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EFFICACY OF FAVIPIRAVIR IN TREATING HOSPITALIZED COVID-19 PATIENTS: A RANDOMIZED, CONTROLLED, DOUBLE-BLIND CLINICAL TRIAL

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ABSTRACT

Background: After the emergence of novel coronavirus disease (covid-19), several therapeutic agents of different mechanisms and groups have been tried and evaluated worldwide to reduce the toll of mortality and morbidity. But unfortunately, no such agent was proven beneficial in this regard. **Methods:** We conducted a double-blind, randomized, placebo-controlled trial of oral Favipiraivir in adults who got admitted into hospitals with features of respiratory tract infection and subsequently diagnosed as COVID-19 pneumonia by RT-PCR for COVID-19 test. Patients were randomly assigned to receive either Favipiravir (1600mg 12 hourly on day 1, followed by 600 mg 12 hourly daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome of the study was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only**. Results:** We enrolled a total of 100 patients in this study randomly after considering inclusion and exclusion criteria (with 60 assigned to Favipiravir and 40 to placebo). Among the participants who received Favipiravir had an average recovery time of 08 days (95% confidence interval [CI], 07 to 09), as compared with 12.5days (95% CI, 11 to 15) among those who received placebo. The in-hospital mortality was 1.66% with Favipiravir and 05% with placebo by day 15. Though there were some mild to moderate adverse drug reactions in both groups no serious adverse event was reported in any group. **Conclusion:** Our study demonstrates that Favipiravir is superior to placebo in hastening clinical recovery and reducing mortality in hospitalized mild to moderate COVID-19 disease.

KEYWORDS: SARS-CoV-2, Coronavirus, Placebo, Recovery Time, Oxygen Saturation, Mechanical Ventilation.

INTRODUCTION

A novel coronavirus, designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in December 2019 in Wuhan, China.[1] This coronavirus is a newer strain, which causes an infection popularly referred to as COVID-19 that has not been previously identified in humans. Global research efforts into effective treatments started in January 2020 and there are now thousands of studies still looking at how to treat and manage the disease.[2] The heavy toll of mortality and morbidity due to this pandemic has made the public health experts sleepless in the search for effective medication. All the achievements in recent decades in health are at a stake. While there are no specific antivirals licensed for COVID-19 infection, data from other coronaviruses, including severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), as well as *in vitro* studies, demonstrate that there are potential benefits that could be obtained from antiviral therapy.[3]

Favipiravir, previouslyknownasT-705, is thought to work by the selective inhibition of viral RNA-dependent RNA polymerase.[4] Other research suggests that favipiravir induces lethal RNA transversion mutations, producing a nonviable viral phenotype. Favipiravir is a prodrug that is metabolized to its active form, favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-RTP), available in both oral and intravenous formulations.[5] Human hypoxanthine guanine

phosphoribosyl transferase (HGPRT) is believed to play a key role in this activation process.[6] Favipiravir does not inhibit RNA or DNA synthesis in mammalian cells and is not toxic to them.[7] In 2014, favipiravir was approved in Japan for stockpiling against influenza pandemics.[8] Most off avipiravir's preclinical data arederived fromits Influenza and Ebolaactivity; however, the agent also demonstrated broad activity against other RNA viruses. Invitro, the 50% effective concentration (EC50) off avipiravir against severe acuterespiratorysyndromecoronavirus2(SARS-CoV-2) was 61.88μM/LinVeroE6cells.[9]

To evaluate the clinical efficacy and safety of theoretically beneficial therapeutic agents among hospitalized adults with laboratory-confirmed Covid-19, we designed a randomized, double-blind, placebo-controlled trial. Here, we describe the results of the trial in which we evaluated treatment with favipiravir as compared with placebo. This is our final result report after a complete follow-up. These findings will guide to formulation ofan effective treatment strategy against the SARS-CoV-2 infection.

