

Pharmacological Effects of Favipiravir on Coronavirus: An Update

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The coronavirus pandemic is the worst health crisis of our time. There is a massive upsurge of the cases and no specific treatment options for this novel virus (SARS-CoV-2). Due to no time for research and development of a new drug or a vaccine, old and existing broad spectrum antiviral drugs were tried and tested. Favipiravir showed promising results in mild to moderate COVID-19 infection in small studies. The drug is approved with precaution under emergency use, as its safety profile is still not clear. We have considered every aspect of favipiravir and compiled all the latest information about the drug in this review article.

Keywords: COVID-19, Coronavirus, SARS-CoV-2, Favipiravir, Fabiflu.

The world is facing the worst health crisis of our time. The Coronavirus Disease (COVID-19) has hit us hard. According to the current record, total incidence of COVID-19 cases till 31-10-2020 was 45,921,794 and mortality was 1,193,912.¹ The causative agent of this COVID-19 infection is a new coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2, (SARS-CoV-2).² New virus requires new therapeutic options but due to lack of time for research and development of a new drug, there is no choice but to test and treat the disease with existing medicines. Many broad spectrum antiviral drugs are trialled but there is hardly any drug which is found to be potent against coronavirus disease. Favipiravir is one drug which has shown encouraging results in an open label control study done on 80 patients in China.³ There was significant reduction in the duration of viral clearance.³ There are many ongoing randomized

and non-randomized controlled trials being conducted on favipiravir to evaluate its efficacy and safety against SARS-CoV-2.⁴ Presently, there are 40 clinical trials registered (clinicaltrials.gov) for evaluation of favipiravir in treatment of COVID-19.⁴

The central drugs standard control organization approved the restricted emergency use of favipiravir tablets for mild to moderate COVID-19 infection based on the little evidence from small studies.⁵ The permission to manufacture and market favipiravir tablets was given to Glenmark Pharmaceuticals by Drugs Controller General of India on 19.06.2020.⁵ Since the literature available on favipiravir is scant, we aim to fill this knowledge gap through this article.

History and Outbreak of Coronavirus

It has been reported that SARS-CoV-2 originated in human from zoonotic reservoirs like

bats, Himalayan palm civets and raccoon dogs in China.⁶⁻⁸ Clinical presentation of COVID-19 disease was similar to MERS-COV epidemic of 2012, but unlike COVID-19 disease MERS-COV was limited to the middle eastern countries only.^{9,10} In 1965 scientist 'Tyrell & Bynoe' found and isolated coronavirus (HCoV) from respiratory tract of an adult suffering from common cold. The most distinguishing feature of the coronavirus seen under the electron microscope was its spikes, giving it a crown like appearance.^{9,11,12} Thus, Tyrell and group of other virologists named it coronavirus in 1968.^{9,11,12,13}

The disease coronavirus causes in human host and their cellular receptors are summarized in Table 1.¹³

The first human case of COVID-19 disease was reported in Wuhan, China in December 2019.¹⁴ The novel coronavirus causing this outbreak was later named SARS-COV-2.¹⁴ The number of cases reported in January 2020 was 9692 and by 31st October, 2020, it was raised to its 45,921,794.^{1,9} The common clinical manifestations found are of lower respiratory tract like pneumonia, dry cough, fever, dyspnea and diarrhea.¹⁵ The confirmed modes of transmission of SARS-CoV-2 infection is from person to person through contact or through larger respiratory droplets and smaller aerosols.^{15,16} Treatment of COVID-19 is based on the severity of the infection and thus it is classified from asymptomatic to critical disease (Table 2).¹⁷

Favipiravir

A favipiravir is structurally 6-fluoro-3-hydroxy-2-pyrazinocarboxamide and a broad spectrum antiviral drug showing in vitro activity against RNA viruses including influenza virus, respiratory syncytial virus and measles virus.¹⁸ The chemical structure of favipiravir is shown Figure 1.¹⁹

Chemical substitution of pyrazine compound was found to show strong anti-influenza virus activity in vitro and in vivo.¹⁹ Favipiravir was discovered as an anti-influenza drug originally.

