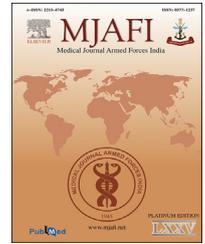




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## Review Article

# Favipiravir: A new and emerging antiviral option in COVID-19

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## ABSTRACT

With over 16 million cases reported from across the globe, the SARS-CoV-2, a mere 125 microns in diameter, has left an indelible impact on our world. With the paucity of new drugs to combat this disease, the medical community is in a race to identify repurposed drugs that may be effective against this novel coronavirus. One of the drugs which has recently garnered much attention, especially in India, is an anti-viral drug originally designed for influenza, called favipiravir. In this article, we have tried to provide a comprehensive, evidence-based review of this drug in the context of the present pandemic to elucidate its role in the management of COVID-19.

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## Introduction

Six months and more than 16 million confirmed cases later, the COVID-19 pandemic has become the worst public-health crisis in a century. Discovery of a new and specific antiviral agent against the SARS-CoV-2 would involve a long and arduous timeline. Hence, by default, repurposed drugs, already in use against other viral infections, have been pressed into quick service. One such drug is favipiravir, initially marketed as an antiinfluenza agent in Japan. This drug has just received emergency approval by the Drug Controller General of India (DCGI) and hence this comprehensive review of favipiravir comes at a timely juncture.

Favipiravir was first used against SARS-CoV-2 in Wuhan at the very epicenter of the pandemic. Then, as the pandemic spread to Europe, this drug received approval for emergency use in Italy, and currently has been in use in Japan, Russia, Ukraine, Uzbekistan, Moldova, and Kazakhstan. Approval has also recently been granted in Saudi Arabia and the UAE. Thereafter, Turkey, Bangladesh, and most recently Egypt have also seen recent commercial launches. In June 2020, favipiravir received the DCGI approval in India for mild and moderate COVID-19 infections. As of the 23rd of July, 2020; there are 32 studies registered on [clinicaltrials.gov](https://clinicaltrials.gov) to assess the utility of this drug in the management of COVID-19 (3 completed, 12 recruiting).<sup>1</sup>

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## Pharmacology

Favipiravir (T-705) is a synthetic prodrug, first discovered while assessing the antiviral activity of chemical agents active against the influenza virus in the chemical library of Toyoma chemicals. A lead compound, A/PR/8/34, later designated as T-1105, and its derivatives were found to have antiviral activities. Favipiravir is derived by chemical modification of the pyrazine moiety of T-1105 (Fig. 1).<sup>2</sup> It has been approved in Japan for the management of emerging pandemic influenza infections in 2014.

## Pharmacokinetics and pharmacodynamics

Favipiravir is administered as a prodrug. It has an excellent bioavailability (~94%), 54% protein binding, and a low volume of distribution (10–20 L). It reaches C<sub>max</sub> within 2 h after a single dose. Both T<sub>max</sub> and half-life increase after multiple doses. Favipiravir has a short half-life (2.5–5 h) leading to rapid renal elimination in the hydroxylated form. Elimination is mediated by aldehyde oxidase and marginally by xanthine oxidase. Favipiravir exhibits both, dose-dependent and time-dependent pharmacokinetics. It is not metabolized by the cytochrome P450 system, but inhibits one of its components (CYP2C8). Thus, it needs to be used with caution when co-administered with drugs metabolized by the CYP2C8 system.<sup>3,4</sup>

## Mechanism of action

Within the tissue, the molecule undergoes phosphoribosylation to favipiravir-RTP, which is the active form of this drug. It exerts its antiviral effect through the following mechanisms:

- This molecule acts as a substrate for the RNA-dependent RNA-polymerase (RdRp) enzyme, which is mistaken by the enzyme as a purine nucleotide,<sup>2</sup> thus inhibiting its activity leading to termination of viral protein synthesis (Fig. 2).
- It gets incorporated in the viral RNA strand, preventing further extension.<sup>5</sup> This mechanism of action, along with preservation of the catalytic domain of the RdRp enzyme across various RNA viruses, explains the broad spectrum of activity of this drug.