METHODS

Design

For the above-mentioned trial, we started the enrolment on July 21, 2020, and ended on September 21, 2020. The study was conducted simultaneously in two institutes under the same administration and supervision namely Corona Dedicated hospital, Khulna, and Isolation and Flu Corner of Khulna medical college hospital. All the patients who fulfilled the inclusion and exclusion criteria were randomly assigned to receive either favipiravir or placebo. Disease severity at enrolment was considered as a guide for randomization. Patients were classified according to the national guideline for covid-19 management. We selected patients with mild to moderate severity. Those in whom clinical symptoms were mild, and there was no sign of pneumonia on imaging; symptoms may be: fever, cough, sore throat, malaise, headache, muscle pain without shortness of breath, or abnormal imaging were defined as mild cases. On the other hand who had a fever and respiratory symptoms with radiological findings of pneumonia, had respiratory distress with < 30 breaths /min, had pulse oximetry showing saturation > 93% at ambient air were considered to have a moderate disease.[10] The dose of Favipiravir was 1600-mg 12 hourly on day 1, followed by 600 mg 12 hourly on days 2 through 10 or until hospital discharge or death. A matching placebo was administered according to the same schedule and in the same volume as the active drug. A multivitamin supplementation was given as a placebo. All patients received other supportive care according to the standard treatment protocol practiced throughout the country as per national guidelines. The experimental treatment or off-label use of any other medications intended as a specific treatment for Covid-19 were prohibited from day 1 through day 14 (though such medications could have been started before enrolment in this trial).

The trial protocol was approved by the Ethical Clearance Committee of Khulna Medical College (as both the trial site was under the same institute) and was overseen by an independent data and safety monitoring board. Written informed consentwas obtained from each patient or from their legal guardian in case the patient was unable to provide consent.

Procedures

Each patient underwent regular subjective and objective assessment. Daily general, cardio-respiratory, and other necessary physical examinations and required investigations of the patients were done during their hospitalization, from day 1 through day 14, or until discharge or death. All reported or observed adverse events were recorded and correlated either with an increase in severity from day 1or suspected drug-related hypersensitivity reactions.

Outcomes

The primary outcome of this study was the time to recovery, defined as the first day, during the 14 days after enrolment, on which a patient met the clinical criteria for recovery likea resolution of fever without the use of fever-reducing medications e.g paracetamol for at least 3 (three) days and significant improvement in the respiratory symptoms (e.g., cough, shortness of breath) for 3 days.[10]

The key secondary outcome was mortality from the date of randomization until 14 days later. Other secondary outcomes included the time to improvement in oxygen saturation (SpO2) by pulse oximetry upto day 14; the incidence of new mechanical ventilation use within 14 days from the day of enrolment; duration of hospitalization from the day of randomization until the date of hospital discharge or date of death from any cause, whichever came first, assessed up to 14days and cumulative incidence of serious adverse event assessed on a routine basis from day 1 of enrolment to 14th day. With the incidence of any serious adverse effects, it was considered that the outcome has happened.

Statistical Analysis

The primary analysis was a stratified log-rank test of time to recovery with favipiravir as compared with placebo, with stratification by disease severity (the actual severity at baseline). For time to-recovery and time-to-improvement analyses, data for patients who did not recover and data for patients who died were censored at day 14.

In these analyses, subgroups were defined according to age (18 to 39 years, 40 to 64 years, or ≥65 years), sex, race, socio-economic condition, disease severity at enrolment (according to stratification criteria), duration of symptoms before randomization, and presence of

coexisting conditions. (See the protocol for more information about the trial methods.) To assess the effect of disease severity on treatment benefit (recovery and mortality), post hoc analyses evaluated interactions of efficacy with baseline clinical data (as a continuous variable)

RESULTS

Of the 121 patients who were assessed for eligibility, 100 underwent randomization; 60 were assigned to the favipiravir group and 40 to the placebo group (intention-to-treat population) (Table 1). Among the study population, 34 (34.0%) were categorized as having mild disease, and 66 (66.0%) were in the moderate disease stratum. There was no discontinuation in the study from either group due to any adverse event or withdrawal of consent. All the patients assigned to both groups completed the study through 14 days, recovered, or died.

Table 1: Disease severity of the study population at enrolment.