Pharmacodynamics and Mechanism of Action

The mechanism of action of Favipiravir is special as other marketed influenza drugs either inhibit entry or release of the virus. For replication of RNA viruses RNA dependent RNA polymerase (RdRp) is needed as it controls the rate of replication and mutation of the virus to adapt within the host surroundings.²⁰ Favipiravir is a prodrug which enters the infected cells through endocytosis and it is transformed to active metabolites favipiravir ribofuranosyl triphosphate (Favipiravir-RTP) through phosphorylation and phosphoribosylation.²¹⁻²⁴ This active favipiravir – RTP competes with purine nucleoside. It binds to and selectively blocks RdRp which in turn prevents viral transcription and replication.²⁵ The disruption in viral RNA replication leads to increased number and frequency of translation mutations which replaces Guanine (G) by Adenine (A) and Cytosine (C) by Thymine (T) or Uracil (U), thereby producing devastating mutagenesis in RNA viruses.^{17,25}

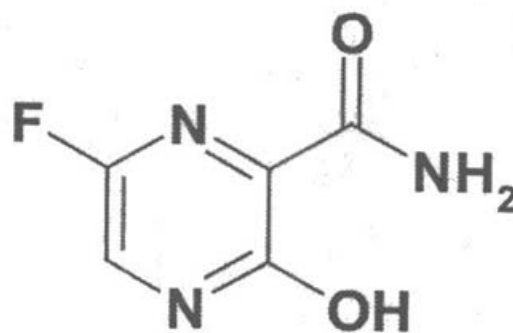


Fig.1. Chemical structure of Favipiravir¹⁹

Table 1. Coronaviruses, hosts, diseases, and receptors¹³

Group	Virus	Host	Disease caused	Cellular receptor
I	229E	Human	Respiratory infection	Human APN
	NL-63	Human	Respiratory infection	ACE2
II	OC43	Human	Respiratory and enteric infection	Neu5,9Ac2-containing moiety
	HKU1	Human	Respiratory infection	
	SARS-COV	Human	Severe acute respiratory syndrome	ACE2

Illustrative diagram of intracellular activation and mechanism of action of favipiravir is shown in Figure 2.²⁵

Pharmacokinetics

On oral administration favipiravir is absorbed well, having bioavailability of 97.6% and plasma protein binding capacity of 54%.²⁴ The volume of distribution of favipiravir is 15-20 liters.²⁴ Considered oral dose in adults on day 1 at 1600 mg twice, then 600 mg twice daily for 4 days followed by 600 mg once daily for 1 day (1600-1day BID+600- 4days BID+ 600-1day once). The estimated AUC on day 1 and day 6 was 446.09 and 553.98 $\mu\text{g hr/ml}$, Cmax was 64.56 and 64.69 $\mu\text{g/ml}$, tmax was 1.5 hours and $t_{1/2}$ of 4.8 ± 1.1 hrs and 5.6 ± 2.3 hrs respectively. Favipiravir is metabolized in liver predominately by Aldehyde Oxidase (AO) and partly by Xanthine Oxidase (XO). It is eliminated by kidney in hydroxylated form.²⁴

Indications of favipiravir

Favipiravir is found to be effective against the following RNA viruses.

Influenza

Favipiravir was discovered during chemical modification of a pyrazine analogue in cells showing anti-influenza virus activity in vitro.²⁵ The drug is selective and powerful blocker of influenza viral RNA polymerase and works

well against all strains of influenza virus and its subtypes. Favipiravir is also found to be effective against influenza viruses sensitive or resistant to neuraminidase and M2 inhibitors including Oseltamivir in vitro.^{25,26}

COVID-19

Many clinical trials with favipiravir are underway for testing its efficacy and safety on SARS-CoV-2. Few studies with favipiravir are shown in Table 3.²⁷ Now the drug is approved in several countries including India. In India, DCGI has allowed restricted emergency use in mild to moderate cases. Thus, currently the drug can only be prescribed after getting informed consent from the patient or their representative for emergency use in prescribed form. Recommended dose on Day 1 is 1800 mg or 9 tablets of 200 mg twice a day followed by 800 mg or 4 tablets of 200 mg twice a day for a maximum of 14 days.

Others

Favipiravir has also been promising in the treatment of Ebola and Norovirus infection.^{21,23}

Drug Interactions

As there is no specific potent drug for COVID-19, multiple therapies are unavoidable considering the complications, severity and preexisting co-morbidities like cardiovascular disease, diabetes, bronchial asthma, hypertension and so