- It has recently been shown that favipiravir induces lethal mutagenesis in vitro during influenza virus infection, making it a virucidal drug.<sup>6</sup> Whether a similar activity is demonstrated against SARS-CoV-2 or not is uncertain.

## Spectrum of antiviral activity

- Influenza:** Favipiravir inhibits 53 types of influenza viruses including seasonal strains A (H1N1), A (H3N2), and influenza B; the A (H1N1)pdm09 pandemic virus; highly pathogenic avian influenza virus A (H5N1) isolated from humans; A (H1N1) and A (H1N2) isolated from swine; and A (H2N2), A (H4N2), and A (H7N2). It is also active against drug-resistant strains of the virus, including M2 and NA inhibitors.<sup>7</sup>
- Ebola:** During the Ebola virus outbreak in 2014, favipiravir was one of the drugs short-listed for trials by the WHO. Although in vitro studies<sup>8,9</sup> showed encouraging results for this drug, with a trend toward survival benefit showed by clinical studies,<sup>10,11</sup> conclusive evidence of benefit was never found. In the JIKI multicenter trial<sup>10</sup> conducted in 126 patients with Ebola, favipiravir in an initial loading dose of 6000 mg followed by 2400 mg/day for 9 days was shown to have some effect in patients with medium to high viremia but not in those with more severe viremia (Ct value < 20). This large dose seemed to have been well tolerated as well. A subsequent retrospective study also found favipiravir-treated patients had a trend toward improved survival times against Ebola virus, although this effect was not statistically significant.<sup>11</sup>
- Activity against other pathogenic RNA viruses:** In addition to its activity against influenza and Ebola viruses, favipiravir has been found to have therapeutic efficacy in cell culture and mouse models of arenavirus, bunyavirus, filovirus, West Nile virus, yellow fever virus, foot-and-mouth-disease virus, and Lassa virus including agents causing viral hemorrhagic fevers and encephalitis.

## Role in SARS-CoV-2

Shannon et al.<sup>12</sup> found that the SARS-CoV-2–RdRp complex is at least 10-fold more active than any other viral RdRp known. Favipiravir acts by inhibiting this viral RdRp enzyme, allowing