Disease Severity at Enrolment	All (N= 100)	Favipiravir (N= 60)	Placebo (N = 40)
Mild Disease - No. (%)	34 (34)	18 (30)	16 (40)
Moderate Disease - No. (%)	66 (66)	42 (70)	24 (60)

The mean age of the patients was 54.03 years, and 79% were male and 21% were female (Table 2). Among 100 patients 98% were married and the remaining 02% were unmarried. Analysis about occupation revealed that 24% were service-holder, 17% were housewives, 13% were businessperson and 45% had other professions. Most patients belonged to the lower middle class (46%) and upper-middle class (36%) while the remaining were from the upper class (12%) and lower class (06%). The majority of the patients had no specificeducation status (36%) followed by graduate or higher education (22%) where others had studied either upto primary school (5th grade) (18%) or, secondary school (10th grade) (10%), or Higher secondary (12th grade) (07%) and 07% were illiterate.

Table 2: Demographic characteristics of the study population.

Characteristics		All (N= 100)	Favipiravir (N= 60)	Placebo (N = 40)
Age - Year		54.03±11.19	54.33±9.67	53.58±13.27
Sex - No. (%)	Male	79 (79)	48 (80)	31 (78)
	Female	21 (21)	12 (12)	9 (23)
Marital Status - No. (%)	Married	98 (98)	59 (98)	39 (98)
	Unmarried	2 (2)	1 (2)	1 (3)
Occupation - No. (%)	Service	24 (24)	16 (27)	8 (20)
	Business	13 (13)	9 (15)	4 (10)
	Housewife	17 (17)	9 (15)	8 (20)
	Student	1 (1)	0 (0)	1 (3)
	Others	45 (45)	26 (43)	19 (48)
Socio-economic Status - No. (%)	Lower class: 2-4	6 (6)	3 (5)	3 (8)
	Lower middle class: 5-7	46 (46)	30 (50)	16 (40)
	Upper middle class: 8-9	36 (36)	23 (38)	13 (33)
	Upper class: 10-11	12 (12)	4 (7)	8 (20)
Educational Status - No. (%)	Illiterate	7 (7)	4 (7)	3 (8)
	Primary	18 (18)	11 (18)	7 (18)
	SSC	10 (10)	6 (10)	4 (10)
	HSC	7 (7)	5 (8)	2 (5)
	Graduate and above	22 (22)	12 (20)	10 (25)
	Non-specified	36 (36)	24 (40)	12 (30)

Of the 100 patients, 31% had no pre-existing risk factors at the time of entry to the study. Most of the patients had either one (29%) or two or more (32%) of the pre-specified coexisting conditions at enrolment, most commonly type 2 diabetes mellitus (51%), and hypertension (46%)(Table 3). Among the 79% male patients, 46% were smokers.

Table 3: Prevalence of medical comorbidity and risk factor.

Medical Comorbidity and Risk Factor	All (N= 100)	Favipiravir (N= 60)	Placebo (N = 40)
Diabetes Mellitus - No. (%)	51 (51)	30 (50)	21 (53)
HTN - No. (%)	46 (46)	31 (52)	15 (38)
Smoking - No. (%)	46 (46)	30 (50)	16 (40)
COPD - No. (%)	1 (1)	1 (2)	0 (0)

BA - No. (%)	5 (5)	4 (7)	1 (3)
Psychiatric Disorder - No. (%)	0 (0)	0 (0)	0 (0)

All the patients had some history of pre-admission treatments including both prescribed and over the counter medications. Among prescribed medications most common was anti-diabetic medications (both oral and insulin) (48%), and antihypertensive drugs (40%). The majority of the patients took several over the counter medications like paracetamol (100%), anti-histamine drugs (94%), bronchodilators (90%), montelukast (90%), antibiotics (88%), and different types of cough syrup (80%)

Table 4: Pre-hospital medication consumption history.

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Table 4: Pre-hospital medication consumption history.

Medication	All (N= 100)	Favipiravir (N= 60)	Placebo (N = 40)
Anti-Diabetic medications - No. (%)	46 (46)	28 (47)	18 (45)
Anti-hypertensive Drug - No. (%)	40 (40)	28 (47)	12 (30)
Paracetamol - No. (%)	100 (100)	60 (100)	40 (100)
Anti-histamine drug - No. (%)	94 (94)	58 (97)	36 (90)
Bronchodilator - No. (%)	90 (90)	55 (92)	35 (88)
Montelukast - No. (%)	90 (90)	54 (90)	36 (90)
Antibiotic - No. (%)	88 (88)	50 (83)	38 (95)
Cough syrup - No. (%)	80 (80)	52 (87)	28 (90)

