g/l	41 ± 4	38 ± 5	43 ± 3*

Table 1 (cont)

Characteristic	Number (%) (*n* =37)	With severe pneumonia Number (%) (*n* = 20)	With non-severe pneumonia Number (%) (*n* = 17)
Treatment			
Favipiravir	37 (100)	20 (100)	17 (100)
Chloroquine/hydroxychloroquine	37 (100)	20 (100)	17 (100)
Lopinavir/ritonavir	6 (16)	4 (20)	2 (12)
Darunavir/ritonavir	29 (78)	16 (80)	13 (77)
Azithromycin	20 (54)	12 (60)	8 (47)
Oxygen therapy	24 (65)	20 (100)	4 (24)
Mechanical ventilation	8 (22)	8 (40)	0 (0)
CVVH	2 (5)	2 (10)	0 (0)
ECMO	1 (3)	1 (5)	0 (0)

Table 1 (cont)

Characteristic	Number (%) (*n* =37)	With severe pneumonia Number (%) (*n* = 20)	With non-severe pneumonia Number (%) (*n* = 17)
Non-serious adverse event[†]			
Any non-serious adverse event	31 (84)	20 (100)	11 (65)
Acute kidney injury	8 (22)	6 (30)	2 (12)
Acute respiratory distress syndrome	6 (16)	6 (30)	0 (0)
Anemia	4 (11)	4 (20)	0 (0)
Delirium	4 (11)	4 (20)	0 (0)
Diarrhea	14 (38)	6 (30)	8 (47)
Fever	11 (30)	9 (45)	2 (12)
Hyperkalemia	6 (16)	6 (30)	0 (0)
Hypernatremia	2 (5)	2 (10)	0 (0)
Hypotension	6 (16)	6 (30)	0 (0)
Leucopenia	3 (8)	2 (10)	1 (6)
Liver enzyme increase	16 (43)	12 (60)	4 (24)
Multi-organ failure	9 (24)	8 (40)	1 (6)
Nausea/vomit	3 (8)	2 (10)	1 (6)
Pulmonary embolism	3 (8)	3 (15)	0 (0)
Rash	2 (5)	1 (5)	1 (6)
Thrombocytopenia	2 (5)	2 (10)	0 (0)

Table 1 (cont)

Characteristic	Number (%) (*n* =37)	With severe pneumonia Number (%) (*n* = 20)	With non-severe pneumonia Number (%) (*n* = 17)
Serious adverse event*			
Any serious adverse event#	7 (19)	7 (35)	0 (0)
Acute kidney injury (stage 3)	3 (8)	3 (15)	0 (0)
Hypotension	3 (8)	3 (15)	0 (0)
Liver enzyme increase (grades 3-4)	3 (8)	3 (15)	0 (0)
Multi-organ failure	4 (11)	4 (20)	0 (0)

*p-value <0.05 between severe and non-severe pneumonia group; †Adverse event terms are based on DAIDS (2017)

SD: standard deviation; kg: kilogram; BMI: body mass index; kg/m^2: kilogram per square meter; RA: room air; g/dl: gram per deciliter; mm3: cubic millimeter; U/l: unit per liter; ng/ml: nanogram per milliliter; mg/dl: milligram per deciliter; CVVH: continuous veno-venous hemofiltration; ECMO: extracorporeal membrane oxygenation

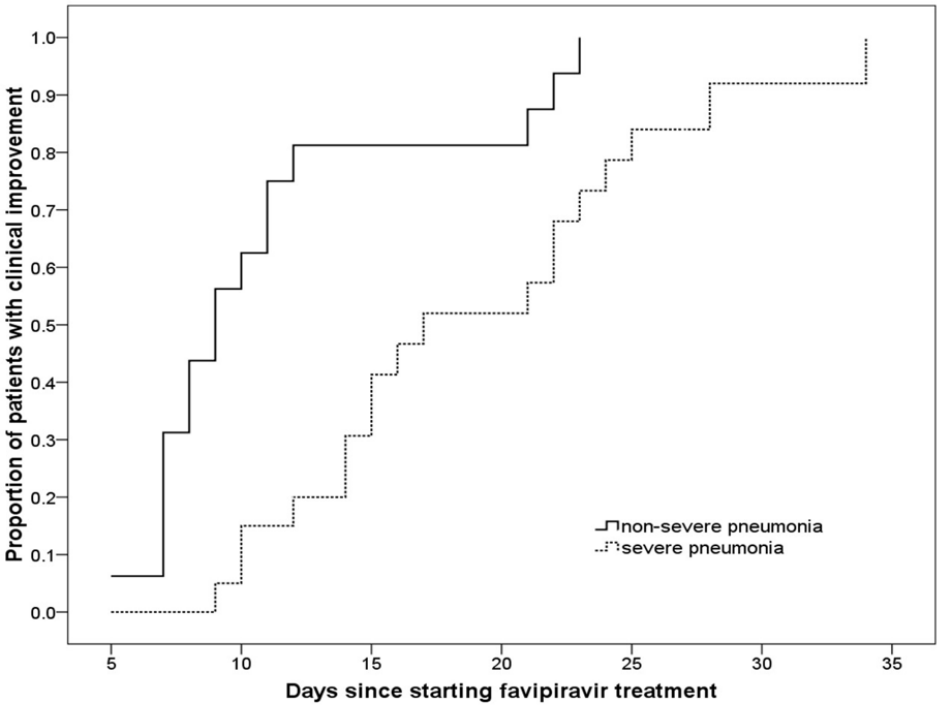

Fig 1 - Kaplan-Meier plot of cumulative proportion of COVID-19 pneumonia patients with clinical improvement following favipiravir treatment, Chakri Naruebodindra Medical Institute, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (12 March - 30 April 2020).

