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Review

Role of favipiravir in the treatment of COVID-19

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ABSTRACT

The coronavirus disease-2019 (COVID-19) outbreak all over the world has led the researchers to strive to develop drugs or vaccines to prevent or halt the progression of this ailment. To hasten the treatment process, repurposed drugs are being evaluated. Favipiravir is one such oral drug that was approved for new and reemerging pandemic influenza in Japan in 2014 and has shown potent *in vitro* activity against severe acute respiratory syndrome coronavirus-2. It has a wide therapeutic safety margin indicated by a wide CC50/EC50 ratio for a high dose. From the clinical studies in COVID-19, it has shown rapid viral clearance as compared to lopinavir/ritonavir (LPV/RTV) and superior recovery rate than umifenovir. Overall, favipiravir has shown promising results in clinical studies in China, Russia, and Japan, and more trials are underway in multiple countries, including USA, UK, and India. Recently, treatment guidelines from many countries and some states from India have included favipiravir in the treatment protocol. This review provides insights into the evidence-based evolving role of favipiravir in the management of COVID-19 infection with emphasis on benefits of initiating an early antiviral therapy with special focus on favipiravir, its pharmacodynamic, pharmacokinetic, *in vitro*, clinical data, and inclusion in the treatment protocols of COVID-19.

Background of pandemic

The coronavirus disease-2019 (COVID-19) pandemic that originated in December 2019 in Hubei Province of China has walloped every continent except Antarctica. COVID-19 is an infectious disease associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel coronavirus (Perlman, 2020; Zhang et al., 2020). Although the world has survived numerous pandemics in old times, this one is an unprecedented global health challenge that has redefined our lives and continue to have a devastating socioeconomic impact around the world.

SARS-CoV-2 is a positive-sense single-stranded ribonucleic acid (RNA) virus, which has an incubation period of up to 14 days and an infectivity rate (R_0) from 1.5 to more than 6 in some regions. Viral shedding may be seen 1–2 days before symptoms and may continue for 1–2 weeks in mild-moderate cases and in severe cases it may go beyond 2 weeks. In the early phase of infection, the viral titers may be at its peak. In approximately 30%–60% of patients shedding virus, there may be no symptoms. There is a higher risk of infection and severe symptoms in the elderly population and among those having comorbid conditions. Symptoms usually appear between 2 and 14 days after exposure. Approximately 80%–90% of infections are mild or moderate and many may be asymptomatic (Auwaerter, 2020). Dyspnea can occur in approximately 40% of symptomatic at around weeks after symptom onset, which leads to progressive illness (severe in 14% and critical in 5%), including the hyper inflammatory phase causing multiorgan system failure (Berlin et al., 2020).

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Hit early-hit hard principle with antivirals

Clinical studies have shown that antivirals previously tested for other coronaviruses like SARS-CoV and MERS-CoV as well as other RNA virus infections, shorten the course of the disease by targeting the key enzymes of SARS-CoV-2 thus interfering with the viral cycle inside the host cell, reducing the viral load and viral shedding (Saber-Ayad et al., 2020). The antiviral drugs administered shortly after the onset of symptoms can shorten the course of clinical illness and it can reduce the infectiousness to others by reducing viral shedding (Saber-Ayad et al., 2020; Mitjà and Clotet, 2020). Goyal et al. (2020) has performed a mathematical modeling to predict the impact of promising antiviral treatment. It has been reported that if a patient receives antiviral therapy in the early phase of infection, there are high chances that the duration of shedding and intensity of the effector immune response may decrease; however, there may be a limited impact on viral area under the curve (AUC) possibly owing to higher levels of early SARS-CoV-2 replication. Hence, it was predicted that the only option to limit viral AUC is dosing of antivirals at the earliest, possibly at the presymptomatic phase before the peak viral load (Goyal et al., 2020). This supports the hit hard hit early principle.

Why early antiviral treatment is key?