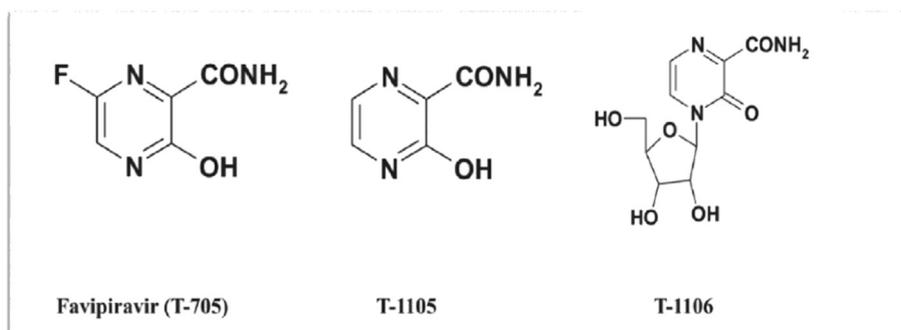


Fig. 1 – Chemical structure of favipiravir.<sup>2</sup>

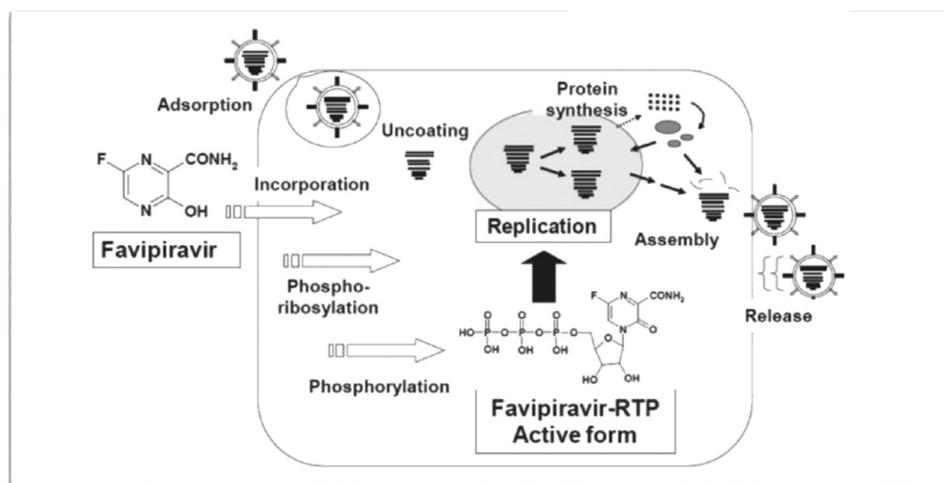


Fig. 2 – Mechanism of action of favipiravir.<sup>2</sup>

facile insertion of favipiravir into viral RNA while sparing human DNA. They 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. For instance, the higher dosing of favipiravir used in Ebola was based on preclinical studies showing the target concentrations needed to inhibit the Ebola virus (EC<sub>50</sub>: 67 mM)<sup>8</sup> were higher than that in influenza (EC<sub>50</sub>: 0.48 mM).<sup>13</sup> Despite these high doses, the predicted target concentrations could not be achieved when PK studies were performed on 66 patients in the JIKI trial.<sup>14</sup> Wang et al.<sup>15</sup> found that the high concentrations of favipiravir (EC<sub>50</sub>: 61.88 μM) were needed to inhibit SARS-CoV-2 infection in Vero cells. Thus, it is difficult to ascertain the basis on which the current dose of this drug has been established in SARS-CoV-2. Despite this uncertainty, the dose in clinical use in most countries, including India, is 1800 mg bid on day 1, followed by 800 mg bid on days 2–14.

### Clinical trials in COVID-19

Over the past few months, clinical studies have been performed all over the world to assess the efficacy of favipiravir in the management of COVID-19. The major clinical studies are summarized here.

#### China

Chen et al.<sup>16</sup> had conducted a prospective, open-label multicentric trial in China to compare two treatment arms in the management of clinically confirmed COVID-19 (maximum duration of symptom onset before randomization: 12 days). 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). The study comprised 240 patients with 1:1 randomization to both groups. The authors found 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,  $p = 0.1396$ ). Post hoc analysis demonstrated that 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,  $P = 0.0199$ ) and earlier resolution of fever and cough ( $p < 0.0001$ ). There was no significant differences between the two groups in terms of the incidence of auxiliary oxygen therapy or noninvasive mechanical ventilation. 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.

The most important drawback of this study was the inclusion of clinically confirmed, rather than virologically confirmed, cases. In this cohort, only 46.55% patients in favipiravir group and 38.33% in umifenovir group were nucleic acid-positive at enrollment. 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 using umifenovir as the control arm, when adequate information about the efficacy of this drug was unclear. The sample size was calculated assuming 50% reduction in time to clinical recovery using umifenovir, with no data supporting this hypothesis.

Another open-labeled nonrandomized study<sup>17</sup> from China compared the effect of favipiravir (day 1: 1600 mg twice daily; days 2–14: 600 mg twice daily) vs lopinavir/ritonavir (day 1–14: 400/100 twice daily) in the treatment of COVID 19. Both groups received interferon-alpha (5 million units twice daily) by nasal inhalation. Those aged 16–74 years, positive for SARS-CoV-2, symptom onset within the past 7 days and mild-moderate disease were recruited. From 30 January to 14 February, 56 patients with laboratory-confirmed COVID 19 were screened, of which 35 patients met eligibility for favipiravir. From 24th January to 30th January, 91 laboratory-confirmed COVID-19 patients who were already on lopinavir/ritonavir treatment were screened for eligibility, of which 45 were eligible for control arm.

