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Clinical Evidence of Favipiravir in the Management of COVID-19 Disease

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Abstract

Favipiravir is an oral drug used for the treatment of new or re-emergent influenza when other anti-influenza agents are not effective. Favipiravir is metabolized to ribosyl triphosphate form which inhibits RNA polymerase involved in influenza viral replication. We have observed that several clinical trials have been conducted in Russia, China, and Japan to evaluate the efficacy of Favipiravir in COVID-19 patients. Results showed that the rate of clinical recovery was high in moderate patients. The drug also showed faster viral clearance and improvement in chest imaging. The mortality rate was low in younger patients. Favipiravir was proven to reduce the duration of signs and symptoms in patients with mild to moderate COVID-19 patients. The common adverse events observed were diarrhea, kidney injury, increased serum uric acid. Overall Favipiravir significantly achieved viral clearance, improved clinical status and is generally well tolerated. Further studies are being conducted to evaluate the efficacy and safety of Favipiravir in COVID-19 patients.

Keywords: Favipiravir; Viral clearance; Anti-influenza; SARS-CoV-2

Abbreviations

SARS-CoV-2-Severe Acute Respiratory Syndrome Coronavirus 2; COVID 19-Coronavirus Disease; WHO-World Health Organization; MERS-CoV-Middle East respiratory syndrome; 2019-nCoV-2019 novel coronavirus; ACE-Angiotensin Converting Enzyme; AT2-Angiotensin 2; RNA-Ribonucleic Acid; PCR-Polymerase Chain Reaction; ALT-Alanine Transaminase; AST-Aspartate Aminotransferase; HIV-Human Immunodeficiency Virus; CRP-C Reactive Protein; AOT-Auxiliary Oxygen Therapy; NMV-Noninvasive Mechanical Ventilation; ULN-Upper Limit of Normal; IL-6-Interleukin; FPV-Favipiravir; LPV-Lopinavir; RTV-Ritonavir; IFN-Interferon.

Introduction

A novel Coronavirus (CoV) named '2019 novel coronavirus' or 'COVID-19' by the World Health Organization (WHO) has led to the recent outbreak of pneumonia that began in December 2019 in Wuhan City, Hubei Province, China [1,2]. SARS-CoV-2 viruses primarily affect respiratory system where fever, dry cough and dyspnea are the most commonly observed symptoms [3]. As of 28th Sep 2020 over 32.7 million COVID-19 cases and 991 000 deaths have been reported to WHO [4].

The highly pathogenic viruses such as SARS-CoV, MERS-CoV and 2019-nCoV cause severe respiratory syndrome in humans, and the other four human coronaviruses such as HCoV- NL63, HCoV-229E, HCoV- OC43 and HCoV-HKU1 cause mild upper respiratory diseases in immunocompetent hosts [5].

The pathogenesis of COVID-19 involves the entry of SARS-CoV-2 into the target cells by binding with the human ACE2 receptors which are present in lungs [6]. The binding of virus to ACE 2 leads to increased production of angiotensin-2 by the enzyme ACE. The increased AT2 increases pulmonary vascular permeability and causes lung injury [7]. Moreover SARS-CoV-2 antigen cells attach to the dendritic cell which activates macrophages and leads to excessive release of pro-inflammatory cytokines and chemokines. During this pandemic, drugs like Remdesivir, Hydroxychloroquine, Ritonavir, Lopinavir, Favipiravir, Interferons, Azithromycin and several others are being explored for the treatment of COVID-19. There is no vaccine presently available for this disease and several vaccines are under development.

Favipiravir is the drug, indicated for the treatment of new or re-emergent influenza against which anti-influenza agents are ineffective [8,9]. Favipiravir is metabolized in cells to a Ribosyl Triphosphate Form (favipiravir RTP) which selectively inhibits RNA polymerase involved in influenza viral replication [9-11]. Here, we report the available clinical evidence of Favipiravir in COVID-19.