COVID-19 has placed an enormous burden on the healthcare system due to its transmission dynamics and polyphasic nature of illness. Currently, there is a lack of evidence of the development of herd immunity, availability of an effective vaccine would likely take some time. Therefore, therapeutic strategies based out of potent antiviral drugs against SARS-CoV-2 are essential to curtail the impact of subsequent local waves of COVID 19. Torneri et al. (2020) demonstrated the impact of antiviral intervention on local outbreaks in a simulation study. The implementation of antiviral drugs together with quarantine showed a substantial reduction of the final size and the peak incidence of the outbreak. The model supported the administration of antiviral drug to the diagnosed and traced individuals, to suppress the outbreaks that are most challenging. This role of effective antivirals to alter the spread of COVID-19 by influencing the viral load and infectiousness of the infected upon quarantine need to be tested in robust clinical trials in a larger population. However, currently the antiviral drugs, including favipiravir, are mostly evaluated in clinical studies as a treatment strategy. On this basis, favipiravir is used in clinical practice in the treatment of COVID-19 in a few countries, wherein it is approved. However, the benefits of antiviral intervention on local outbreak in community transmission is yet to be deciphered. Finally, the practical utility of such an intervention strategy will depend upon the dose, duration, and cost of it along with implementation challenges.

Wu et al. (2020) has performed ranking of the parameters at the baseline, which influences the progression of COVID-19 by orthogonal partial least-squares discriminant analysis. Only comorbidity and time from illness to antiviral treatment are statistically significantly associated with the severity of disease in the multivariate analysis. It has also shown that the time for antiviral therapy initiation is significantly shorter in mild illness as compared to severe illness.

A retrospective cohort study from New York in 678 hospitalized patients with COVID-19 showed that high viral load was independently associated with mortality (adjusted odds ratio [aOR] 6.05 and $p < 0.001$) and intubation (aOR 2.73 and $p < 0.001$) than patients with medium and low viral load (Magleby et al., 2020). Viral load in the upper respiratory tract (URT) peaks early in mild patients (4 days) as compared to in moderate-severe patients (8 days). Similarly, viral load in lower respiratory tract (LRT) peaks early in mild patients (6 days) than in moderate-severe patients (11 days); however, variability in data can occur because of inconsistency in cycle threshold (Ct) value of gene, the use of different RT-PCR or RNA extraction kits, and combining samples to URT and LRT specimen (Figure 1) (Weiss et al., 2020).

Favipiravir — a repurposed drug for COVID-19

Every country is attempting to manage this pandemic through contact tracing, accelerated testing, treatment, and physical distancing. To develop an oral therapy or vaccines, efforts are being made by many researchers to unravel the effect of known antiviral drugs against COVID-19. Thus, to repurpose the potential antiviral drugs is a pragmatic way to speed up the drug approval process. The RdRp (RNA-dependent RNA polymerase) lies in the core of coronavirus replication machinery, nsp12 protein, which has an important role in the viral life cycle, lack of host homologs and a high level of sequence and structural conservation making it a target for therapeutic interventions (Shannon et al., 2020). Drugs like nucleoside analogs and small molecule drugs that are metabolized intracellularly into their active ribonucleoside 5′-triphosphate (RTP) forms and incorporated into the nascent viral RNA by error-prone viral RdRps leading to chain termination or leads to the accumulation of deleterious mutations. Favipiravir, an oral, broad spectrum RdRp inhibitor, an already approved drug for new and reemerging pandemic influenza in Japan and has an established and well-characterized safety profile (https://www.pmda.go.jp/files/000210319.pdf/2020). Reports of *in-vitro* studies have demonstrated that favipiravir can have an effective concentration against the SARS-CoV-2 infection within a safe therapeutic

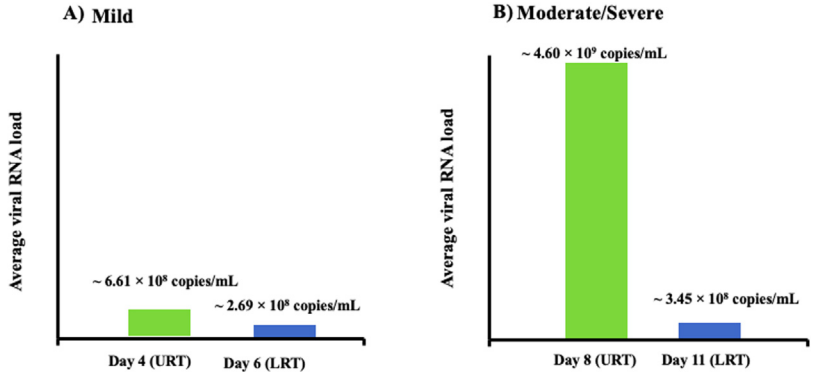

Figure 1. Average viral load and disease severity (Weiss et al., 2020).
LRT, lower respiratory tract and URT, upper respiratory tract.
Note: Average peak SARS CoV-2 load from URT and LRT as per clinical severity.

dose. Additionally, favipiravir, being an oral formulation and considering ~80% burden of patients with mild to moderate COVID-19, is hence likely to address the unmet clinical needs of a sizeable majority of the population of COVID-19, which mostly can be treated on an outpatient basis. Furthermore, the COVID-19 task force committee of India has ranked favipiravir as one of the most promising drugs based on readiness score considering the strength of scientific evidence, importance of mechanism of action and target, strength of results at the preclinical stage, availability of human safety data, bioavailability, clarity, and certainty of formulation method, progress of clinical trials in COVID-19, and certainty of manufacturing. Early clinical studies from China have shown promising results in terms of reduction in viral load as well as improvement in clinical and radiological outcomes (Cai et al., 2020; Chen et al., 2020).

