

A Review on Antiviral Activity of Favipiravir

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ABSTRACT

The emerging severe acute respiratory syndrome coronavirus 2 pandemic endangers patients and physicians all over the world. The potency of COVID-19 antiviral drugs is still a matter of debate. The growing understanding of COVID-19 virology and clinical manifestations is resulting in a larger pool of potential pharmacological targets. Favipiravir is included in the treatment regimen of many countries, including some regions of India, that have recently updated their treatment standards and is expected to be an effective treatment for SARS-CoV-2 infection, as it can be used to treat many different types of RNA virus infections such as Ebola, influenza, and the foot-and-mouth disease virus can be treated with this new nucleoside analogue. This review describes the status, mechanisms, pharmacokinetics, and antiviral effect of Favipiravir.

Keywords: Favipiravir; Coronavirus; Antiviral activity; Toxicity.

INTRODUCTION

COVID-19 is a respiratory infection that was first seen at the end of 2019 in Wuhan, Hubei Province, China, as a result of the spread of a new coronavirus.¹ COVID-19 has now been declared a pandemic, and new treatments are desperately needed as we step beyond the containment phase.² There is currently no cure for the disease, and vaccines have yet to be developed. In addition to virus mutations, COVID-19's pathophysiology is incompletely understood, as well as geographic variances. SARSCoV-2 is primarily transmitted between people via respiratory droplets or droplet

nuclei. As a result, rather than pharmacological therapy and immunization, the mainstay of COVID-19 management has become social distance and minimizing the spread of disease by respiratory droplets.³

Drug repurposing is a new strategy in which existing medicines that have already been proven safe in humans are repurposed to treat diseases, and it has been followed by several pharmaceutical companies to speed up the development of therapeutic medications.^{4,5} The repurposed drugs, which were previously used to treat other viral infections, were put to work quickly. Favipiravir, for example, was originally marketed in Japan as an anti-influenza drug. The Drug Controller General of India has just given this drug emergency approval.⁶

In Japan, Favipiravir was approved in 2014 to treat cases of influenza that had not responded to standard treatment.⁷ Because of its effectiveness in targeting several strains of influenza, it has been studied in other countries to treat novel viruses such as Ebola and, most recently, COVID-19.^{8,9} Favipiravir, a repurposed drug currently approved by the US Food and Drug Administration for the treatment of COVID-19, works by inhibiting the viral RNA-dependent RNA polymerase (RdRp).¹⁰

FAVIPIRAVIR: REPURPOSED NUCLEOSIDE ANALOGUE

Many scientists are trying to figure out how antiviral medications work against COVID-19 in the hopes of generating an oral treatment or vaccine. As a result, repurposing potential antiviral medications makes sense as a strategy to speed up the drug permitting process.¹¹ Favipiravir is a broad-spectrum antiviral medication (Fig. 1) that has been found to be useful in the treatment of virus infections.¹²

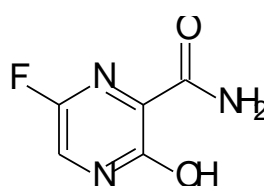


fig.1 Favipiravir

Clinical studies in COVID-19 have shown that it has a faster viral clearance rate than lopinavir/ritonavir and a higher recovery rate than umifenovir. Overall, Favipiravir has shown promise in clinical trials in China, Russia, and Japan. Many countries treatment guidelines, as well as some Indian states, have recently included Favipiravir in the treatment protocol.¹³ The safety profile makes it a promising medication against a wide range of RNA viruses, according to in vitro, in vivo, and clinical evidence.¹⁴

MECHANISMS OF ACTION

Favipiravir-exact RTP's antiviral mechanism is unknown. However, three mechanisms of action have been proposed:

a) misincorporation of one or two consecutive Favipiravir-RTP into viral RNA, which inhibits further RNA extension (chain termination); b) binding of the Favipiravir-RTP to the active site of RdRp, which blocks enzyme activity; and c) lethal mutagenesis.¹⁵

This is a precursor that becomes antiviral after being incorporated into human cells infected with HIV. Favipiravir is phosphoribosylated and further phosphorylated once it enters infected cells, resulting in an active form known as Favipiravir ribofuranosyl-5-triphosphate (Favipiravir-RTP).¹⁶ Several studies indicate that lethal mutagenesis is one of Favipiravir's mechanisms of action for different viruses.¹⁷

Recently, it was discovered that Favipiravir causes lethal mutagenesis in vitro during influenza virus infection. At both a low multiplicity of infection (MOI; 0.0001 PFU/cell) and a high MOI (10 PFU/cell), Favipiravir significantly reduced viral titer. Sequence analysis of different nucleoprotein (NP) clones revealed an increase in the number of detectable G to A and C to T transversion mutations, as well as an increase in mutation frequency and a shift in the nucleotide profiles of the NP gene analysed from different clones.¹⁸ However, no T-705 resistant mutants were found to be viable. According to these findings, Favipiravir has a virucidal effect. A similar mechanism is

thought to control with other viruses inhibited by Favipiravir, which could explain Favipiravir's broad-spectrum virus inhibition.¹⁹

