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Review Article

Emergency Approval of Favipiravir for Covid19 Infection in India

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Abstract

Novel Coronavirus or COVID-19 pandemic was first reported in Wuhan City, China in December 2019. According to WHO database the spread of infection has resulted in over 30 million infected people and over 943000 deaths worldwide till 19th September, 2020. Till date, unavailability of vaccines and specific antiviral drugs is a cause of grave concern. Worldwide,the search for the specific antiviral medication is underway. The Drug controller General of India (DCGI) has recently approved Favipiravir for emergency usage in mild to moderate Covid19 Indian patients. Favipiravir, an old antiviral drug marketed under the brand name Avigan by Fujifilm Toyama Chemical Co. Ltd, Japan, originally produced for Ebola Virus Disease has shown affirmative results in the treatment of COVID-19 across the globe. This article is an updated literature review conducted to determine the efficacy and safety of the drug Favipiravir (FPV) in general and in the treatment of COVID-19 across the globe. An extensive search was performed using keywords such as Favipiravir and SARSCoV-2 in platforms like Google Scholar and PubMed for the time period of 1st June 2000 to 31st July 2020. Common adverse effects of the drug include increased Liver enzymes and hyperuricaemia. Trials reported from Japan and Russia has proved the efficacy and safety of Favipiravir in Covid19 although published data from an Indian clinical trial is awaited. It appears to be a promising drug considering its oral formulation and safety profile, however, efficacy data from Indian patients are still awaited to recommend its wide spread usage.

Keywords: Favipiravir; COVID-19; Coronavirus

Introduction

The Coronavirus has created a global health crisis that made a huge impact on our daily life. On 31st December 2019, a cluster of pneumonia cases was reported by Wuhan Municipal Health Commission, China. Five days later, WHO published the report of the first outbreak. Since then the number of infected cases is rising every day. On 11th March 2020 due to the alarming levels of severity and spread of the infection, the World Health Organisation (WHO)

declared COVID-19 as a pandemic. The virus is a positive-sense RNA virus that belongs to the family *Coronaviridae* [1]. 17,338,525 unique cases and 673,070 deaths are reported as of July 30th, 2020 [2]. Researchers have revealed more than 30 agents that include Western medicines, natural products, and traditional Chinese medicines that might work against COVID-19 [3]. Many drugs such as chloroquine, remdesivir, arbidol, and favipiravir are currently undergoing clinical studies to test their efficacy and safety in the treatment of coronavirus disease [3].

Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a broad-spectrum antiviral drug that is discovered by Toyama Chemical Co. Ltd [4,5]. It is commonly used in Japan for the treatment of influenza since 2014. The drug targets RNA-dependent RNA polymerase (RdRp) enzymes, which is necessary for the replication of viral genomes. Favipiravir has a molecular weight of 157.1 g/mol and it has a high absorption rate of 97.6% [5].

It is commonly used to inhibit the replication of influenza A and B and can be used as an alternative option for other influenza strains, e.g. those that are resistant to neuraminidase inhibitors. It can also be used against other pathogens like COVID 19, Ebola virus, Lassa virus, arenaviruses, bunyaviruses, and filoviruses, which are known to cause fatal hemorrhagic fever [5]. Thus, it makes Favipiravir a promising drug for COVID 19. The clinical characteristics of COVID-19 include fever, cough, dyspnea, and pneumonia. The drug has been approved for use against COVID-19 in India, Russia and parts of the Middle East [6]. The Indian Central Drugs Standard Control Organization (CDSCO) has approved the generics of Favipiravir under the brand name of FabiFlu. According to Glenmark Pharmaceuticals, FabiFlu will be available as a prescription-based medicine, priced at INR 103 ($1.35)/tablet [7].

Structural analysis

Favipiravir (T-705) has both enol and ketone tautomers, the enol form having a structure resembling an aromatic phenol and the ketone form has a series of four conjugated double bonds, with hydrogen on the ring and nitrogen and ortho to the carbonyl group. Studies show that the enol form is more stable than the ketone form (referred to as T-705K). It is predicted that Gibb's energy of the enol form is 5.7kcal/mol lower than that of the keto form at 298K [8].