Baseline characteristics of both arms did not show statistically significant differences. Compared with the lopinavir/ritonavir arm, however, patients in the favipiravir arm showed a statistically significant shorter median length of time to viral clearance (4 days vs 11 days,  $p < 0.001$ ), improvement in chest CT findings at day 14 after randomization (91.4% vs 62.2%,  $P = 0.004$ ) and lower incidence of adverse effects (11.43% Vs 55.56%  $P$  value  $< 0.001$ ). Multivariate analysis showed that favipiravir was independently associated with faster viral clearance and chest CT scan improvement. With the limitations of nonrandomized study and the lack of blinding, a potential selection bias may have confounded the results.

### Japan

A Japanese observational study group recorded the details of hospitalized COVID-19 patients in Japan to assess the safety and efficacy of favipiravir.<sup>18</sup> From February to May 2020, a total of 2158 cases were registered from 407 hospitals. In more than 90 percent of cases, favipiravir was administered at a dose of 1800 mg orally on day 1 followed by 800 mg twice daily on subsequent days. The median duration of therapy was 11 days. Rates of clinical improvement at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5%, and 40.1% and 60.3% for mild, moderate, and severe disease, respectively. Thus, vast majority of patients with mild and moderate disease recovered from the illness, whereas in those with severe disease, the results were not encouraging. The mortality rates at the time of survey were 5.1%, 12.7%, and 31.7% for mild, moderate, and severe disease, respectively. It is to be stressed that this study had no control arm which precludes direct comparison of the clinical course with those who did not receive the agent.

Favipiravir in combination with nafomostat (transmembrane protease serine 2 inhibitor, previously used successfully in MERS-CoV-2 infection, acute pancreatitis and DIC) was found to be useful in a small case series consisting of 11 serious patients with COVID-19 in Japan. The median age, time from symptom onset to admission in the ICU, and  $\text{PaO}_2/\text{FiO}_2$  ratio on admission were 68 years (IQR 60–69), 8 days (IQR 7–11), and 131 (IQR 114–198) respectively. All patients needed oxygen therapy, eight patients (73%) needed invasive mechanical ventilation, and 3 patients (27%) needed extracorporeal membrane oxygenation (ECMO). Of the 11 patients, 7 were successfully weaned from mechanical ventilation, 1 patient with DNR order died. Nine and 7 patients were discharged from the ICU and the hospital, respectively. One patient had been weaned of ventilation was still in the hospital at the time the paper was published. A prospective clinical trial (jRCTs031200026) with this combination is expected to be initiated in Japan soon.<sup>19</sup>

### Ongoing trials

#### Russia

A phase 3 Russian trial COVIDFPR 01 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04434248) Identifier: NCT04434248) is ongoing and includes 330 patients from 30 medical centers across 9 Russian regions. Phase 1 of the trial ended within 10 days, after recruiting 60 patients with coronavirus infection with moderate illness. They were

randomized in a 1:1:1 ratio of high-dose favipiravir (1800 mg twice daily on day 1 followed by 800 mg twice daily for next 13 days) vs low-dose favipiravir (1600 mg twice daily on day 1 followed by 600 mg twice daily for next 13 days) vs standard of care (SOC). Favipiravir was quite safe with no demonstrable side effects. Fever returned back to normal in 68% of patients on favipiravir within 3 days as compared with 6 days in the control group. After first 4 days of treatment, 65% of the 40 patients who took favipiravir tested negative for the virus, twice as many compared with the standard therapy group. At the end of day 10, 35 of 40 (87.5%) patients tested negative for the virus. In the pivotal phase of the trial, the dose of favipiravir will be selected based on results from the pilot study and compared with the SOC as previously mentioned. The study aims to look upon the rate of viral elimination by day 10, time to viral elimination in a time frame of 28 days, and time to clinical improvement.<sup>20</sup>

#### Saudi Arabia

An ongoing open-labeled randomized controlled trial from Saudi Arabia is evaluating the efficacy of favipiravir and hydroxychloroquine combination therapy Identifier: NCT04392973] in the management of moderate to severe COVID-19. The experimental arm consists of favipiravir (dose: 1800 mg twice daily on day 1 followed by 800 mg twice daily for a total period of 10 days or till hospital discharge) plus hydroxychloroquine (400 mg twice daily on day 1 followed by 200 mg twice daily for next 4 days). The control arm includes the SOC treatment in COVID 19. The primary endpoint of the trial is time to clinical improvement and time to a negative PCR test.<sup>21</sup> Results of this trial are eagerly awaited.