Literature Review

We searched the PubMed database and Google search for English articles using the keywords "novel coronavirus", "SARS-CoV 2", "Favipiravir" and COVID-19.

Our search resulted in 4 clinical trials with available results for Favipiravir use in managing COVID-19 patients.

Russia: Phase II/III Multicentre, Randomized Clinical Trial

This study was conducted in April and May 2020.

Favipiravir was compared with Standard of Care (SOC) in hospitalized patients with moderate COVID-19 pneumonia. The numbers of patients enrolled in the study were 60. The patients included were hospitalized men and non-pregnant women of 18 years or older, patients who had moderate PCR-confirmed COVID-19, and patients who signed informed consent form.

The patients in the study were randomized in 1:1:1 ratio to receive either Favipiravir 1600 mg BID on Day 1 followed by 600 mg BID on Days 2-14 (1600/600 mg), or Favipiravir 1800 mg BID on Day 1 followed by 800 mg BID on Days 2-14 (1800/800 mg), or SOC. The primary efficacy endpoint was the elimination of SARS-CoV-2 by Day 10. Qualitative Real-Time RT PCR test was performed. The secondary endpoints were viral clearance by Day 5, time to normalization of body temperature, changes on CT scan by Day 15, and incidence and severity of adverse events related to the drug [8].

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In Favipiravir group drug was administered for a period of 10.9 ± 2.8 days. In standard of care group hydroxychloroquine or chloroquine was administered to 15/20 (75.0%) patients, lopinavir/ritonavir was used in 1/20 (5%) patient, where 4/20 (20%) did not receive the treatment. The additional therapy included antibiotics, anticoagulants, immunosuppressants and symptomatic treatment.

Both dosing regimen of Favipiravir showed similar virological response. By day 5, there was 62.5% of viral response with Favipiravir as compared to SOC treatment (p=0.018) in moderate patients (Table 1).

Variable	Day	Favipiravir (N=40)	SOC (N=20)	P-Value
Viral clearance	5	25(62.5%)	6(30.0%)	0.018
	10	37(92.5%)	16(80.0%	0.155

Table 1: Virological response.

SOC- Standard of Care

The decrease in body temperature observed with Favipiravir was significantly low when compared with Standard of care (Table 2).

Variables	Favipiravir	SOC	P-Value
Median time to body temperature normalization (<37ºC)	2 days (IQR 1-3)*	4 days (IQR 1-8)	0.007
Improvement in chest CT scans by day 15	36 (90.0%)	16 (80.0%)	0.283
*IQR-Interquartile Range			

Table 2: Secondary outcomes.

Adverse drug reactions to Favipiravir were reported in 7/40 (17.5%) patients, including diarrhea, nausea, vomiting, chest pain and an increase in liver transaminase levels. All the adverse drug reactions were mild to moderate. The two patients who died in this study had the increased risk of severe disease, including diabetes mellitus, arterial hypertension, obesity, CRP >50 mg/L, and supplemental oxygen at baseline.

China: Prospective, Randomized, Controlled, Open-Label, Multicentre Trial

The study was conducted from February 20 to March 1, 2020 in hospitals of Wuhan, Hubei, China. The number of patients enrolled in the study was 240. The eligible patients in the study were 18 years or older, symptoms within 12 days, diagnosed COVID-19 pneumonia patients. Patients allergic to Favipiravir or Arbidol, elevation in ALT/AST (>6XULN) or with chronic liver disease, patients whose survival rate were<48hours, pregnant woman, HIV patients were excluded [12].

Patients were randomized in 1:1 ratio and received either Favipiravir (1600 mg, twice first day followed by 600 mg, twice daily, for the following days) or Arbidol (200 mg, three times daily) plus standard care for 7 days. The treatment could even be extended to 10 days. The primary efficacy was clinical recovery rate at day 7. The secondary efficacy was latency to pyrexia, the rate of AOT or NMV, all-cause mortality, dyspnea and rate of respiratory failure. Safety outcomes included adverse events occurred during treatment. All patients were assessed for body temperature, viral infections, SPO2, chest CT, IL-6, blood biochemistry, urinalysis, coagulation function, C-reactive protein and SARS-CoV-2 nucleic acid. All the parameters were assessed on 3rd and 7th day with additional CT scan of chest.