The structural analysis of Favipiravir indicated that there are four possible tautomers. F3 is the most stable structure followed by F1, F4, and F2. The tautomers are found to be available if the needed energy for tautomer formation is being supplied by processes such as intermolecular reactions and bonding [9].

Tautomerism is more feasible in small molecules compared to large molecules. Since Favipiravir is a small heterocyclic molecule, it can exhibit tautomerism. The highest energy level values for the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LOMO) could reveal the effects of the tautomerism process. The distribution patterns of HOMO and LOMO also detects the effects of tautomer formations. The energy difference between HOMO and LOMO levels which indicates the gap between two levels can also detect the effects of molecular conformational changes. It has been observed that the number of atoms is fixed in the tautomers but the movement of H atom among N and O atomic sites can bring about significant characteristic changes for the evaluated tautomeric structures [9].

The activity of the drug against COVID-19 has been detected by Molecular Docking simulations that use the tautomeric ligands and available protease(6LU7) and polymerase(6NUR) targeting enzymes. The values of binding energy and inhibition constant (KI) can be used to recognize the quantitative efficacy of each of the ligands on targets. The values of EB and KI obtained indicate that F1 is strongly capable of interacting with each polymerase and protease compared to the other F structures. The EB values for both protease and polymerase indicated that protease can be a better target for F1. The interaction of F ligands with protease is observed to be much stronger than with polymerase [9].

Mechanism of action

In viral replication, viral polymerases play a vital role. Depending upon the needs of a particular virus and genome type, RNA-dependent RNA polymerase, RNA-dependent DNA polymerase, DNA-dependent RNA polymerase, and DNA-dependent DNA polymerases are found [10]. These viral polymerases work as a single protein and carry out multiple functions related to viral replication, which includes recognizing the initial binding sites, controlling forward elongation of RNA, and termination of the replication process [10].

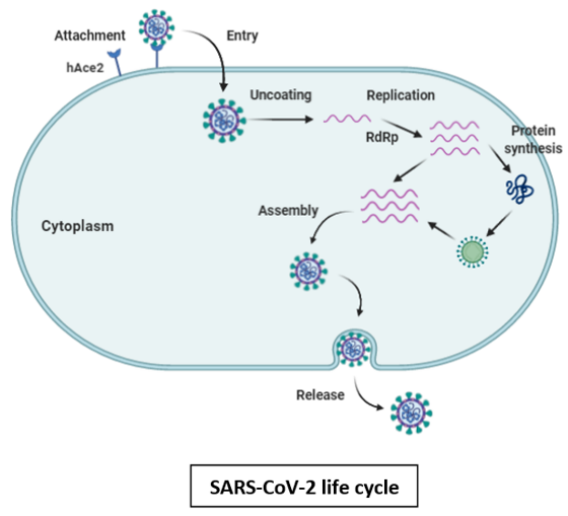

Figure 1

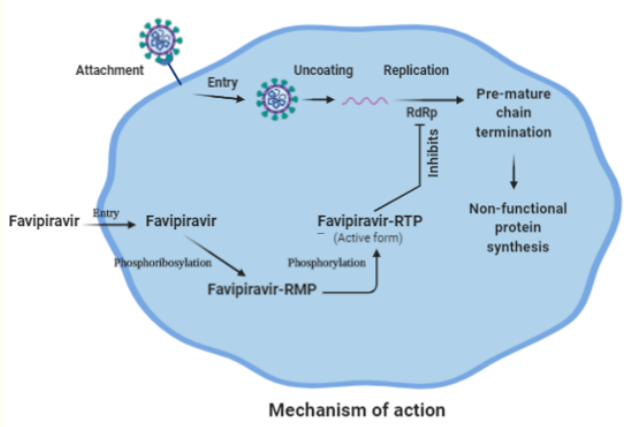

Figure 2

RNA dependent RNA polymerase (RdRp) is an essential enzyme found in RNA viruses that helps in the process of viral RNA replication. RdRps are multi-domain (α and β) proteins belonging to the Structural Classification of Proteins (SCOP) class 2.7.7.48 [11]. They catalyze RNA-template dependent formation of phosphodiester bonds between ribonucleotides in the presence of divalent metal ions [12]. The average length of the core RdRp domain is less than 500 amino acids and is folded into three subdomains; thumb, palm, and fingers resembling a right-handed cup [12]. Many viral polymerases own additional domains like methyltransferase or endonuclease domain to carry out functions related to RNA synthesis [11].