#### The USA

The research team at Stanford Medicine have recently commenced a double-blind, placebo-controlled trial (favipiravir vs placebo for 10 days) to assess the utility of favipiravir in reducing symptoms and the duration of viral shedding in outpatients with COVID-19. About 120 patients are expected to be enrolled beginning July 6, 2020.<sup>22</sup>

#### Indian trial

A randomized, multicenter, open-labeled clinical trial in Indian patients has just been completed, with results expected to be published soon. This trial evaluated the efficacy and safety of favipiravir in patients hospitalized with mild to moderate COVID-19 infection. Conducted in hospitals across India, 150 patients were randomized, with 72 to the favipiravir arm and 75 to the SOC arm. Those in the favipiravir arm received 3600 mg on day 1, then 1600 mg on days 2–14. Daily nasopharyngeal swabs were collected from all participants till two consecutive swabs were negative. The primary endpoint was time to cessation of shedding of SARS-CoV-2 as determined by two consecutive negative swabs. Other secondary endpoints analyzed in this study were clinical cure rates as determined by the treating physician with recovery of fever, respiratory rate, oxygen saturation, and cough relief. The trial also looked at other secondary endpoints such as time from randomization to initial requirement of high flow supplemental oxygen or ventilatory support and time from randomization to hospital discharge.

Final data are being analyzed and under review but we can reveal<sup>23</sup> that there was 28.7% faster viral clearance in the favipiravir-treated patients compared with those who received SOC (5 versus 7 days) with 2/3rd of favipiravir-treated patients achieving viral clearance in week 1. Treating clinicians judged 70% of patients in the favipiravir limb to be clinically cured by day 4 versus 44% in the SOC arm. These initial results were indeed promising but need to be confirmed in larger studies.

### Side effects/adverse effects

The Japanese study<sup>18</sup> discussed previously found that adverse reactions were seen in around 20% of the patients who received favipiravir (at a dose lower than 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,<sup>24</sup> but a Japanese study suggesting otherwise.<sup>25</sup> Overall, favipiravir has a good safety profile, as was confirmed by a large systematic review.<sup>26</sup> In the following sections, we give a brief overview of the adverse effect profile of this drug:

#### Hyperuricemia

Favipiravir use results in a dose-dependent increasing trend in the prevalence of hyperuricemia.<sup>24</sup> A systematic review conducted by Pilkington et al. found similar trends across multiple studies.<sup>26</sup> This is however not associated with clinical

manifestations. There has been no evidence that hyperuricemia caused by favipiravir leads to clinical manifestations; however, longer follow-up periods would be required to fully assess this risk.

#### Teratogenicity

There is evidence that favipiravir has a teratogenic potential and embryotoxicity. The Japanese drug safety bureau approval advises that favipiravir be given a strong warning against use in women of reproductive age and recommends precautionary statements on packaging and prescription alerts. The bureau also recommends that favipiravir should be avoided where alternative drugs could be used.<sup>24</sup> Effective contraceptive methods during and for 7 days after the end of treatment need to be instructed to men who have received this treatment. Before favipiravir is prescribed to women of child-bearing age, it is imperative to rule out pregnancy with a negative urine pregnancy test.

The following figure lists the adverse effect profile of this drug and the frequency with which these are encountered (Fig. 3).

#### Dose and cost

The recommended dosage of favipiravir for adults is 1800 mg orally twice daily on 1st day followed by 800 mg orally twice daily, up to maximum of 14 days. The 14-day course in India costs Rs 10,200.