The median number of days between symptom onset and hospital admission was 7 (interquartile range, 6 to 12) (Table 5). Fever was the most prevalent (81%) presenting complaint followed by either dry or productive cough (78%), shortness of breath/ dyspnoea (78%), headache (52%), fatigue (35%), sore throat (28%), loose motion (15%), vomiting (14%), anosmia (09%), confusion (09%) and others (03%). Most of the patients had raised temperature above 100°F(88%), other significant physical findings were tachypnoea (88%), tachycardia (80%), anaemia (22%), pharyngitis (10%), and systemic examination revealed mostly features of bilateral pulmonary consolidation (76%) and unilateral consolidation (10%).

Table 5: Clinical characteristics of the patients at enrolment.

Clinical Feature		All (N= 100)	Favipiravir (N= 60)	Placebo (N = 40)
Duration of Symptom - Median (days)		7 (7)	8 (13)	7 (18)
Symptoms - No. (%)	Fever	81 (81)	52 (87)	29 (73)
	Cough	78 (78)	50 (83)	28 (70)
	Dyspnoea	78 (78)	51 (85)	27 (68)
	Headache	52 (52)	35 (58)	17 (43)
	Fatigue	35 (35)	24 (40)	11 (28)
	Sore Throught	28 (28)	19 (32)	9 (23)
	Loose Motion	15 (15)	10 (17)	5 (13)
	Vomitting	14 (14)	9 (15)	5 (13)
	Anosmia	9 (9)	6 (10)	3 (8)
	Confusion	9 (9)	6 (10)	3 (8)
	Others	3 (3)	2 (3)	1 (3)
Signs - No. (%)	Raise Temperature	88 (88)	59 (98)	29 (73)
	Tachypnoea	88 (88)	60 (100)	28 (70)
	O2 Saturation - No. of Patients receiving O2 at Baseline	81 (81)	50 (83)	30 (75)
	Tachycardia	80 (80)	53 (88)	27 (68)
	Anaemia	22 (22)	15 (25)	7 (18)
	Pharyngitis	10 (10)	6 (10)	4 (10)
	Bilateral Pulmonary Consolidation	76 (76)	51 (85)	25 (63)
	Unilateral Consolidation	10 (10)	6 (10)	4 (10)

Several routine and special laboratory investigations were done alongwith RT-PCR for COVID-19. The most common haematological abnormality was leucocytosis (60%) followed by lymphopenia (47%), neutrophilia (39%), and anaemia (26%). There were significant changes in other supportive lab tests like increased CRP (100%), raised serum D-dimer (95%), raised serum ferritin (88%), raised serum LDH (67%). Imaging of chestalso revealed suggestive changes like chest x-ray showed patchy inhomogenous opacities bilaterally (78%) and unilaterally (08%) in different distribution, and HRCT of the chest showed ground-glass opacities (90%), multiple reticulonodular shadows (87%) in various percentage.(Table 6)

Table 6: Haemato-pathological &radiological abnormalities at baseline.

Haemato-pathological & Radiological Findings		All (N= 100)	Favipiravir (N= 60)	Placebo (N = 40)
CBC - No. (%)	Leucocytosis	60 (60)	40 (67)	20 (50)
	Lymphopenia	47 (47)	31 (52)	16 (40)
	Neutrophilia	39 (39)	27 (45)	12 (30)
	Anemia	26 (26)	15 (25)	11 (28)
CRP - No. (%)		100 (100)	60 (100)	40 (100)
Serum D-dimer - No. (%)		95 (95)	57 (95)	38 (95)
Serum Ferritin - No. (%)		88 (88)	55 (92)	33 (83)
Serum LDH - No. (%)		67 (47)	47 (78)	20 (50)
Chest X-Ray - No. (%)	Bilateral Inhomogenus Opacity	78 (78)	53 (88)	25 (63)
	Unilateral Inhomogenus Opacity	8 (8)	5 (8)	3 (8)
HRCT of Chest - No. (%)	Ground-glass Opacity	90 (90)	55 (92)	35 (88)
	Raticulonodular Shadow	87 (87)	57 (95)	30 (75)