PHARMACOKINETICS

The drug Favipiravir has a complex nonlinear pharmacokinetic profile that varies with dose and time.²⁰ More research is needed to understand how to dose patients with Favipiravir. According to research findings in patients with acute uncomplicated influenza outside of Japan, larger loading and maintenance doses are necessary to keep target drug levels, increasing the possibility of pharmacogenomic factors in drug clearance among populations. Besides this, the majority of research findings indicate that Favipiravir exposure gradually decreases, making dosing difficult.²¹

Favipiravir is a prodrug that is taken orally and has a bioavailability of 94%. It has a low volume of distribution and a 54% protein binding. In a single dose, the maximum concentration of drug reaches plasma in 2 hours. Tmax and half-life increase with multiple dosing. Favipiravir has a short half-life and is rapidly eliminated in the hydroxylated form by renal elimination.²²

ANTIVIRAL ACTIVITY ON A BROAD SCALE

Vaccines and licenced antiviral therapies are currently unavailable for the majority of severe diseases, emphasising the need for effective antiviral agents. Favipiravir is a newer antiviral drug which can be used to combat viral pandemics such as ebola, H1N1 flu, lassa fever, canine distemper virus, and hemorrhagic fever. In the next sections, the efficiency of Favipiravir against a variety of pathogenic agents and associated viruses, such as picoronavirus and murine norovirus, is explained.²³

a) Ebola:

Based on studies in mouse models, research published in 2014 suggested that Favipiravir may be effective against ebola.²⁴ In addition, for thousands of patients worldwide Favipiravir has a good safety profile and is immediately available. It can be used orally in Ebola infected

patients.²⁵ Although in vitro tests for this drug were promising, and clinical studies suggested a trend toward survival benefit, real evidence of benefit was never discovered. A subsequent study discovered that Favipiravir-treated patients had a trend towards improved Ebola virus survival times though this effect was not clinically meaningful.²⁶

b) Influenza:

Favipiravir is being stocked for 2 million people as a precaution against new influenza strains. This drug reduces viral load by acting as a chain terminator at the site of viral RNA incorporation.²⁷ Favipiravir has been demonstrated to be efficacious in influenza-infected mice and ferrets, outperforming Oseltamivir in mouse models. The efficacy of this generic medicine in two animal species convinced us that it would be effective in people and might be used as the standard treatment of choice for influenza. In Japan and the United States, clinical trials for seasonal influenza medications were done, and for the treatment of novel or re-appearing influenza viruses, favipiravir was licensed in Japan.²⁷ It defends against 53 different types of influenza viruses.²⁸

c) Foot-and-mouth disease virus:

The foot-and-mouth disease (FMD) is life threatening, but transmission is not always easy to predict, despite the huge quantities of FMD virus released into the environment and the intense susceptibility of host species to infectious disease. In endemic areas, virus spread is defined by frequent direct and indirect animal contact.²⁹ Favipiravir (T-705) can function in cell culture as a lethal mutagen for FMDV. The viral secretion inhibition is a very important factor for treating FMDV-infected pigs because the pigs are known to be significant amplifiers and excrete around 1000 times more viruses than other hosts such as cattle. Because this compound can be administered by food, a large number of animals can be treated relatively quickly.³⁰

d) Yellow fever virus (YFV):

YF was historically regarded as one the most dangerous infectious diseases caused by the yellow fever virus which is a prototype of its kind Flavivirus. YFV is also transmitted to

humans via *Haemogogus*, *Sabethes* and *Aedes* mosquitos in tropical and subtropical regions of South America and Africa. It circulates mostly among mosquitoes and nonhuman primates in the sylvatic (or jungle) cycle (NHPs).³¹ Favipiravir has a wide spectrum of activity, probably through inhibition of viral polymerase, against many different RNA, including YFV. Even though in the YFV hamster model T-705 was slightly less effective.³²

e) West Nile virus:

The West Nile virus (WNV) is an enveloped plus-strand RNA neurotropic flavivirus spread by mosquitos that poses a global threat to humans and animals.³³ It is spread enzootically by various native bird species, as well as ornithophilic *Culex* mosquitos that can enter the human body. Favipiravir, which is currently on the market in Japan, has been shown to be a potent in vitro and in vivo inhibitor of WNV and other RNA viruses.³⁴

f) Canine distemper virus:

Canine distemper virus (CDV) is an extremely infectious pathogen of the Morbillivirus-Paramyxoviridae family that causes disease and severe immunosuppression in animals. The virus infects animal families such as Canidae, Felidae which affects the respiratory, gastrointestinal, and neurological systems causing health problems. In CDV-infected cells, it effectively blocked viral replication suggesting that it could be used to treat CDV infections. Favipiravir was previously shown to inhibit CDV3 and CDV-11 replication in cells.^{35,36} This drug showed efficacious antiviral effects at predetermined intervals after virus infection. Favipiravir treatment reduced the viability of Vero cells slightly but it had no effect on DH82 cells.³⁶

DRUG-DRUG INTERACTION

Favipiravir is a drug that is still being studied in clinical trials.³⁷ The daily dose of paracetamol should not exceed 3 g due to a slight increase in exposure when combined with drug.³⁸ Anti-diabetic medications such as Pioglitazone, Rosiglitazone may also benefit from it. Antihypertensive potential of Treprostinils for pulmonary hypertension may also be enhanced.