The current review provides an overview of *in-vitro* data, dosing rationale, and pharmacological profile of favipiravir. A brief discussion about the available evidences from the completed clinical trials and medical appraisal of favipiravir for COVID-19 is summarized. Additionally, some light is thrown on the treatment recommendations pertaining to its inclusion in treating COVID-19 and the approval status in other countries.

Favipiravir: profile, clinical evidence, and recommendations in treatment guidelines

Background of a promising repurposed drug for COVID-19

Favipiravir was discovered through the screening of a chemical library for antiviral activity against the influenza virus by the Toyama Chemical Co., Ltd. by chemical modification of a pyrazine analog in a pyrazine carboxamide derivative (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) (Furuta et al., 2017). The worldwide development of favipiravir was conducted by FUJIFILM and MediVector (https://adisinsight.springer.com/drugs/800014667/2020). It is a prodrug (T-705) with lower molecular weight of 157.1 g/mol. It was approved for medical use in Japan, in 2014, for the treatment of the new or reemerging pandemic influenza virus infections (Shiraki and Daikoku, 2020; Hayden and Shindo, 2019). In February 2020, favipiravir was also approved for the treatment of novel influenza in China and is further being studied in the Chinese population for experimental treatment of the emergent COVID-19 (Li and De Clercq, 2020).

Favipiravir has proven efficacy against a broad range of influenza viruses, including A(H1N1)pdm09, A(H5N1), and A (H7N9) avian virus. Additionally, it may halt the replication of several other RNA viruses, including arenaviruses, phleboviruses, hantaviruses, flaviviruses, Western equine encephalitis virus, noroviruses, and ebola virus (Furuta et al., 2013)

Mechanism of action (Table 1; Figure 2)

Favipiravir (prodrug) is a purine base analog that is converted to active favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP) by intracellular phosphoribosylation. It is a selective and potent inhibitor of RNA-dependent RNA polymerase (RdRp) of RNA viruses. Favipiravir is incorporated into the nascent viral RNA by error prone viral RdRp, which leads to chain termination and viral mutagenesis (Baranovich et al., 2013). The RdRp existing in various types of RNA viruses enables a broader spectrum of antiviral activities of favipiravir (Shannon et al., 2020; Jin et al., 2013). After RNA viral incorporation, favipiravir-RTP works as a mutagen, which is capable of fleeing coronavirus repair machinery. The favipiravir-RTP adds to the pressure on CoV nucleotide content, which already has a low cytosine (~17.6%) in the SARS-CoV-2 genome. In total, along with the increased frequency of mutation, favipiravir-RTP has a positive effect on SARS-CoV-2 by a cytopathic effect, which is induced by the virus, reduction in the number of viral RNA, and infectious particles (Shannon et al., 2020). Favipiravir has a strong binding affinity to RdRp with a docking score of −6.925. Hence, favipiravir targets the Achilles heel (RdRp complex) of SARS-CoV-2.

In vitro *data against SARS CoV-2*

A recent *in vitro* study by Wang et al. (2020a,b) reported the efficacy of favipiravir to reduce the SARS-CoV-2 infection. Favipiravir has half-maximal effective concentration (EC_{50}) of 61.88 μM, half-cytotoxic concentration (CC_{50}) >400 μM, and a selectivity index (SI) >6.46. The EC_{50} is similar to its EC_{50} against Ebola (67 μM), which justifies the need for a high dose to achieve a pharmacologically relevant target trough concentration of 40–80 μg/mL in COVID-19 (Du and Chen, 2020a). The wide gap between CC_{50} and EC_{50} gives a comfortable safety margin for a high dose of favipiravir.

