JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Favipiravir and COVID 19

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ABSTRACT

Coronavirus disease 2019 (COVID-19), the highly contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a catastrophic effect on the world's demographics resulting in more than 2.9 million deaths worldwide, emerging as the most consequential global health crisis since the era of the influenza pandemic of 1918. Since its emergence in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) has caused over 240 million confirmed cases and more than 5 million deaths worldwide at the time of writing. The World Health organization (WHO) declared it to be a global pandemic in March 2020. Favipiravir was first used against SARS-CoV-2 in Wuhan and in June 2020, favipiravir received the DCGI approval in India for mild and moderate COVID-19 infections. This study summarizes the effect of favipiravir against COVID-19.

Keywords: Favipiravir, COVID-19, Adverse drug reactions, SARS-CoV

Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) were two highly pathogenic coronaviruses with zoonotic origin which emerged in 2002 and 2012. It caused fatal respiratory illness in humans, emerging as a new public health concern. Later in 2019, a novel coronavirus designated as SARS-CoV-2 emerged in the city of Wuhan, China, and caused an outbreak of unusual viral pandemic. [1]

Favipiravir was first used against SARS-CoV-2 in Wuhan at the very epicenter of the pandemic. Later, it was approved in various countries. In June 2020, favipiravir received the DCGI approval in India for mild and moderate COVID-19 infections. [2]

Mechanism of action

Favipiravir functions as a prodrug and undergoes ribosylation and phosphorylation intracellularly to become the active favipiravir-RTP. Favipiravir-RTP binds to and inhibits RNA dependent RNA polymerase (RdRp), which ultimately prevents viral transcription and replication. [3]

Pharmacodynamics and kinetics

Favipiravir is a prodrug. It has an excellent 54% protein binding, bioavailability (~94%) and a low volume of distribution (10–20 L). After 2 hrs, it reaches Cmax in a single dose. After multiple doses, both Tmax and half-life increases. Favipiravir has a rapid renal elimination in the hydroxylated form. Aldehyde oxidase mediates the elimination. Xanthine oxidase is also involved in the eliminaation but marginally. Favipiravir exhibits both, dose-dependent and time-dependent pharmacokinetics. Cytochrome P450 system does not metabolize it but inhibits one of its components (CYP2C8). Thus, it has to be used with caution when coadministered with drugs metabolized by the CYP2C8 system. [4]

Role in COVID 19

A randomized control study conducted by Shannon et al found that the SARS-CoV-2–RDRp complex is at least 10-fold more active than any other viral RdRp known. Favipiravir inhibits the viral RdRp enzyme and allows facile insertion of favipiravir into viral RNA while sparing the DNA of humans. This study concluded that nucleoside analogs (such as favipiravir) are promising candidates for the treatment of COVID-19. The optimal dose of favipiravir is difficult to establish from the limited preclinical, in vitro data. [5] For example, the higher doses of favipiravir used in Ebola was based on preclinical studies showing the target concentrations that was needed to inhibit the Ebola virus (EC50: 67 mM) were higher than that in influenza virus (EC50: 0.48 mM). [6,7]

When the PK studies were performed on 66 patients in the JIKI trial, the predicted target concentration could not be achieved. [8] Wang et al. study revealed that high concentrations of favipiravir (EC50: 61.88uM) were needed to inhibit SARS-CoV-2 infection in Vero cells.[8] Thus, it is difficult to conclude that the basis for the current dose of this drug established for SARS-CoV-2. Despite this uncertainty, the dose in clinical practice in most countries, including India, is 1800 mg bid on day 1, followed by 800 mg bid on days 2–14.

Clinical trials

A prospective, open-label multicentric trial by Chen et al. in China compared two treatment arms in the management of medically confirmed COVID-19. Conventional therapy plus umifenovir (Arbidol) (200 mg thrice a day) or favipiravir (1600 mg twice daily followed by 600 mg twice daily) for 7 days (extendable to 10 days). Maximum duration of symptom onset before randomization was 12 days. The study included 240 patients with 1:1 randomization to both groups. The study revealed that the clinical recovery rate at day 7 did not differ significantly between the two groups (61.21% for favipiravir vs 51.67% for umifenovir, 95% CI: −0.0305 to 0.2213, p = 0.1396). Also, favipiravir-treated patients showed a trend toward clinical improvement at day 7 among those with moderate COVID-19 (71.43% vs 55.86%, 95% CI: 0.0271 to 0.2843, P = 0.0199) (Revealed by the post hoc analysis) and early resistance towards fever and cough ($p < 0.0001$). There were no significant differences between the two groups in terms of the incidence of or noninvasive mechanical ventilation or auxiliary oxygen therapy. The two groups were comparable in terms of all-cause mortality, dyspnea after taking medications, and respiratory failure. All these were considered mild side effects. [9]

The most important drawback of this study was the inclusion of medically confirmed, rather than virologically confirmed, cases. Only 46.55% patients in favipiravir group and 38.33% in umifenovir group were nucleic acid–positive at enrollment in the study. The authors stated that the inclusion criteria were designed as per the prevalent Chinese guidelines for definition of COVID case, and that the sensitivity of viral PCR at the time was only 30–50%. Another important drawback was the usage of umifenovir as the control arm, when adequate information about the efficacy of this drug was unclear.

Adverse drug reactions

The Chen et al study found that adverse reactions were seen in around 20% of the patients who received favipiravir (at a dose lower than what was approved for COVID-19). The adverse effects were relatively minor and included hyperuricemia and diarrhea in 5% of the participants and reduced neutrophil count and transaminitis in 2% of the participants. One study showed occurrence of psychiatric symptoms in association with favipiravir. Effect of favipiravir in QTc prolongation is still uncertain, with some pharmacodynamic studies suggesting a positive association, but a Japanese study suggesting otherwise.25 Overall, favipiravir has a good safety profile, as was confirmed by a large systematic review: [10,11, 12]

The following figure lists the adverse effect profile of this drug and the frequency with which these are encountered

ADR	>1	0.5-<1	<0.5
Hepatic	Liver enzymes increased	Rash	Pruritis
Gastrointestinal	Diarrhea		Bilirubin increased
Hematologic	Neutrophil count decreased; White blood cell count decreased	Glucose urine present	
Metabolic	Blood uric acid increased		Blood potassium decreased

Conclusion

The oral route of administration is the major advantage of favipavir and that it can be administered in patients who are symptomatic but not severe enough to be hospitalized. About 87% of patients have mild to moderate disease and can be treated at home. So, this drug could potentially be used in large numbers of patients. Another important aspect of favipiravir that should be noted is that, early after the onset of symptoms for COVID, the drug can be useful in reducing viremia. Its helps in shortening the duration of viral shedding and could also have an epidemiological advantage as it could reduce viral transmission at home and in the society. The role of favipiravir in prophylaxis in exposed but healthy humans is also being looked at in an ongoing trial. Favipiravir is also being evaluated in combination with other antiviral drugs such as umifenovir to see if these drugs act in a complimentary or synergistic manner. [13,14]

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