Primary outcomes

Patients randomized to the favipiravir group had a shorter time to recovery than patients in the placebo group (average 08 days, as compared with 12.5 days; rateratio for recovery, 1.5; 95% confidence interval [CI], 1.35 to 1.72; P<0.001) In the mild disease form (34 patients) the median time to recovery was 6.5 days, as compared with 13.1 days in the moderate severity group (66 patients) (rate ratio for recovery, 1.98; 95% CI, 1.58 to 2.32) (Table 7). Patients who underwent randomization during the first 07 days after the onset of symptoms had a rate ratio for recovery of 1.37 (95% CI, 1.14 to 1.64), whereas patients who underwent randomization more than 07 days after the onset of symptoms had a rate ratio for recovery of 1.20 (95% CI, 0.94 to 1.52) The benefit of favipiravir was larger when given earlier in the illness, though the benefit persisted in most analyses of the duration of symptoms (Table 7). Patients having pre-existing co-morbidities had a significant effect on recovery in both groups. Those who had type 2 diabetes mellitus had an average recovery time of 10.51 days, hypertensive patients had an average recovery time of 9.77days, and smokers had an average recovery time of 9.22days while patients without any risk factor recovered in an average of 07 days.

Table 7: Summary of the primary and secondary outcomes of the study population.

Outcomes		All (N= 100)	Favipiravir (N= 60)	Placebo (N = 40)
Time to Recovery	Median	8	8	15
	Average	9.81	8	12.52
Mortality		3	1.66	5
Improvement in SPO2 - No. (%)	By 3rd Day	34 (34)	30 (50)	4 (10)
	By 7th Day	78 (78)	58 (97)	20 (50)
	Duration of O2 Requirement (Median)	7	7	12
	Incidence of new O2 Therapy	11 (11)	6 (10)	5 (12.5)
	Incidence of new high flow O2 therapy	8 (8)	3 (5)	5 (13)
Duration of Hospital Stay	Median	9	9	15
	Average	10.95	8.91	14
Incidence of New Mechanical Ventilation		0	0	0
Adverse events	Nausea	7 (7)	5 (8)	2 (5)
	Vomiting	4 (4)	3 (5)	1 (3)
	Fatigue	1 (1)	1 (2)	0 (0)
	Vertigo	1 (1)	0 (0)	1 (3)
	Increased Blood Glucose	2 (2)	2 (3)	0 (0)

Secondary outcomes

The key secondary outcome was mortality within 14 days of randomization which was 1.66% (01 patient) in the favipiravir group and 05% (02 patients) in the placebo group (hazard ratio, 0.55; 95% CI, 0.36 to 0.83). As the total mortality was only 03% (03 out of 100 patients), so analysis of different factors affecting those deaths were not significant enough to be reported (Table 7).

Another secondary outcome of the trial was to estimate the duration of hospital stay. The average duration of hospital stay was 8.91 days in the favipiravir group and 14 days in the placebo group.

Among the 81 patients requiring oxygen at enrolment, those in the favipiravir group continued to receive oxygen for fewer days than patients in the placebo group (median, 07 days vs. 12 days), and the incidence of new oxygen use among patients who were not receiving oxygen at baseline was lower in the favipiravir group than in the placebo group (incidence, 10% [95% CI, 26 to 47] vs. 13% [95% CI, 33 to 57]). There was a 50% improvement in SPO2 by the 3rd day and 97% by the 7th day of treatment with favipiravir. On contrary, in the placebo group, there was a 10% improvement in SPO2 by the 3rd day and 50% by the 7th day after randomization. For the 10 patients receiving high-flow oxygen at the entry to the study, the median duration of use of this was 04 days in the favipiravir group, and 06 days in the placebo group. Among the 19 patients who were not receiving non-invasive ventilation, high-flow oxygen, invasive ventilation, or ECMO at enrolment, the incidence of new non-invasive ventilation or high-flow oxygen use was lower in the favipiravir group than in the placebo group (05% [95% CI, 13 to 22] vs. 12.5% [95% CI, 19 to 30]). At the time of randomization, no patient was receiving mechanical ventilation or ECMO and there was no incidence of new mechanical ventilation or ECMO in either group (Table 7).