Pharmacokinetics of favipiravir (Du and Chen, 2020b)

Favipiravir undergoes metabolic activation through ribosylation and phosphorylation to form the activated metabolite favipiravir-RTP in the tissues. Favipiravir at 1600 mg on day 1, then 400 mg twice-a-day from day 2 to day 6 followed by 400 mg once-a-day on day 7 has an estimated AUC of 1452.73 μg h/mL on day 1 and 1324.09 μg h/mL on day 7. It is primarily metabolized by hepatic enzyme aldehyde oxidase and partially by xanthine

Table 1
Features and properties of favipiravir (Furuta et al., 2013; https://pubchem.ncbi.nlm.nih.gov/compound/Favipiravir/2020; Caroline et al., 2014).

Chemical name	6-Fluoro-3-oxo-3,4-dihydropyrazine-2-carboxamide
Alternative names	T-705, Fapilavir, and favilavir
Class	Antiviral agent
Spectrum of activity	RNA viruses, including West Nile virus, yellow fever virus, foot-and-mouth disease virus, enterovirus, and rift valley fever
Mechanism of action	Favipiravir-RTP binds to and inhibits RNA-dependent RNA polymerase (RdRp), which ultimately prevents viral transcription and replication
Route of administration	Oral
Posology	Prophylaxis (from ongoing clinical trial [NCT04448119]): 1600 mg orally twice daily on day 1 followed by 800 mg orally twice a day on days 2–25. Treatment: 1800 mg twice a day on day 1, followed by 800 mg twice a day maximum up to 14 days in mild to moderate COVID-19 patients.
Pharmacokinetics	Elimination half-life is 2–5.5 h, Bioavailability is 97.6%, mean Cmax is 51.5 μg/mL, parent volume of distribution is 15–20 L, and metabolites are cleared renally.
Pharmacodynamics	54% plasma protein-bound, functions as a prodrug and undergoes ribosylation and phosphorylation intracellularly
Most frequent adverse effects	Mild to moderate diarrhea, increase of blood uric acid and transaminases, and decrease in the neutrophil counts Overdose causes but are not limited to reduced body weight, vomiting, and decreased locomotor activity
ATC code	J05AX27

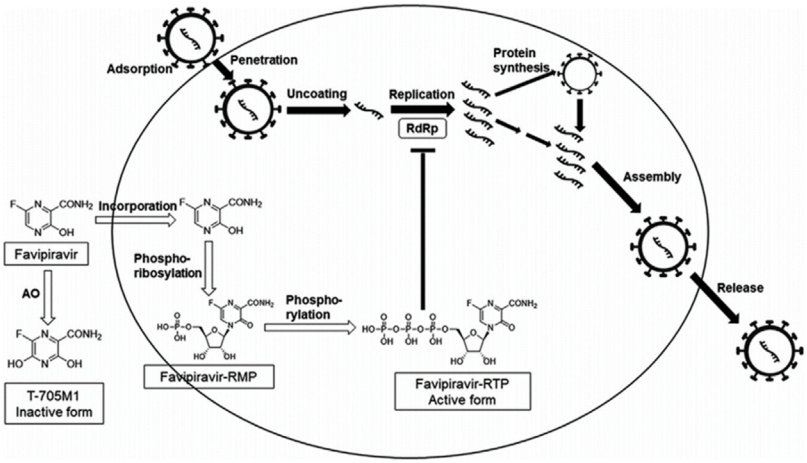

Figure 2. Favipiravir MOA in SARS-CoV-2.

oxidase to an inactive oxidative metabolite that is excreted in the hydroxylated form by the kidneys (Madelain et al., 2016). It exhibits a nonlinear pharmacokinetics.

It is capable of boosting its own concentration by dose- and time-dependent self-inhibition of aldehyde oxidase. The self-inhibition of metabolism and formation of favipiravir–inactive metabolite in the liver after continuous use may result in an increase in circulating favipiravir/inactive metabolite ratio, and thus facilitate the uptake and activation of favipiravir-RTP in the tissues. A decrease in trough concentrations of favipiravir does not mean a decreased exposure of the active metabolite favipiravir-RTP in the tissues (Du and Chen, 2020a). It is predicted to exceed plasma concentrations over the EC_{90} by more than two-fold that further supports its sufficient systemic antiviral exposure (Arshad et al., 2020).

When favipiravir was administered orally (day 1: 1200 mg twice a day; days 2–4: 800 mg twice a day) in volunteers with mild to moderate hepatic impairment, a 1.4–1.8-fold increase in C_{max} and AUC was observed. However, in severe hepatic impairment favipiravir (day 1: 800 mg twice a day; days 2–3: 400 mg twice a day) resulted in 2.1-fold and 6.3-fold increase in C_{max} and AUC, respectively (Fabiflu Prescribing Information).