The viral RNA converts into a negative-sense RNA after the first replication. Favipiravir or T-705 (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) selectively inhibits replication of the influenza virus *in vitro* and *in vivo*. T-705 has been shown to be converted to T-705-4-ribofuranosyl-5-triphosphate (T-705RTP) by intracellular enzymes and then functions as a purine analog. That means it acts as a fake nucleotide that can selectively inhibit RNA-dependent RNA polymerase (RdRp) of the influenza virus [12]. Favipiravir (T-705) can also be converted to T-705RMP and T-705RTP by cellular kinases; T-705RTP is misidentified as a natural purine nucleotide by influenza virus polymerase so it gets incorporated instead of guanosine and adenosine that introduces point mutations in the viral genome.

Favipiravir terminates elongation after incorporating a single favipiravir molecule and after incorporating two consecutive favipiravir molecules, the synthesis of this complementary viral RNA is halted by chain termination which ultimately disrupts viral translation process [13-15].

As the host cell enzymes can differentiate between T-705, T-705RMP and T-705RTP from the natural nucleotides it is observed that T-705 doesn't have any influence on cellular DNA or RNA synthesis, thus making this drug effective for treating COVID-19 patients [16].

Pharmacokinetics

After oral administration of Favipiravir, at 2hrs the concentration of the drug increases to the maximum plasma concentration rapidly with a short-half-life of 2 - 5.5hrs [17, 18]. Plasma protein binding of the drug in human is 54% whereas the bound percentage of FPV to human serum albumin and α-1 acid glycoprotein were observed to be 65% and 6.5% respectively. The parent drug is eliminated from the body through the process of metabolism mainly by aldehyde oxidase (AO) and partially by xanthine oxidase resulting in the production of an inactive oxidative metabolite T-705M1. Most of the metabolites are excreted through the kidneys under hydroxylated forms which increases up to 80-100% after 7 days [17, 19]. The progression of FPV in the liver, followed by the gall bladder and segments of the intestinal tract after intravenous administration of FPV in mice, suggests rapid excretion of favipiravir by the liver in mice. The pharmacokinetic analysis of intravenous administration of the drug in cynomolgus macques after repetition of the

dose, indicated obvious non-linear pharmacokinetics one time and over a range of doses and a consistent decline in plasma concentration after 7 days of continuous administration in the nonhuman primates is also observed. From the trial for Ebola Virus Disease (EVD) named as the JIKI trial, favipiravir plasma concentration indicated that steady state trough concentration decreased on day 4 compared to day 2. The in-vivo biodistribution and kinetics of uptake and elimination of FPV after single and repeated doses, an ^{18}F radiolabelled favipiravir was developed. The dynamic distribution of the radiolabelled drug was evaluated by positron emission tomographic dynamic scans and gamma counting in naïve mice and favipiravir predosed mice (loading dose 250 mg/kg b.i.d, day 1 and a dosage of 150 mg/kg twice daily for 3 days). It was observed in the naïve mice, that tail venous administration of the radiolabelled favipiravir resulted in the rapid uptake and excretion via liver, kidneys and intestine. In the predosed mice, there was 25 - 30% decrease in the plasma concentration whereas tissue distribution in the liver, stomach, brain and muscle tissues increased 2 - 5 times. It is assumed that tissue retention of favipiravir might be dependent on its ribosylated and phosphorylated form. The increased distribution by predosing is assumed to promote cellular uptake and the efficacy of the drug against a broad spectrum of viruses [17]. Studies *in vitro* indicate that FPV has the ability to inhibit the activity of AO in concentration-dependant and time-dependant manner which explains the self-inhibition of the inactivation metabolism of the parent drug and increased plasma parent/inactive metabolite ratio (T705/T705M1) after chronic dosing. An increased circulating ratio (T705/T705M1) in mice supposedly facilitates the cellular uptake and entraps the FPV in tissues owing to the increase of extracellular to an intracellular concentration gradient. This further explains the rapid clearance of FPV after repeated administration. The formation of T-705 RTP is also observed in human peripheral blood mononuclear cells (PBMCs) and the terminal half-life ($t_{1/2}$) was about 2h in PBMCs. The $t_{1/2}$ was shorter in PBMC than that in the lungs (4.2h). It is suggested that the detection of T-705 RTP in PBMC might serve as surrogate depending upon the availability of peripheral blood [18].