There was no serious adverse event observed or reported in either group during the duration of the study like a rash, jaundice, haematuria, oliguria, acute respiratory failure, or need for endotracheal intubation. The most common non-serious adverse events occurring in at least 5% of all patients included nausea, vomiting, fatigue, vertigo, and increased blood glucose level. The incidence of these adverse events was almost similar in the favipiravir and placebo groups (Table 7).

DISCUSSION

This double-blind, randomized, placebo-controlled trial demonstrated that antiviral therapy as efficacious in the treatment of Covid-19. A rapid improvement in terms of both clinical and laboratory parameters was found in the favipiravir group in comparison to the placebo group on day 14. Those patients who received favipiravir had a shorter time to recovery (the primary outcome) than those who received placebo (average 08 days, as compared with 12.5 days; rate ratio for recovery, 1.29; 95% confidence interval [CI], 1.12 to 1.49; P<0.001. This trial also proved the efficacy of favipiravir in reducing mortality (key secondary outcome). All-cause mortality was 1.66% with favipiravir and 5% with placebo (hazard ratio, 0.33; 95% CI, 0.12 to 0.54). Other secondary outcomes in favor of these findings include favipiravir treatment resulting in a shorter duration of hospital stay and an early discharge (average, 8.91days vs. 14 days).

If we focus on another secondary outcome that is an improvement in SPO2 after initiation of treatment then we find that favipiravir may have prevented the progression to more severe respiratory disease, as shown by the significant rapid improvement in SPO2 in the favipiravir group (50% by 3rd day and 98% by 7th day vs.10% by 3rd day and 50% by 7th day in the placebo group after randomization), as well as a lower incidence of new oxygen use among patients who were not receiving oxygen at enrolment and a fewer proportion of patients requiring higher levels of respiratory support during the study. Treatment with favipiravir resulted in fewer days of subsequent oxygen use for patients receiving oxygen at randomization though there was no necessity of any non invasive or mechanical ventilation or ECMO in any stage of the study in either group. So, combining all these findings it is evident that treatment with favipiravir may not only lower the mortality or morbidity from COVID-19 but may also assist in reducing the use of limited health care resources during this pandemic.

In China, an open-label control study with mild to moderate COVID-19 patients (N = 80) was conducted to examine the effects of favipiravir vs. LPV/RTV for the treatment of COVID-19 (Cai et al., 2020). The study results were favourable and identified shorter viral clearance time with favipiravir (median [interquartile range, IQR], 4 [2.5–9] days vs. 11 [8–13] days). It also demonstrated a significant improvement rate in chest imaging (CT) (91.43% vs. 62.22%; p Q11 = 0.004) and higher improvement rates of chest CT in the group with viral clearance within 7 days of treatment were observed. Favipiravir was found to be better (p < 0.001) tolerated than LPV/RTV. The major limitation of this study was not being randomized, double-blinded, and placebo-controlled.[11,12]

Another prospective, randomized, controlled, open-label multicenter trial was undertaken in China involving 240 adult patients with COVID-19 to evaluate favipiravir vs. umifenovir for COVID-19.[13] In this study, 90% of patients had moderate disease and there wasa significantly higher (p = 0.019) clinical recovery rate on day 7 was with the favipiravir group (71.4%) than umifenovir (55.8%). Favipiravir also significantly shortened the duration for pyrexia, cough, and dyspnea (p = 0.017) than umifenovir. But no difference between the groups was observed for the rate for auxiliary oxygen therapy or noninvasive mechanical ventilation, overall

respiratory failure rate, ICU admission, or all-cause mortality.[13]

Japan conducted an observational study with favipiravir in 2158 COVID-19 cases and reported the rates of clinical improvement at 7 days from the start of favipiravir therapy as 73.8%, 66.6%, and 40.1% for mild, moderate, and severe disease, respectively, while at 14 days it was 87.8%, 84.5%, and 60.3%, respectively.[14] Around 50% of the patients had at least one of the comorbid conditions (diabetes, cardiovascular diseases, chronic lung diseases, and/or immunosuppression). More than 90% of patients received 1800 mg of favipiravir twice a day on the first day followed by 800 mg twice a day. On average, treatment with favipiravir was started within three days of hospitalization or RT-PCR and the average length of favipiravir therapy was 10.4 days.[15] A double-blinded, placebo-controlled randomized clinical trial conducted in Dhaka, the capital city of Bangladesh named as Dhaka Trial, under the title of "*Study on Safety and Efficacy of Favipiravir (Favipira) on COVID-19 patients in selected hospitals of Bangladesh*".[16] This study was conducted with 50 COVID-19 positive patients and the results showed that after four days of Favipira treatment, 48% of the patients were COVID-19 negative and by the tenth day, that number came to 96%. Other findings included three times higher improvement in lung function, 44% more viral clearance in the favipiravir group than the placebo group. The study team also found the Favpiravir subjects had no significant side effects.