Use of favipiravir in patients with moderate renal impairment (GFR < 60 mL/min and ≥30 mL/min) results in a 1.5-fold increase in C_{trough} than in patients with normal renal function; however, there is no evidence of its use among patients with GFR < 30 mL/min (Fabiflu Prescribing Information).

Safety profile

Favipiravir has an established and well-characterized safety profile from 4000+ patients (Pilkington et al., 2020). The common adverse events (AEs) include gastrointestinal AEs, uric acid elevations, decrease of neutrophil count, increase of aspartate aminotransferase (SGOT), increase of alanine transaminase (SGPT), psychiatric symptom reactions, and increase in blood triglycerides. The proportion of serious AEs was 0.4% and 1.1% discontinuation due to AEs (Fabiflu Prescribing Information). Similar proportions of AEs were reported between low and high doses of favipiravir. It demonstrates a favorable safety profile with respect to total and serious AEs.

Contraindications, precautions, and warning

It is contraindicated in pregnant and lactating women. Because of the observation of its teratogenic potential in animal studies, it is contraindicated in pregnant and suspected pregnant women. It is found distributed in sperms; hence, it is advised to use effective contraceptive methods by both women and men of reproductive age during the course and 7 days post-therapy (Nagata et al., 2015; Delang et al., 2018). Additionally, it is contraindicated in patients with hypersensitivity, severe hepatic impairment, and severe renal impairment. Favipiravir should be administered with care in patients with gout or a history of gout, with hyperuricemia (Fabiflu Prescribing Information).

Drug–drug interactions

Precautions are advised while administrating pyrazinamide, repaglinide, theophylline, famciclovir, and sulindac (Obach et al., 2004). The partial data are available regarding its interaction with other drugs. Previous studies report an increased AUC of acetaminophen and acetaminophen glucuronide with coadministration of favipiravir (Obach et al., 2004). A potential risk of drug interaction occurs between the drugs that inhibit aldehyde oxidase, and favipiravir needs to be monitored cautiously. It needs to be carefully administered and monitored in the elderly; however, clinical studies are yet to be conducted in children.

Indications and dosing regimen

The dosing regimen is an important part of successful antiviral therapy. The approved favipiravir dosing regimen for influenza in Japan is a loading dose of 3200 mg on day 1, followed by a maintenance dose of 600 mg twice daily on days 2–5 (Furuta et al., 2017; Wang et al., 2020a,b). The JIKI trial conducted during the Ebola virus disease (EVD) outbreak demonstrated an improved survival rate in patients with moderate to high (Ct ≥20) viral load with the higher dose of favipiravir (day 0: 6000 mg and from day 1 to day 9: 2400 mg/day) (Sissoko et al., 2016). Similarly, Bai et al.'s (2016) study showed a significant reduction in viral load with favipiravir in patients with moderate viral load at baseline. These findings support the role of favipiravir in viral load reduction in medium to high viremia though not in very high viremia of EVD. In the perspective of COVID-19 treatment, a higher dose of favipiravir needs to be considered to have an impact on the viral load, since EC50 of favipiravir is higher than that of influenza. The current recommended regimen of favipiravir is 1800 mg of loading dose BID on day 1 followed by 800 mg BID from day 2 to maximum of day 14 (Fabiflu Prescribing Information).

Table 2
Summary of clinical evidence in patients with COVID-19 infection.

Author [reference]	Study type	Comparative studies				
		Variables	Favipiravir	*vs.*	Lopinavir/ritonavir[a]	p Value
Cai et al. (2020)	Interventional, open label, non-randomized clinical study	Viral clearance rate	4 days		11 days	<0.001
		Chest computed tomography	91.4%		62.2 %	0.004
		Adverse events	11.4%		55.6%	<0.001
		Variables	Favipiravir	*vs.*	Umifenovir	p Value
Chen et al. (2020)	Interventional, open label, randomized, and multicenter clinical trial	Clinical recovery rate at day 7	71.4%		55.8%	0.0199
		Latency for fever and cough relief	Significantly shorter		Higher	<0.0001
		Dyspnea after medication	3.5%		11.7%	0.0174