#### DCGI approval

Considering the emergency and unmet medical need in COVID-19, Glenmark was granted permission to manufacture

	≥ 1%	0.5 - < 1%	< 0.5%
Hypersensitivity		Rash	Eczema, pruritus
Hepatic	AST (GOT) increased, ALT (GPT) increased, γ-GTP increased		Blood ALP increased, blood bilirubin increased
Gastrointestinal	Diarrhoea	Nausea, vomiting, abdominal pain	Abdominal discomfort, duodenal ulcer, haematochezia, gastritis
Hematologic	Neutrophil count decreased, white blood cell count decreased	Glucose urine present	White blood cell count increased, reticulocyte count decreased, monocyte increased
Metabolic disorders	Blood uric acid increased 4.79%, Blood triglycerides increased		Blood potassium decreased
Respiratory			Asthma, oropharyngeal pain, rhinitis, nasopharyngitis
Others			CPK increased, blood urine present, tonsil polyp, pigmentation, dysgeusia, bruise, vision blurred, eye pain, vertigo,

Fig. 3 – Figure depicting adverse effects of favipiravir (source: Fabiflu monograph).

and market favipiravir for restricted emergency use in the country on 19th June 2020, for the treatment of mild to moderate COVID-19 disease. This approval is contingent on the provision of the complete report of the ongoing clinical trial within three months of approval.

## Drug interactions

**Pyrazinamide:** Concomitant use of pyrazinamide with favipiravir increases the levels of uric acid. Regular uric acid level monitoring is mandatory when these drugs are used together.

**Repaglinide:** Favipiravir inhibits the metabolism of repaglinide through the CYP2C8 pathway, thus increasing its potential to cause toxicity (hypoglycemia, headache, increase incidence of upper respiratory tract infections, etc). Cautious concomitant use is recommended.

**Theophylline:** Theophylline increases the blood levels of favipiravir and adverse reactions to favipiravir may occur.

**Famciclovir, sulindac:** Efficacy of these drugs may be reduced when coadministered with favipiravir.

**Acyclovir:** Acyclovir may delay the conversion of favipiravir into the active moiety, thus reducing its antiviral efficacy.<sup>27</sup>

## Conclusions

The frightening speed with which the COVID-19 pandemic has spread across the world has only served to expose how inadequate our available antiviral drug options are. Repurposed antiviral drugs have all been accelerated into treatment after rapidly conducted clinical trials. Older, pre-existing antiviral drugs such as oseltamivir and ribavirin have not been shown to be effective against SARS-CoV-2. The most promising antiviral drug to date is another repurposed drug, remdesivir, which has been shown to be effective in several well-conducted trials. When used in moderately severe, nonventilated patients, it has been shown to improve time to clinical recovery,<sup>28,29</sup> and a trend toward reduced mortality,<sup>28</sup> although a significant mortality benefit has not been demonstrated. The effect of this drug appears modest at best, with further large scale trials urgently needed to evaluate its place in the management of COVID-19.

Favipiravir, a drug which has a similar mechanism of action to remdesivir but is orally administered, has less strong supportive data to back its use, but is nevertheless emerging as an agent that is worth considering in mild to moderate cases. The preliminary results from the first Indian study with this drug have been encouraging with small but significant improvement in time to clinical recovery and a two-day shorter viral shedding time. Put in perspective, a Cochrane review of 20 trials of oseltamivir in influenza showed this widely used drug reduced the time to clinical alleviation of symptoms by 16.8 h only.<sup>30</sup>

The main advantages of favipiravir are that it is administered orally and that it can be given in patients who are symptomatic but not ill enough to be hospitalized. As most COVID-19 patients (85%) have mild to moderate disease and can be treated at home, this drug could potentially be used in

large numbers of patients. As with any antiviral, it should be stressed that favipiravir should be administered early after the onset of symptoms for it to be effective in reducing viremia. Its role in potentially shortening the duration of viral shedding could also have an epidemiological impact as it could reduce viral transmission at home and in the community. The role of favipiravir in prophylaxis in exposed but healthy contacts is also being looked at in an ongoing trial.<sup>31</sup> 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.<sup>32</sup>