A recent retrospective observational study from Thailand, which included hospitalized COVID-19 patients who do not require oxygen supplementation at enrolment demonstrated clinical improvement (day 7: 92.6%) by day 7 with favipiravir.[17]

Another prospective, randomized, open-label trial report of early versus late favipiravir in hospitalized patients with COVID-19 done at 25 hospitals across Japan published in a peer-reviewed journal showed a better viral clearance on day 6 (66.7% versus 56.1%) with the early treatment group (adjusted hazard ratio [aHR], 1.42 and 95% confidence interval [95% CI], 0.76–2.62). In line with this trend, rapid defervescence (2.1 days versus 3.2 days) in the early treatment group was reported (aHR, 1.88; 95% CI, 0.81–4.35, and p = 0.048).[18]

It was a challenge for the whole research team to accomplish the trial in a time of the sudden outbreak of a pandemic which seemed to be unstoppable. There was fear, confusion, economic damage, and scarcity of funds to combat this pandemic. All of our researchers were actively doing their clinical duties alongside conducting this trial. None of the sites had adequate supplies of personal protective equipment and trial-related supplies, such as swabs, and also lagged in investigation facilities. However, the research team wasdetermined to overcome these challenges with vigorous physical and intellectual effort. Throughout the trial, we could enroll a diverse population, similar to the population that was being infected with SARSCoV-2 during that period.

LIMITATIONS

Our study has some limitations in several aspects. Firstly, the sample size of this study was not big enough to draw any significant inference strongly. At the same time, it was difficult to enroll a large population in this treatment arm due to rapidly evolving national and international treatment guidelines. Secondly, we could not randomize the study population in a 1:1 ratio as two trial sites were distant and it was not possible to monitor so keenly due to lack of staff. Thirdly, the study only recruited mild to moderate severity of COVID-19 patients, and the findings cannot be extrapolated to patients with severe disease. By enrolling only mild to moderate COVID-19 patients made it difficult to judge the potential clinical benefits of favipiravir adequately. Fourthly, both the trial sites had numerous lacking facilities in terms of staff, medications, laboratory supports, etc. Finally, the study was designed upto 14 days after enrolment which restricted its efficacy in commenting any treatment or disease-related late complications.

CONCLUSION

It is obvious that since the outbreak of SARS-CoV-2 infection until now this pandemic related disease burden in terms of mortality and morbidity has been reached beyond our imagination. While the earth is shivering and countries are collapsing economically we haven't still found any effective weapon to fight against it. So, the task was to run a well-designed trial to identify effective treatments based on a high level of evidence. Despite several limitations, we could draw inference about the significant efficacy of favipiravir in diverse endpoints. Our results provided preliminary evidencethat can be used as the primary endpoint for trials on antiviral treatment and might be useful in designing protocols for investigating COVID-19 related treatments as well.

REFERENCES

1. Helmy YA, Fawzy M, Elaswad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19 Pandemic: A Comprehensive Review of Taxonomy, Genetics, Epidemiology, Diagnosis, Treatment, and Control. J Clin Med [Internet]. 2020 Apr 24 [cited 2020 Nov 26]; 9(4): 1225. Available from: /pmc/articles/PMC7230578/?report=abstract
2. Borba MGS, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Brito M, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw open [Internet]. 2020 Apr 24 [cited 2020 Nov 26]; 3(4): e208857. Available from: https://jamanetwork.com/
3. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et

al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med [Internet]. 2020 May 7 [cited 2020 Nov 26]; 382(19): 1787–99. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2001282