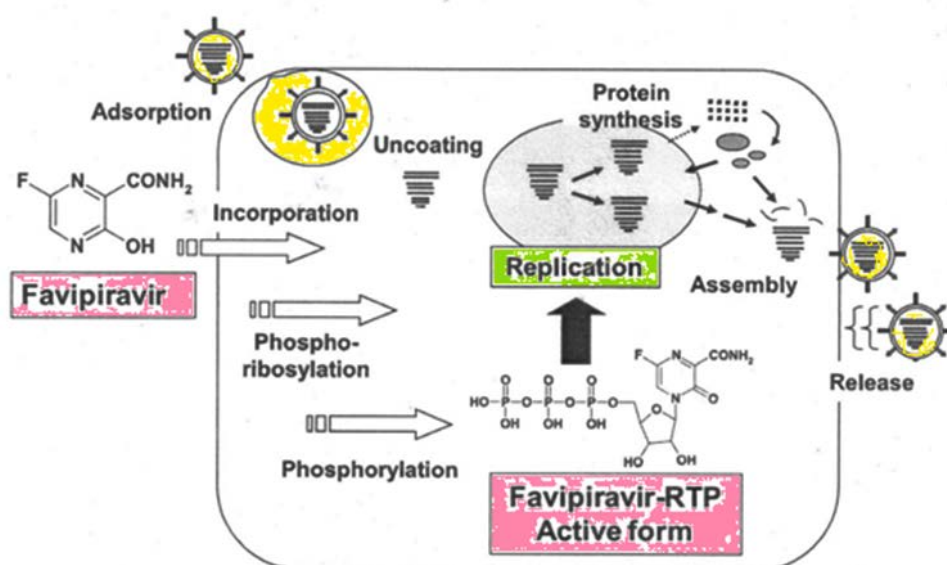
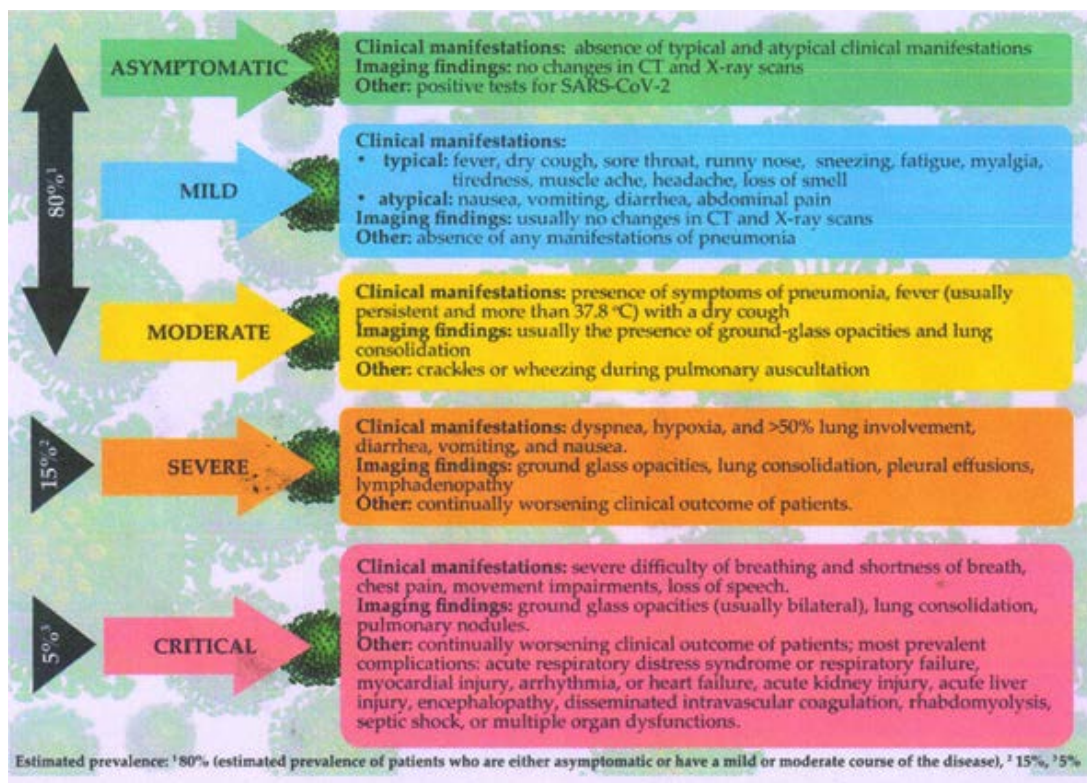


Fig. 2. Illustrative diagram of intracellular activation and mechanism of action of favipiravir