Certain bronchodilators such as aminophylline, theophylline can be increased in concentration by the drug. It causes diarrhea and raises the levels of AST, ALT, -GTP, uric acid, and triglycerides in the blood. It can lower neutrophil, WBC, and potassium levels in the blood. In addition, adverse events such as asthma, blurred vision, eye pain and vertigo are less common.³⁷

The balance of reabsorption and tubular secretion in the proximal tubules controls uric acid management in the kidney. Favipiravir hinders the kidneys from excreting uric acid by blocking organic anion transporters. As a result, Favipiravir is thought to lower uric acid excretion in the urine leading to an increase in uric acid levels in the blood. After stopping Favipiravir, elevated uric acid levels returned to normal.³⁹

TOXICITY PROFILE

The Favipiravir toxicity profile is still not confirmed in humans and data on toxicity are primarily based on animal trials. These studies demonstrated that Favipiravir overdose decreased body weight as well as locomotive activity may be related with vomiting. The following adverse events have been reported in repeated dose toxicity study: toxicity to testes, increased vacuolization in hepatocytes, improper functioning of hematopoietic tissue such as significantly reduced production of red blood cells and elevated functional parameters like aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin. Favipiravir should not be used during pregnancy because it is classed as a teratogen. Two significant side effects are: hyperuricemia and QT prolongation.⁴⁰

IN VITRO FINDINGS AGAINST SARS COV-2

Wang et al. (2020) evaluated the efficacy of Favipiravir in decreasing SARS-CoV-2 infection in an in vitro investigation. Favipiravir has a half-maximal effective concentration (EC₅₀) of 61.88 μM, a cytotoxic concentration (CC₅₀) greater than 400 μM, and a selectivity index (SI) more than 6.46. The EC₅₀ is comparable to its EC₅₀ against ebola (67μM), justifying the necessity for a high dose to attain a pharmacologically relevant target trough concentration of 40-80 g/mL

in COVID-19 (Du YX et al., 2020a). The large difference between CC50 and EC50 provides a reasonable safety buffer for high Favipiravir doses.⁴¹

To investigate the safety and efficacy of Favipiravir throughout the treatment of mild and moderate COVID19 patients it was a randomised, controlled, open-label, phase 3 clinical trial [NCT04349241]. From the 18th of April to the 18th of May, 100 patients were selected. Favipiravir 3200 mg was given to 50 individuals on day one followed by 600 mg twice a week (days 2–10). 50 patients were given 800 mg of Hydroxychloroquine on day one, 200 mg twice (days 2–10), and oral Oseltamivir 75 mg/12 h/day for 10 days. Patients from Ain Shams University Hospital and Assiut University Hospital were enrolled. In terms of demographics and comorbidities both halves were equivalent. The average onset of SARS-CoV-2 PCR negative in the HCQ and Favipiravir arms was 8.1 and 8.3 days, respectively. 55.1 percent of individuals in the HCQ arm were PCR negative on or before the seventh day after diagnosis compared to 48 percent in the Favipiravir arm ($p= 0.7$). Four patients in the FVP arm developed transitory transaminitis while around 20 patients in the HCQarm had heartburn and nausea. Only one patient in the HCQ-arm died as a result of acute myocarditis, which resulted in abrupt heart failure. In patients with mild to moderate COVID-19 infection, Favipiravir is a safe and effective alternative to hydroxychloroquine.⁴²

There appears to be no specific drug to treat COVID-19 while it rages over the world, hence another trail is being pursued to determine the efficiency of Favipiravir against coronavirus. A 64-year-old woman reported with fatigue, joint discomfort, and loss of appetite. After testing positive on the SARS-CoV-2 antigen test, she was brought to the hospital for COVID-19 medication. When she arrived at the hospital, she stated that she had been suffering from a high fever for about a week. In COVID-19, the dosage schedule for Favipiravir is 1800 mg twice a day on day 1 and 800 mg twice a day on day 2 and afterwards for 10 days (maximum 14 days).

The fever was reduced by discontinuing Favipiravir and diagnosed her with Favipiravir-induced drug fever based on positive results from a drug-induced lymphocyte stimulation test. Along with the remission of the fever, there was a drop in the serum concentration of Favipiravir. In COVID-19 patients using Favipiravir, drug fever should be considered in the differential diagnosis of relapsing fever episodes.⁴³

CONCLUSION

The COVID-19 pandemic has surfaced as one of the world's most serious deadly diseases. In addition to its relatively high fatality, the virus efficient transmission and apparent virulence have pushed satisfactory outcomes not just in terms of vaccines but also in terms of effective therapies. Various studies on the interaction between antiviral medications and coronavirus have been undertaken at the same time as vaccination and drug research is still ongoing. The review summarises the pharmacokinetics, mechanism of action ,clinical trials and antiviral activity of Favipiravir.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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