Single arm studies

Study		Variables	Outcome at day 7	Variables	Outcome at day 14
Doi et al. (2020b)	Observational registry	Clinical recovery rate — mild	73.8%	Clinical recovery rate — mild	87.8%
		Clinical recovery rate — mod	66.6%	Clinical recovery rate — mod	84.5%
		<60 yrs.: clinical recovery rate	79.0%	<60 yrs.: clinical recovery rate	92.4%
Rattanaumpawan et al. (2020)	Multicenter observational study	Clinical improvement (without O2 supp.)	92.5%	–	–
		Clinical improvement (overall)	66.7%	–	–
		Poor prognostic factors by multivariate analysis	Lower favipiravir loading dose (≤45 mg/kg/day) (p = 0.006)	–	–

[a] *Note*: A moderate-sized, randomized trial failed to find a virological or clinical benefit of lopinavir/ritonavir over SOC; hence, comparing favipiravir to lopinavir/ritonavir, was essentially comparing favipiravir to placebo (Cao et al., 2020).

Global clinical studies of favipiravir usage in COVID-19 (Table 2)

An open-label control study in Chinese (N = 80) patients with mild to moderate COVID-19 was conducted to examine the effects of favipiravir *vs.* LPV/RTV for the treatment of COVID-19 (Cai et al., 2020). Favorable results were obtained with favipiravir revealing shorter viral clearance time (median [interquartile range, IQR], 4 [2.5–9] days *vs.* 11 [8–13] days). It also showed a significant improvement rate in chest imaging (CT) (91.43% *vs.* 62.22%; p = 0.004) and higher improvement rates of chest CT in the group with viral clearance within 7 days of treatment were observed. Multivariate logistic regression showed that the antiviral therapy independently affected the CT changes. Multivariable Cox regression showed that favipiravir was significantly (p = 0.026) associated with faster viral clearance, additionally the timing of antiviral therapy reached near significance (p = 0.055). Favipiravir was better (p < 0.001) tolerated than LPV/RTV. The major limitation of this study was that it was not randomized, double-blinded, and placebo-controlled (Cai et al., 2020; Dong et al., 2020).

Another prospective, randomized, controlled, open-label multicenter trial involving 240 adult patients with COVID-19 from China was conducted to evaluate favipiravir *vs.* umifenovir for COVID-19 (Chen et al., 2020). Around 90% patients had moderate disease and the clinical recovery rate on day 7 was significantly higher (p = 0.019) with the favipiravir group (71.4%) than umifenovir (55.8%). Favipiravir significantly shortened the latency to relief for pyrexia and cough than umifenovir. No difference between the groups was observed for rate for the auxillary oxygen therapy or noninvasive mechanical ventilation, overall respiratory failure rate, ICU admission or all-cause mortality; however, dyspnea was significantly (p = 0.017) lesser in the favipiravir group than in the umifenovir group (Chen et al., 2020).

The preliminary report of the favipiravir observational registry from Japan in 2158 COVID-19 cases 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 (http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_en_200529.pdf/2020). However, the clinical improvement rate among patients less than 60 years of age were 79% and 92.4% at day 7 and day 14, respectively. Approximately 52.3% patients aged more than 60 years and around half of the patients had atleast one of the comorbodities (diabetes, cariovascular diseases, chronic lung diseases, and /or immunospuression. More than 90% of patients received 1800 mg of favipiravir twice a day on first day followed by 800 mg twice a day. On average, favipiravir was started within three days of hospitalization or RT-PCR and the average length of favipiravir therapy was 10.4 days. One important limitation at this point is that these clinical studies are not published in a peer-reviewed journal and may lack the robust clinical guidance (Esposito et al., 2020). Hyperuricemia (15.5%) and liver function (7.4%) abnormalities were the most commonly observed AEs associated with favipiravir use (http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_casereport_en_200529.pdf/2020).

The Russian Government approved favipiravir for the treatment of COVID-19, on the basis of encouraging early readouts from ongoing open-label randomized adaptive design clinical trial [COVID-FPR-01] in a 390-patient population. Results from 60 patients (40 on favipiravir and 20 on SOC) showed faster fever resolution (3 days *vs.* 6 days), rapid viral elimination (4 days *vs.* 9 days), and RT-PCR negativity up to 87.5% by day 10 (https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/russian-drug-to-treat-covid-to-be-delivered-to-hospitals-in-june/articleshow/76131135.cms/2020; https://clinline.ru/reestr-klinicheskih-issledovanij/180-23.04.2020.html).

An recent retrospective observational study from Thailand, which included hospitalized patients with COVID-19 who do not require oxygen supplementation demonstrated clinical improvement (day 7: 92.6%) by day 7 with favipiravir. Additionally, a multivariate analysis demonstrated a lower favipiravir loading dose (≤45 mg/kg/day) [p = 0.006] as one of the day-7 prognostic

factors, which negatively impact the clinical outcomes (Rattanaumpawan et al., 2020).