Table 2. The severity of SARS-CoV-2 infection with typical characteristics.¹⁷

on. Therefore, potential drug-drug interactions should be considered as favipiravir is new in the market. So far few confirmed and significant drug interactions are known. Cytochrome P-450 (CYP) does not metabolize favipiravir.²⁸ Pyrazinamide when co-administered with favipiravir increases blood uric acid level as reabsorption of uric acid in renal tubules is increased.²⁸ Favipiravir with repaglinide increases the blood level of repaglinide by inhibition of CYP2C8.²⁸ When favipiravir is used along with theophylline, blood concentration of favipiravir is raised due to the interaction of theophylline with xanthine oxidase (XO).²⁸ Efficacy of famciclovir and sulindac is reduced when co-administered with favipiravir due to inhibition of aldehyde oxidase (AO).²⁸

Contraindications of favipiravir Pregnancy

Favipiravir is found to be teratogenic in animal studies. Early embryonic death was seen in rats and teratogenicity was detected in mouse, rat, rabbit and monkey at doses similar or lower than clinical dose.²⁸

Fertility

Histopathological changes in testis of rats and young dogs were observed after exposure to favipiravir.²⁸ In rats, changes on the testis and sperm along with low fertility were reported. Thus, in general low fertility may occur due to changes in testis and sperm in male and markable anestrus in females at high doses.²⁸

Severe Renal and hepatic impairment

Since favipiravir is heavily metabolized in liver and excreted in urine, it is contraindicated in severe hepatic and renal failure.²⁸

Gout and hyperuricemia

Favipiravir has shown to increase blood uric acid loads which is reversed on drug discontinuation.²⁹

Undesirable effects and adverse drug reactions

Favipiravir observational study was conducted in Japan in 2,158 patients and subsequently adverse effects were reported in 24.65% of the subjects. The most prominent adverse events was hyperuricemia in 15.52% of

Table 3. Clinical trials involving Favipiravir²⁷

Study type	Trial outcome and design	Conclusion	Comment
Exploratory Randomized, Controlled Trial. ³³	29 COVID-19 confirmed cases were randomized(1:1:1) to either receive Favipiravir for 14 days or Baloxavir Marboxil (80 mg once a day orally on Day 1 and Day 4) or control group. All patients received existing antiviral treatment including lopinavir/ritonavir (400 mg/100 mg, bid, orally) or darunavir/ cobicistat (800 mg/150 mg, qd, orally) and arbidol (200 mg, tid, po.). All of them used in combination with interferon -a inhalation. On day 14, PCR was undetectable in all control group and 77% and 70 % in Baloxavir and Favipiravir groups, respectively. Furthermore, there was no significant difference between all groups in clinical improvement. One patient in the baloxavir marboxil group, and two patients in the favipiravir group transferred to ICU within seven days after trial initiation. Among all 29 patients, there was no death.	Findings do not support that adding either baloxavir or favipiravir under the trial dosages to the existing standard treatment benefit COVID-19 patients.	Small sample size, non-blinded trial. Concurrent use of other antivirals leads to misinterpretation of results.
Prospective, randomized, controlled, open-label multicenter trial. ³⁴	236 moderate/severe confirmed COVID-19 cases randomized; 116 to receive Favipiravir for 10 days and 120 to receive Umifenovir (Arbidol) for 10 days and all patients received conventional therapy. Upon results, clinical improvement at day 7 (primary end point), did not significantly differ between two groups. Whereas, in post-hoc analysis for moderate COVID-19 patients showed a significant higher clinical improvement in the Arbidol group (62/111, 55.86%) compared to Favipiravir group (70/98, 71.43%). Favipiravir led to shorter latencies to relief for both pyrexia and cough. Whereas, no significant differences were found between both groups in the rate of auxiliary oxygen therapy (AOT) or non invasive	Favipiravir, compared to Arbidol, did not significantly improve the clinically recovery rate at Day 7. Favipiravir significantly improved the latency to relief for pyrexia and cough.	Number of severe and critically ill patients were more in favipiravir that undermine the benefit of Arbidol.