The side-effect profile of the drug also seems acceptable with asymptomatic hyperuricemia and mild, reversible elevation in transaminases being the most frequently reported adverse effects. In the Indian trial, no special safety signal was elicited. It is however teratogenic and must never be used in pregnant women. The main disadvantage is a high pill burden which works out to a loading dose of 18 tablets on the first day and then 8 tablets a day for the rest of the course. With the recent launch of 400 mg dose with one of the manufacturers, these concerns about the high pill burden will be partially alleviated. The recommended duration of treatment, extending to 2 weeks may also be a disadvantage. Here again, the manufacturers specify that the drug can be stopped in a week if the patient has made a complete recovery by then.

Thus, in conclusion, favipiravir may emerge as a valuable drug in the treatment of mild to moderate symptomatic SARS-CoV-2–infected cases. Furthermore, larger RCTs are urgently needed before this drug can be unreservedly recommended however.

## Disclosure of competing interest

The authors have none to declare.

## REFERENCES

1. Clinicaltrials.gov. Search of: favipiravir | Covid19 - list results - clinicaltrials.Gov [online] Available at: <https://clinicaltrials.gov/ct2/results?cond=Covid19&term=favipiravir&cntry=&state=&city=&dist;> 2020. Accessed July 23, 2020
2. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antivir Res.* 2013 Nov;100:446–454.
3. Toyama Chemicals. Summary of Product Characteristics of Avigan.
4. Madelain V, Nguyen TH, Olivo A, et al. Ebola virus infection: review of the pharmacokinetic and pharmacodynamic properties of drugs considered for testing in human efficacy trials. *Clin Pharmacokinet.* 2016 Aug;55:907–923. <https://doi.org/10.1007/s40262-015-0364-1>.
5. Jin Z, Smith LK, Rajwanshi VK, Kim B, Deval J. The ambiguous base-pairing and high substrate efficiency of T-705 (favipiravir) ribofuranosyl 5'-triphosphate towards influenza A virus polymerase. *PLoS One.* 2013;8, e68347.
6. Baranovich T, Wong SS, Armstrong J, et al. 705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro. *J Virol.* 2013;87:3741–3751.