DISCUSSION

As no specific antiviral agent for COVID-19 is widely recommended at present, there is a pressing need to evaluate effectiveness of repurposing other effective antiviral agents, especially in treating COVID-19 patients with severe symptoms (NIH, 2021). The active metabolite of favipiravir, favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP) inhibits RNA polymerase of RNA viruses, such as influenza and Ebola (Bai *et al*, 2016; Sissoko *et al*, 2016; Kerber *et al*, 2019; Du and Chen, 2020). The present observational study shows favipiravir was effective and relatively safe in treating COVID-19 pneumonia patients, with median time to clinical improvement after receiving favipiravir of a little over a week for patients with non-severe pneumonia and twice as long among the severe group. The mortality rate was 5% compared to 25% in a previous study in patients with COVID-19 pneumonia who did not receive any antiviral drug (Richardson *et al*, 2020).

An open-label, randomized, controlled trial on COVID-19 patients showed overall clinical recovery at day 7 of patients receiving favipiravir, which is not different from arbidol-treated patients, but those in favipiravir group demonstrated shorter time for normalization of body temperature and for cough relief (Chen *et al*, 2020a). Another small open-label, randomized, controlled trial evaluating effect of favipiravir compared to standard care also reported patients in favipiravir group have shorter time to body temperature normalization and higher proportion achieving viral clearance at Day 5 of treatment (Ivashchenko *et al*, 2020).

A review of the literature (up to 27 March 2020) on safety of favipiravir in COVID-19 patients based on 29 studies of 4,299 participants concluded favipiravir is relatively safe regarding total and serious adverse events; however, increases in blood uric acid is a safety concern, as well as possibility of teratogenicity and QT interval (QTc) prolongation, but data support the safety and tolerability of favipiravir in short-term use (Pilkington *et al*, 2020). In the present study approximately one-fifth of the patients developed serious adverse events, but exclusively in patients with severe COVID-19 pneumonia and such patients could naturally develop liver injury, kidney impairment and multiple organ failure.

In addition to favipiravir, all COVID-19 pneumonia patients received chloroquine or hydroxychloroquine, ~75% darunavir/ritonavir and the others lopinavir/ritonavir, and ~50% azithromycin. Although hydroxychloroquine and chloroquine were previously considered to have clinical benefits in treatment of COVID-19 based on *in vitro* activity and results from uncontrolled studies and small randomized trials, there is growing evidence at the time of manuscript revision that these drugs do not have a significant therapeutic effect. A randomized, controlled, open-label platform trial comparing 1,561 hospitalized patients prescribed hydroxychloroquine with 3,155 receiving usual care reported hydroxychloroquine does not reduce the risk of death among hospitalized patients (Horby *et al*, 2020). Another multicenter, blinded, placebo-controlled randomized trial of 242 hospitalized patients receiving hydroxychloroquine with 237 receiving placebo also found no effect of the drug on mortality and clinical status at Day 14 (Self *et al*, 2020). Likewise, no difference in clinical status at Day 15 is found in mild-to-moderate hospitalized COVID-19 patients receiving hydroxychloroquine plus azithromycin or azithromycin *vs* standard care in a multicenter, randomized, controlled, open-label trial (Cavalcanti *et al*, 2020). Indeed, a recent meta-analysis reported that hydroxychloroquine with or without azithromycin failed to show favorable effect on clinical outcome, radiological outcome, and rate of viral clearance (Ghazy *et al*, 2020). Regarding lopinavir/ritonavir, a recent randomized, controlled, open-label trial, no benefit was observed with lopinavir/ritonavir treatment beyond standard care (Cao *et al*, 2020). Moreover, in another

open-label, non-randomized, control study, Cai *et al* (2020) reported COVID-19 patients who received favipiravir plus inhaled interferon-α had a shorter viral clearance time and significant improvement in chest imaging compared to those treated with lopinavir/ritonavir plus inhaled interferon-α. Another small observational study showed that COVID-19 critically ill patients who received favipiravir had shorter ICU length of stay than those who received lopinavir/ritonavir, without difference in mortality, development of ARDS, and multi-organ failure (Kocayiğit *et al*, 2020). Taken together, beneficial effect of chloroquine, hydroxychloroquine, azithromycin, and lopinavir/ritonavir has not been demonstrated, while favipiravir seems to improve some clinical outcome in COVID-19 patients.

The strengths of this study were (i) no missing data of the patients allowing accurate determination of factors affecting outcomes, and (ii) all study patients treated with the same standard of care. Limitations were (i) observational study with a relatively small sample size, and (ii) no control group receiving medications without favipiravir or with remdesivir (for example).

In conclusion, the study confirms favipiravir as one of the potential drugs for treatment of COVID-19 pneumonia, with acceptable safety profile and no serious adverse events. Given the small cohort of patients enrolled, further large-scale randomized controlled trials to assess favipiravir efficacy is warranted.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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