Clinical recovery rate at day 7 in moderate patients were high in Favipiravir group when compared to Arbidol (Table 3).

Variable	Favipiravir (N=116)	Arbidol (N=120)	Rate ratio (95% CI)	P-Value
Moderate patients	70 (71.43%)	62 (55.86%)	0.1557 (0.0271,0.2843)	0.0199
Severe patients	1 (5.56%)	0 (0.00%)	0.0556 (-0.0503, 0.1614)	0.4712

Table 3: Comparison of clinical recovery rate at day 7.

Pyrexia and cough relief were significantly reduced with Favipiravir treatment when compared to Arbidol treatment (P<0.0001) (Tables 4 and 5).

Variable	Favipiravir group	Arbidol group
Total patients	N=71	N=74
Day 1	15 (21.13)	2 (2.70)
Day 2	23 (32.39)	8 (10.81)
Day 3	19 (26.76)	18 (24.32)
Day 4	10 (14.08)	15 (20.27)
Day 5	1 (1.41)	16 (21.62)
Day 6	-	5 (6.76)
Day 7	-	3 (4.05)
Day 8	-	-
Day 9	-	-

Table 4: Time to pyrexia relief.

Variable	Favipiravir group	Arbidol group
Total patients	N=78	N=73
Day 1	1 (1.28)	3 (4.11)
Day 2	2 (2.56)	1 (1.37)
Day 3	23 (29.49)	7 (9.59)
Day 4	20 (25.64)	11 (15.07)
Day 5	10 (12.82)	12 (16.44)
Day 6	10 (12.82)	10 (13.70)
Day 7	3 (3.85)	3 (4.11)
Day 8	7 (8.97)	6 (8.22)
Day 9	1 (1.28)	17 (23.29)

Table 5: Time to cough relief.

The incidence of auxiliary oxygen therapy (AOT) or noninvasive mechanical ventilation (NMV) was 27/120 (22.50%) in the Arbidol group and 21/116 (18.10%) in the Favipiravir group (P=0.4015) (DRR: -4.40%, 95% CI: -14.64% ~ 5.85%). A post-hoc analysis showed that incidences of dyspnea occurred only 4/116 (3.45%) patients in the Favipiravir group and 14/120 (11.67%) patients in the Arbidol group (P=0.0174). The most frequently observed Favipiravir-associated adverse event was raised serum uric acid (16/116, OR: 5.52, P=0.0014).

Japan: Observational Study

This was conducted in Japan and enrolled 2158 COVID-19 patients. The study provided required information of demographics, illness, duration of the drug, and use of additional medications and clinical status at day 7 and 14 from use of favipiravir and Clinical outcome after one month from hospital admission to hospital. The data were collected using the survey function of RED Cap [10].

After administration of Favipiravir the clinical status were recorded as improved, worsened, and unchanged. Improvement was high for mild disease at day 14 (Table 6).The mortality rate was high for severe disease patients (Table 7).Clinical improvement was high was for those patients who are 59 years old or younger (Table 8). Mortality rate observed were high for those above 60 years old or older and low for those below 59 years old or younger (Table 8).

Favipiravir*	Mild	Moderate	Severe
Day 7	73.8%	66.6%	40.1%
Day 14	87.8%	84.5%	60.3%
*IQR-Interquartile Range			

Table 6: Rate of clinical improvement at day 7 and 14.

Mortality rate	
Mild	5.1%
Moderate	12.7%
Severe	31.7%

Table 7: Clinical outcome after one month from hospital admission.

After start of Favipiravir	59 years old or younger	60 years old or older
Day 7	79.0%	55.0%
Day 14	92.4%	73.8%

Table 8: Clinical status when stratified by age.