7. Sleeman K, Mishin VP, Deyde VM, Furuta Y, Klimov AI, Gubareva LV. In vitro antiviral activity of favipiravir (T-705) against drug-resistant influenza and 2009 A(H1N1) viruses. *Antimicrob Agents Chemother*. 2010;54:2517–2524.
8. Oestereich L, Lüttke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. *Antivir Res*. 2014 May;105:17–21.
9. Smither SJ, Eastaugh LS, Steward JA, Nelson M, Lenk RP, Lever MS. Post-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model. *Antivir Res*. 2014 Apr;104:153–155.
10. Sissoko D, Laouenan C, Folkesson E, et al. Experimental treatment with favipiravir for ebola virus disease (the JIKI trial): a historically controlled, single-arm proof-of-concept trial in Guinea. *PLoS Med*. 2016 Mar 1;13, e1001967.
11. Kerber R, Lorenz E, Duraffour S, et al. Laboratory findings, compassionate use of favipiravir, and outcome in patients with ebola virus disease, Guinea, 2015-A retrospective observational study. *J Infect Dis*. 2019 Jun 19;220:195–202.
12. Shannon A, Selisko B, Le N, et al. Favipiravir Strikes the SARS-CoV-2 at its Achilles Heel, the RNA Polymerase. *bioRxiv*; 2020 May 15.
13. Furuta Y, Takahashi K, Fukuda Y, et al. In vitro and in vivo activities of anti-influenza virus compound T-705. *Antimicrob Agents Chemother*. 2002;46:977–981.
14. Nguyen TH, Guedj J, Anglaret X, et al. Favipiravir pharmacokinetics in Ebola-Infected patients of the JIKI trial reveals concentrations lower than targeted. *PLoS Neglected Trop Dis*. 2017 Feb 23;11, e0005389.
15. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020 Mar;30:269–271.
16. Chen C, Zhang Y, Huang J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. *medRxiv*; 2020, 2020 Apr 15.
17. Cai Q, Yang M, Liu D, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. 2020 Mar 18. Engineering (Beijing).
18. James Ives M. Preliminary report of favipiravir observational study in Japan released [Internet]. News-Medical.net, [cited 23 July 2020]. Available from: <https://www.news-medical.net/news/20200602/Preliminary-report-of-Favipiravir-Observational-Study-in-Japan-released.aspx>; 2020.
19. Doi K, Ikeda M, Hayase N, Moriya K, Morimura N, Covid-Uth Study Group. Nafamostat mesylate treatment in combination with favipiravir for patients critically ill with Covid-19: a case series. *Crit Care*. 2020 Jul 3;24:392.
20. RDIF and ChemRar launch final stage of favipiravir clinical trial [Internet]. Prnewswire.com, [cited 23 July 2020]. Available from: <https://www.prnewswire.com/ae/news-releases/rdif-and-chemrar-launch-final-stage-of-favipiravir-clinical-trial-301064181.html>; 2020.
21. Search of: NCT04392973 - list results - ClinicalTrials.gov [Internet]. Clinicaltrials.gov, [cited 23 July 2020]. Available from: <https://clinicaltrials.gov/ct2/results?cond=&term=NCT04392973&cntry=&state=&city=&dist=&2020>.
22. Investigational antiviral study finds faster clinical improvement in patients with COVID-19 [Internet]. Pharmacy Times, [cited 24 July 2020]. Available from: <https://www.pharmacytimes.com/news/favipiravir-study-finds-faster-clinical-improvement-in-patients-with-covid-19; 2020>.
23. Personal Communication..
24. Pharmaceuticals and Medical Devices Agency. Report on the Deliberation Results – Avigan. Japan. Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau; 2011. Available at: [www.pmda.go.jp/files/000210319.pdf](http://www.pmda.go.jp/files/000210319.pdf). Accessed July , 2020.
25. Kumagai Y, Murakawa Y, Hasunuma T, et al. Lack of effect of favipiravir, a novel antiviral agent, on the QT interval in healthy Japanese adults. *Int J Clin Pharm Ther*. 2015;53, 866–674.
26. Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir – a potential treatment in the COVID-19 pandemic? *J Virus Erad*. 2020 Apr 30;6:45–51.
27. Catherine M, Neil S, Brian G, Wayne N. Favipiravir and Remdesivir Appear to Be Relatively Unencumbered with Drug-Drug Interactions - Anesthesia Patient Safety Foundation [Internet]. Anesthesia Patient Safety Foundation; 2020 [cited 14 August 2020]. Available from: <https://www.apsf.org/article/favipiravir-and-remdesivir-appear-to-be-relatively-unencumbered-with-drug-drug-interactions/>.
28. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19 - preliminary report. *N Engl J Med*. 2020 May 22.
29. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe covid-19. *N Engl J Med*. 2020 Jun 11;382:2327–2336.
30. Heneghan CJ, Onakpoya I, Jones MA, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. *Health Technol Assess*. 2016 May;20:1–242.
31. [Internet]. Appili Set to Evaluate Favipiravir as Preventive Measure against Covid-19. Pharmaceutical Business review; 2020 [cited 24 July 2020]. Available from: <https://www.pharmaceutical-business-review.com/news/appili-therapeutics-favipiravir-canada-trial/>.
32. Tirumalaraju D, Tirumalaraju D. Glenmark Starts Phase III Favipiravir Combination Trial for Covid-19 [Internet]. Clinical Trials Arena; 2020 [cited 26 July 2020]. Available from: <https://www.clinicaltrialsarena.com/news/glenmark-favipiravir-combo-trial/>.