Latest prospective, randomized, open-label trial of early *versus* late favipiravir in hospitalized patients with COVID-19 published in a peer-reviewed journal done at 25 hospitals across Japan showed a trend toward 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, faster 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) (Doi et al., 2020a).

Indian clinical trial of favipiravir — an update

Recently, a phase 3, open label, randomized, multicenter study (CTRI/2020/05/025114, Glenmark Pharmaceuticals) was initiated in India to determine the efficacy of favipiravir in patients infected with mild to moderate COVID-19 in line with the global trials ongoing for this drug (http://www.ctri.nic.In/Clinicaltrials/pdf_generate.php?trialid=43504&EncHid=&modid=&compid=%27%2743504det%27/2020). The study enrolled patients with both mild (N = 90) and moderate (N = 60) COVID-19 by stratified randomization based on baseline disease severity. The primary objective of this study was to evaluate the clinical efficacy and safety of favipiravir combined with standard supportive care. The primary endpoint was time until the cessation of oral shedding of SARS-CoV-2 virus. The secondary endpoints included — time from randomization to clinical cure based on clinician assessment, rate of clinical cure at day 4/7/10/14, rate of SARS-CoV2 RT-PCR negativity at day 4/7/10/14, time from randomization to first time use of high flow supplemental oxygen/noninvasive ventilation/mechanical ventilation/extracorporeal membrane oxygenation, and time from randomization to hospital discharge. The total duration of study participation had been a maximum of 28 days from the day of randomization. The results from this study will be pivotal in the further substantiation of global evidence on the efficacy and safety therapy against COVID-19.

Global treatment guidelines/recommendations

The current Centers for Disease Control and Prevention (CDC) guidance for the clinical care of patients with COVID-19 (as of March 2020) stresses on the absence of specific treatment for COVID-19 and emphasizes that management should include the prompt implementation of recommended infection deterrence and control measures and managing complications (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html/2020). At the time of writing of the manuscript, Japan, Russia, Saudi Arabia, Thailand, Kenya and four states, including Maharashtra from India have recommended the usage of favipiravir oral therapy in mild to moderate COVID-19 in the treatment guidelines. The Japanese Association for Infectious Diseases recommended 3600 mg (1800 mg BID) on day 1 and 1600 mg (800 mg BID) from day 2 onwards, for up to 14 days (http://www.sukl.cz/file/92991_1_1/2020). The Russian guidelines for the treatment of COVID-19 infection recommended favipiravir in moderate to severe COVID-19 with or without immunomodulatory agents like tocilizumab, baricitinib, tofacitinib (https://static-0.rosminzdrav.ru/system/attachments/attaches/000/050/584/original/03062020_%D0%9CR_COVID-19_v7.pdf/2020). The Russian guidelines recommend a dosage regimen for patients weighing less than 75 kg as 1600 mg BID on day 1 and 600 mg BID from days 2–10. For patients weighing from 75 kg to 90 kg (inclusive): 2000 mg BID on day 1 and 800 mg BID on days 2–10. For patients weighing over 90 kg: 2400 mg BID on day 1 and further 1000 mg BID on days 2–10. The Saudi Ministry of Health protocol included favipiravir in mild to moderate cases in adults (1600 mg/dose BID on the first day; followed by 600 mg/dose BID for 7–10 days) as well as in pediatric patients (10–15 kg; loading dose: One tablet PO BID for one day; maintenance dose from day 2; half tablet (100 mg) PO BID); 16–21 kg: loading dose of two tablets PO BID one day (maximum 800 mg/day) and maintenance dose (from day 2) of one tablet PO BID (maximum 400 mg/day). It is also recommended in severe cases (https://www.moh.gov.sa/Ministry/MediaCenter/Publications/Documents/MOH-therapeutic-protocol-for-COVID-19.pdf/2020). Similarly, the Thailand Department of Disease Control has recommended the use of favipiravir in mild and moderate COVID-19 cases in both adult and pediatric patients.

The Maharashtra state guidelines have recommended the use of favipiravir for mild symptomatic patients with or without comorbidities or having red flag signs, as well as moderate COVID-19 disease with pneumonia ((Revision 2: 22-06-2020) — Corona-2020/CR No.58/Aa-5/2020, 2020). The recommended therapeutic dose of favipiravir is 1800 mg twice a day on day 1, followed by 800 mg twice a day for 7 days if needed it can be continued up to maximum 14 days.