Mortality rate	
Below 59 years	1.8%
Above 60 years*	20.8%

Table 9: Mortality rate.

The most common adverse events were hyperuricemia (335 patients; 15.52%) followed by liver injury or liver function test abnormalities (159 patients; 7.37%) (Table 10).

Number of Patients	2158
Number of patients with adverse events	532 (24.65%)
Number of adverse events reported	626
Hyperuricemia	335 (15.52%)
Liver injury	159 (7.37%)

Table 10: Safety outcomes.

China: Open-Label Nonrandomized Control Study

This study was conducted in Shenzhen, China from 30 January to 14 February 2020. The numbers of patient's enrolled were 80. The patients included were 16–75 years old, respiratory or blood samples tested positive for the novel coronavirus, if duration from disease onset to enrolment was less than 7 days, willing to take contraception during the study and within 7 days after treatment, and if there is no difficulty in swallowing the pills [13].

This study examined the effects of Favipiravir (FPV) versus Lopinavir (LPV)/Ritonavir (RTV) for the treatment of COVID-19.

Favipiravir arm: Oral FPV (Day 1: 1600 mg twice daily; Days 2–14: 600 mg twice daily) plus interferon (IFN)-α by aerosol inhalation (5 million U twice daily)

Control arm: LPV/RTV (Days 1–14: 400 mg/100 mg twice daily) plus IFN-α by aerosol inhalation (5 million U twice daily.

All participants also received IFN-α1b 60 μg twice daily by aerosol inhalation and the standard care included oxygen inhalation, oral or intravenous rehydration, electrolyte correction, antipyretics, analgesics, and antiemetic drug.

Primary efficacy was time of viral clearance and improvement in rate of chest computed tomography CT scans on 14th day of treatment. Secondary efficacy was total number of adverse reactions.

Median time of viral clearance for patients treated with Favipiravir was 4 days which was significantly shorter than Lopinavir which was 11 d (IQR: 8-13) (P<0.001).

When the improvement rates of the chest CT changes for Favipiravir and Lopinavir/Ritonavir were compared no significant changes were observed on Days 4 and 8 (P>0.05).

However, after 14 days of treatment improvement rate in chest CT changes were significantly higher in Favipiravir treatment than those in LPV/RTV (91.4% vs. 62.22%) (Table 11).

Chest CT change	FPV (N= 35)	LPV/RTV (N=45)	P-value
Improve*	32(91.43%)	28(62.22%)	0.004
Worse	1(3.23%)	9(20.00%)	
Constant	2(6.45%)	8(17.78%)	

Table 11: Improvement in rate of chest CT changes.

- CT- Computed tomography
- FPV- Favipiravir
- LPV/RTV- Lopinavir/ Ritonavir

Most common adverse reactions observed were Diarrhea, nausea, vomiting, rash, liver and kidney injury. The numbers of adverse reactions in FPV group were significantly fewer when compared with LPV/RTV (P <0.001) (Table 12).

Characteristics	Treatment FPV (N=35)	LPV/RTV (N=45)	P-value
Total number of adverse reactions	4 (11.43%)	25 (55.56%)	< 0.001

Table 12: Adverse reactions after medications.

FPV- Favipiravir

LPV/RTV- Lopinavir/ Ritonavir

India: Randomized, Open-Label, Parallel-Arm, Multicenter, Phase 3 Study

This study was conducted from May 14th to July 3rd 2020. The numbers of patients enrolled in the study were 150. The eligible patients included were 18-75 years, patients infected with SARS- CoV-2, patients who were willing to use effective contraception during study period and for >7 days following the last treatment, female patients who confirms negative pre- treatment pregnancy test, patients whose symptom onset was not more than 7 days for mild disease and 10 days for moderate disease [14].