An Open-Label Control Study. ³	mechanical ventilation (NMV). 80 confirmed mild to moderate severity cases of COVID-19 were assigned to receive either Favipiravir (n = 35) or Lopinavir /ritonavir (n = 55) (control group) for 14 days and both groups received interferon (IFN)- α aerosol inhalation. FPV showed preferable outcomes compared to control arm, including shorter viral clearance (4 (2.5–9) d vs 11 (8–13) d, $P < 0.001$) and significant improvement in chest imaging (improvement rate of 91.43% vs 62.22%, $P = 0.004$).	Favipiravir showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance.	Only mild to moderate cases were included in the study.
Randomized-controlled open-label interventional phase 3 clinical trial ³⁵	100 COVID-19 patients were recruited. 50 patients received favipiravir 3200 mg at day 1 followed by 600 mg twice (day 2–day 10). 50 patients received hydroxychloroquine 800 mg at day 1 followed by 200 mg twice (day 2–10) and oral oseltamivir 75 mg/12 h/day for 10 days. PCR negativity for SARS-CoV-2 was 8.1 and 8.3 days in HCQ-arm and favipiravir-arm respectively, difference was not statistically significant ($p = 0.7$). Fever and dry cough were reported more frequently in favipiravir arm (36% and 38% respectively) than HCQ-based therapy (24% and 30% respectively) but this was not statistically significant ($p > 0.05$). In the favipiravir-arm 4 patients (8%) experienced elevated liver transaminases 3–5 times the upper normal limit between Day 7 and Day 14, but improvement was seen within 2 weeks after the end of therapy. In the HCQ-based arm there was one death due to an acute heart failure resulting from myocarditis on Day 8.	Favipiravir was found to be a safe and effective alternative to hydroxychloroquine and could be used safely during home isolation in mild to moderate cases	Only mild to moderate patients were included in the study.

individuals followed by impaired liver function test (7.37%), rash (1.44%), diarrhea (0.74%) and acute renal injury with elevated blood creatinine level was found in 0.74% of the patients treated with favipiravir.³⁰

Common adverse reactions of Favipiravir are summarized in Table 4.²⁸

Cost Analysis

Glenmark Pharmaceuticals was the 1st company to launch favipiravir in India under brand name Fabiflu (200 mg tablet) at Rupees (Rs) 103 per tablet in June, 2020.³¹ However, a month later the company reduced the price by 27% to Rs 75 per tablet. At present 5 other companies

Table 4. Adverse reactions observed in Japanese Clinical Studies and the Global Phase III clinical study³⁰

Sl. No	Reactions	≥ 1%	0.5-< 1%	< 0.5%
1	Hepatic	SGOT increased SGPT increased		Blood ALP increased Blood bilirubin increased
2	Gastrointestinal	Diarrhoea (4.79%)	Nausea, Vomiting, Abdominal pain	Abdominal discomfort, Duodenal ulcer, Haematochezia, Gastritis
3	Haematologic	Neutrophil count decreased WBC count decreased		WBC count increased, Reticulocyte count decreased, Monocyte increased
4	Metabolic disorders	Blood uric acid increased (4.79%), Blood triglyceride increased	Glucose in urine present	Blood potassium decreased
5	Respiratory			Asthma, Oropharyngeal pain, Rhinitis, Nasopharyngitis
6	Others			Blood CK (CPK) increased, Blood in urine present, Tonsil polyp, Pigmentation, Dysgeusia, Bruise, Blurred vision, eye pain, vertigo, supraventricular extrasystole
7	Hypersensitivity		Rash	Eczema, Pruritus

Given dose was lower than the approval dose

Table 5. Price trends of favipiravir in Indian market.^{31,32}

Sl no	Pharmaceutical company	Price per tablet in Rs	Total cost for full therapy of 14 days in Rs
1	Glenmark	75/-	9150/-
2	Cipla	68/-	8296/-
3	Hetero	59/-	7198/-
4	Sun Pharma	35/-	4270/-
5	Dr Reddy's	99	12078/-

have been permitted to manufacture and sell the drug by DCGI. Price trends of favipiravir seen as on August 2020 is summarized in Table 5.^{31,32} The recommended therapy for 14 days will have minimum cost of Rs 4,270/- to maximum Rs 12,078/-, for 122 tablets each of 200 mg.

CONCLUSION

The COVID-19 disease does not seem to disappear anytime soon. Currently, a second wave of this pandemic has hit the European Union Countries. Scientists have predicted massive rise

in infections this winter in India. Favipiravir has shown unique account and broad spectrum of antiviral activity against RNA viruses which has driven the researchers to carry out multiple clinical trials on it against the devastating SARS-CoV-2. It was found that favipiravir shortens the time for viral clearance and shows improvement in chest findings. It is considered to be relatively safe for short term use. However, we need more substantial evidence confirming its efficacy and safety. Favipiravir is the drug of choice at present for mild to moderate cases until a new efficient antiviral drug or vaccine is found for COVID-19.

Health care providers must monitor and report any unfavourable outcomes related to its use on COVID-19 patients. Large scale studies are required for corroboration of existing data.

As there is continuous upsurge of cases and frequent changes in the treatment protocols physicians should be updated from time to time about new progress in treatment of COVID-19.

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Conflicts of Interest

None to declare.

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