Dosage regimen

The dosage regimen is very crucial in clinical trials for the treatment of viruses. The IC_{50} of FPV varies on the type of virus being treated. Thus, the dosage requirement would be different in case of various types of treatments [17, 5].

The dosing regimen for COVID-19 includes a loading dose of 3200 mg (1600 mg twice on Day 1) followed by a maintenance dose of 1200 mg (600 mg twice a day) from day 2 to day 14 and has been proven to be effective [20].

A lower plasma concentration of 50% was observed in American patients in comparison to Japanese patients during the clinical development of the drug in USA. So it is assumed that there is a possibility of regional or ethnic difference in the pharmacokinetics of the drug [17].

Drug and drug interaction

The use of multiple drugs in the treatment of COVID-19 might be dangerous in case of patients with comorbidities such as hypertension, diabetes, acute respiratory distress syndrome and acute kidney injury. FPV is not metabolised by the microsomes of human liver but is metabolised to T-705M1 in human liver cytosol by aldehyde oxidase without NADPH. A study on healthy volunteers revealed that post concomitant administration of FPV, the area under the curve (AUC) values of acetaminophen and acetaminophen glucuronide increased by about 20% and 23-34% respectively. In contrast, the AUC value of acetaminophen sulfate was seen to be decreased by 29-35%. The total concentrations of acetaminophen and acetaminophen glucuronide was found to be increased and that of acetaminophen sulfate was significantly decreased in urine samples. Co-incubation with human liver S9 inhibits the formation of acetaminophen sulfate with an IC_{50} value of 24 μg/ml, suggesting inhibition on the sulfate transferase. Although it had no effect on the formation of acetaminophen glucuronide. In combination with favipiravir, the recommended dosage of acetaminophen are 3g per day.

In vitro studies indicate that the potent inhibitors of AO include selective estrogen receptor modulators (raloxifene, tamoxifen), cimetidine, calcium channel blockers (felodipine, amlodipine and verapamil), propafenone and amitriptyline. Although the clinically relevant DDI based on AO inhibition has yet to be established, an obvious DDI between cimetidine and zaleplon is reported. Cimetidine coadministration results in a marked inhibition on AO catalyzed oxozaleplon formation and a warning is included in the zaleplon label. Potential DDIs between these drugs and favipiravir should be carefully monitored. Several drugs, such as citalopram, zaleplon, famciclovir, and sulindac are also metabolized by AO. *In vitro* study shows that favipiravir is a mechanism based inhibitor

of AO in a concentration-dependent manner between 3.14 and 942 µg/mL and the previous clinical study showed a mean steady-state trough concentration of 46.1 µg/ mL in the treatment of EVD. Therefore, potential DDIs between favipiravir and these latter drugs should also be monitored with caution [17].

Clinical trials

In an open-label control study, a total of 147 COVID patients of The Third People's Hospital, Shenzhen was taken to perform an experimental treatment from 30 January to 14 February 2020.

147 people were then divided into two groups (56 patients in FPV arm and 45 patients in the control arm). All patients admitted to both the FPV and the control arms of the study were assessed for eligibility criteria. FPV (Zhejiang Hisun Pharmaceutical Co., Ltd., 200 mg per tablet) was given orally. The dose was 1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2 - 14.

LPV/RTV (AbbVie Inc., 200 mg/50 mg per tablet) were also given orally in the control arm. The dose was LPV 400 mg/RTV 100 mg twice daily. As this study is about FPV so we'll only concentrate on the Favipiravir study.