The patients were randomized in 1:1 ratio to oral favipiravir (1800 mg BID on Day 1 followed by 800mg) plus standard supportive care for up to a maximum of 14 days or standard supportive care alone which included antipyretics, cough suppressants, antibiotics, and vitamins. All subjects were hospitalized per prevailing treatment guidelines and to allow daily RT-PCR testing, and were discharged only after 2 consecutive negative SARS-CoV-2 tests and clinical cure were achieved. The primary endpoint was time to cessation of oral shedding of the SARS-CoV-2 virus (Maximum-28 days). Real time RT-PCR test was performed. The secondary endpoints were time to clinical cure of signs and symptoms, time to first use of high flow supplemental oxygen, ventilation and time to hospital discharge. All the clinical symptoms and vital sign parameters were assessed twice daily on Days 1-28.

The time to cessation of viral shedding was 5 days in Favipiravir group and 7 days in the control group (P=0.129) (Table 13).

	Favipiravir	Control	Log -rank P value	Hazards ratio (95% CI)	Hazard Ratio P value
No. of patients	N=72	N=75	0.01290	1.367 (0.944, 1.979)	0.098
No. of events (%)	70 (97.2)	68 (90.7)			
Time to event, median days (95%CI)	5.0	7.0			

Table 13: Time to cessation of SARS-CoV-2 oral shedding.

The time to cure clinical symptoms among symptomatic patients was significantly faster with Favipiravir treatment compared with control. The time to use of oxygen therapy, ventilation or ECMO was 5 days with Favipiravir treatment and 2 days in control group (P=0.034) (Table 14).

Variables	Favipiravir	Control	Log -rank P value	Hazard Ratio (95% CI)	Hazard Ratio P value
Time to clinical cure	3.0	5.0	0.0297	1.749 (1.096, 2.792)	0.019
Time to use of oxygen, ventilation or ECMO	5.0	2.0	0.0653	0.065 (0.005, 0.809)	0.034

Table 14: Analysis of time to event endpoints, ITT population.

Favipiravir was associated with high number of adverse events when compared with control (36% Vs 8%) respectively. Most common adverse events observed were increased blood uric acid, abnormal liver function and viral pneumonia (Table 15).

	Favipiravir (N=73) n (%)	Control (N=75) n (%)
Overall TEAEs	26 (35.6)	6 (8.0)
Blood uric acid increased	12 (16.4%)	0
Abnormal liver function	5 (6.8%)	2 (2.7%)
Viral pneumonia	2 (2.7%)	0
Gastrointestinal disorder	1 (1.4%)	2 (2.7%)

Table 15: Treatment emergent adverse event.

Discussion

Favipiravir is the drug indicated for the treatment of new or re-emergent influenza against which anti-influenza agents are ineffective and has been repurposed for use in COVID-19. There was also news saying that the time to resolution of symptoms in patients with severe pneumonia was shorter with Favipiravir intake when compared with placebo. Few clinical studies have been conducted with the interventional drug Favipiravir in COVID-19 patients. Clinical data showed that Favipiravir provides rapid antiviral clearance and improves the rate of clinical improvement with a viral clearance of 92% in moderate patients. Favipiravir resulted in high clinical recovery rate in moderate patients when compared with Arbidol. In an observational study, rate of clinical improvement at day 14 with Favipiravir was high for mild and moderate diseases and the mortality rate was low for patients with 59 years old or younger. Favipiravir when compared with Lopinavir/Ritonavir showed faster viral clearance, and also improved the rate of chest CT changes. In recent study of randomized, phase III trial, Favipiravir led to significant improvement in time to clinical cure and is safe and effective in mild to moderate COVID-19 patients. The common adverse events observed with Favipiravir were nausea, diarrhea, kidney injury and increased uric acid. Based on the present evidence, Favipiravir seems to benefit a subset of patients with COVID-19, and large well controlled trials are further needed can provide substantial evidence.

Conclusion

Favipiravir has shown to be beneficial in mild to moderate COVID-19 patients with rapid antiviral clearance and clinical improvement, with alleviation of CT findings. Favipiravir was well tolerated, and adverse events were manageable. Further clinical data in large number of patients would be required to support these findings.

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