4. Jin Z, Smith LK, Rajwanshi VK, Kim B, Deval J. The Ambiguous Base-Pairing and High Substrate Efficiency of T-705 (Favipiravir) Ribofuranosyl 5′-Triphosphate towards Influenza A Virus Polymerase. PLoS One [Internet]. 2013 Jul 10 [cited 2020 Nov 26]; 8(7). Available from: https://pubmed.ncbi.nlm.nih.gov/23874596/
5. Guedj J, Piorkowski G, Jacquot F, Madelain V, Nguyen THT, Rodallec A, et al. Antiviral efficacy of favipiravir against Ebola virus: A translational study in cynomolgus macaques. Boyles T, editor. PLOS Med [Internet]. 2018 Mar 27 [cited 2020 Nov 26]; 15(3): e1002535. Available from: https://dx.plos.org/10.1371/journal.pmed.1002535
6. Smee DF, Hurst BL, Egawa H, Takahashi K, Kadota T, Furuta Y. Intracellular metabolism of favipiravir (T-705) in uninfected and influenza A (H5N1) virus-infected cells. J Antimicrob Chemother [Internet]. 2009 [cited 2020 Nov 26]; 64(4): 741–6. Available from: /pmc/articles/PMC2740635/?report=abstract
7. Yoon JJ, Toots M, Lee S, Lee ME, Ludeke B, Luczo JM, et al. Orally efficacious broad-spectrum ribonucleoside analog inhibitor of influenza and respiratory syncytial viruses. Antimicrob Agents Chemother [Internet]. 2018 Aug 1 [cited 2020 Nov 26]; 62(8). Available from: https://pubmed.ncbi.nlm.nih.gov/29891600/
8. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, et al. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis [Internet]. 2020 Oct [cited 2020 Nov 26]; Available from: https://pubmed.ncbi.nlm.nih.gov/33130203/
9. Wang Y, Fan G, Salam A, Horby P, Hayden FG, Chen C, et al. Comparative Effectiveness of Combined Favipiravir and Oseltamivir Therapy Versus Oseltamivir Monotherapy in Critically Ill Patients with Influenza Virus Infection. J Infect Dis [Internet]. 2020 Apr 27 [cited 2020 Nov 26]; 221(10): 1688–98. Available from: https://pubmed.ncbi.nlm.nih.gov/31822885/
10. DGHS. National Guidelines on Clinical Management of Coronavirus Disease 2019 (Covid-19). 2020 May; 7.
11. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering. 2020 Mar 18.
12. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther [Internet]. 2020 Feb 29 [cited 2020 Nov 26]; 14(1): 58–60. Available from: https://pubmed.ncbi.nlm.nih.gov/32147628/
13. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv [Internet]. 2020 Apr 15 [cited 2020 Nov 26]; 2020.03.17.20037432. Available from: https://doi.org/10.1101/2020.03.17.20037432
14. The Japanese Association for Infectious Diseases. Preliminary Report of the Favipiravir Observational Study in Japan [Internet]. 2020 [cited 2020 Nov 26]. Available from: https://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_en_200529.pdf
15. Esposito S, Noviello S, Pagliano P. Update on treatment of COVID-19: ongoing studies between promising and disappointing results. Le Infez Med., 2020; 2.
16. Bangladesh Society of Medicine. The Dhaka Trial: Clear-Cut Evidence Favipiravir Effective against COVID-19 with Compelling Results [Internet]. Dhaka; 2020 [cited 2020 Nov 26]. Available from: https://www.trialsitenews.com/the-dhaka-trial-clear-cut-evidence-favipiravir-effective-against-covid-19-with-compelling-results/
17. Rattanaumpawan P, Jirajariyavej S, Lerdlamyong K, Palavutitotai N, Saiyarin J. Real-world Experience with Favipiravir for Treatment of COVID-19 in Thailand: Results from a Multi-center Observational Study. medRxiv [Internet]. 2020 Jul 13 [cited 2020 Nov 26]; 2020.06.24.20133249. Available from: https://doi.org/10.1101/2020.06.24.20133249
18. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A prospective, randomized, open-label trial of early versus late favipiravir in hospitalized patients with COVID-19. Antimicrob Agents Chemother [Internet]. 2020 Sep 21 [cited 2020 Nov 26]; 64(12). Available from: http://aac.asm.org/