Global ongoing studies on favipiravir

Around 27 studies, including randomized clinical trials are ongoing in countries such as China (NCT04310228; NCT04319900; NCT04333589), Japan (JapicCTI-205238; jRCTs031190226; jRCTs041190120), Italy (NCT04336904), USA (NCT04358549; NCT04346628), UK (NCT04373733), Canada, Egypt (NCT04345419; NCT04351295; NCT04349241), Thailand (NCT04303299), France (NCT04356495), and Iran (NCT04359615) in COVID-19 patients with favipiravir. Clinical trials have been planned to explore its efficacy over other drugs such as hydroxychloroquine, or with combination drugs such as hydroxychloroquine + azithromycin + zinc or oseltamivir + hydroxychloroquine, and also in combination with drugs, including tocilizumab, chloroquine, and oseltamivir + chloroquine + darunavir + ritonavir. Favipiravir as a post exposure prophylaxis has shown promise in Ebola virus disease. Similarly, its prophylactic role in COVID-19 is currently being explored in an ongoing clinical study (NCT04448119) in Canada and USA. The primary objective of this study is to evaluate the efficacy of favipiravir chemoprophylaxis for the control of outbreaks of COVID-19 in long-term care homes, defined as no new cases of COVID-19 in residents for 24 consecutive days up to day 40 after the start of prophylaxis. The secondary objectives include measures of safety, rates of infection, disease progression, and fatality rates (http://www.tibdn.ca/control-covid/files/protocol/at_download/file/).

Favipiravir medical appraisal for COVID-19

Favipiravir is an established drug for the treatment of influenza and is being explored more for its role in the treatment of COVID-19. It is the first oral antiviral drug approved for mild to moderate COVID-19. The already completed studies in China, Japan, and Russia have shown favipiravir to be a promising cure for this disease (Cai et al., 2020; Doi et al., 2020b; https://www.clinicaltrialsarena.com/news/chemrar-rdif-favipiravir-data/2020).

Favipiravir-RTP is ineffective against deoxyribonucleic acid (DNA)-dependent RNA or DNA polymerases but has an incredible efficacy against the multiple types of RNA viruses over DNA viruses and mammalian cells regardless of resistance to prevailing antiviral drugs (Furuta et al., 2017). The literature supports its wide therapeutic efficacy and safety profile. Notably, studies exhibit the absence of resistance to favipiravir and a broad spectrum antiviral activity, which is a driving force to pursue clinical studies for distressing coronavirus infections (Goldhill et al., 2018). It has a wide therapeutic safety margin for a high dose

and is available as an oral formulation. As 80% of the patients infected with COVID-19 have mild to moderate severity, oral formulation is more convenient. Rapid viral clearance, greater improvement in chest CT changes, and a better clinical recovery rate as compared to other repurposed antiviral drugs from limited clinical studies suggest beneficial antiviral activity of favipiravir. The results of *in vitro* and *in vivo* studies provide insights into the safety margin for a higher dose and efficacy profile against SARS-CoV-2 and reinforce the significance of considering favipiravir to treat COVID-19 outbreak. Recently, in the month of June 2019, it has been approved in India by the Indian Drug Regulator under accelerated approval process for the treatment of mild to moderate COVID-19 under restricted emergency use.

Conclusion

Considering the approved status, evidence on the safety and key indicators of efficacy of favipiravir in COVID-19 from trials/registries in Russia, Japan, China, and Thailand, it appears to be useful in the management of COVID-19, particularly mild to moderate disease; however, large randomized controlled trials are required to demonstrate whether this effect translates to clinical benefits like shortening the disease course, early hospital discharge, and reducing the need for oxygen requirement. It is now commercialized in many countries like Russia, Bangladesh, Pakistan, Jordan, Egypt, and Saudi Arabia for COVID-19 treatment. The rapid viral clearance, higher clinical recovery rate, and availability as an oral drug with proven safety profile makes it the promising drug, repurposed to treat COVID-19. The worldwide ongoing clinical studies on favipiravir will further provide more insights on its clinical efficacy, safety, and therapeutic place in the overall management of COVID-19.

Conflict of interest

Saiprasad Patil and Hanmant Barkate are employees of Glenmark Pharmaceuticals Limited, Mumbai. All other authors have no conflicts of interest to disclose.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with ethics guidelines

This article is based on available literature and previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Contributions

All the authors have contributed to the concept, literature search, writing, and critical review of the manuscript.

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