The efficacy of the treatment was assessed by the time of viral clearance and the improvement rate of chest computed tomography (CT) scans on Day 14 after treatment.

In the FPV arm, 56 patients were taken into account in which 21 were excluded from the study. The rest 35 people were treated with 1600 mg of FPV twice on Day1 and after that 600 mg twice a day from day 2 - 14. After 14 days of drug administration, the reports were compared with the control arm patients.

Some onset symptoms were seen in the patients during this study; Fever (22), cough (12), headache/myalgia (3), diarrhea (1), stuffy nose/sore throat (6). The efficacy of the treatment was determined by analyzing the time of viral clearance and the improvement rate of the chest with the help of computed tomography (CT) scan on Day 14 after treatment.

The total number of adverse events in the FPV arm of the study was 4, (11.43%), compared to 25adverse events (55.56%) in the control arm, which was significantly fewer. It is also seen those treated with FPV appeared to have faster viral clearance. However, the adverse events in the experimental arm were rare and tolerable, and none of the patients needed to discontinue FPV treatment [20].

Ongoing clinical trials

Registration number	Design	Phase	Study title	Region of study	Sponsor
CTRI/2020/05/025114	Randomized, parallel group trial	Phase 3	A Clinical study on Favipiravir compared to standard supportive care in patients with mild to moderate COVID-19	Chhattisgarh, Maharashtra, Gujarat, Delhi	Glenmark Pharmaceuticals
CTRI/2020/06/025799	Randomized, parallel group trial	Phase 3	A study of Favipiravir in patients with mild to moderate coronavirus disease (COVID-19)	West Bengal, Maharashtra, Uttar Pradesh, Gujarat	Glenmark Pharmaceuticals
NCT04425460	Randomized	Phase 3	Amulti-centre, randomized, double-blind, placebo-controlled, phase 3 study evaluating Favipiravir in treatment of COVID-19	China, Germany, Romania	Zhejiang Hisun Pharmaceutical Co. Ltd.
NCT04336904	Randomized	Phase 3	Clinical study to evaluate the performance and safety of Favipiravir in COVID-19	Milano, Italy	GiulianoRizzardini
NCT04346628	Randomized	Phase 2	Oral favipiravir compared to placebo in subjects with mild COVID-19	Stanford University, USA	Stanford University, USA

Table 1

Limitations

Some disadvantages might cause serious concerns in the patients:

- Favipiravir is teratogenic; that means it can disturb the development of a fetus. Therefore, the administration of favipiravir should be avoided in women if pregnancy is confirmed or suspected [9].
- Symptoms of overdose include not only reduced body weight, vomiting, and decreased locomotor activity but also adverse effects on hematopoietic tissues such as decreased red blood cell (RBC) production, and increase in liver function parameters such as aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT) and total bilirubin, and increased vacuolization in hepatocytes [21].
- Testis toxicity was also noted.
- Impairment of mitochondrial function is increasingly recognized as an underappreciated cause of drug toxicity, which has resulted in post-marketing drug withdrawals [22].
- Favipiravir can elevate blood uric acid levels, but this effect is reversed after discontinuation of the drug. Since favipiravir is not used for long periods of time for the treatment of viral infection, the effect on blood uric acid levels was subclinical in most studies [23].
- Glucocorticoids have an overall immunosuppressive effect, and these are often used in patients with inflammatory and autoimmune diseases. While glucocorticoids are also often prescribed in sepsis, available evidence does not favor their use to ameliorate the deleterious effect of lung inflammation caused by viral infections [24].

Conclusion

Favipiravir, a broad spectrum anti-viral drug has been approved on emergency purpose for the treatment of mild to moderate COVID-19 Indian patients. Its main advantage is the oral route of administration which other emergency approval drugs like Remedesivir lack. At the time of writing this article, a vial of Remedesvir was available at Rs. 5000 per vial whereas the cost of Favipiravir tablet was Rs 103 per 200 mg tablet. Hence, the cost advantage is evident with Favipiravir however a head to head clinical trial is required to understand the cost effectiveness between these two Covid19 medications in the country.

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