

Understanding the clinical utility of favipiravir (T-705) in coronavirus disease of 2019: a review

Kritika Srinivasan  and Mana Rao 

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Abstract: The coronavirus disease of 2019 (COVID-19) has caused significant morbidity and mortality among infected individuals across the world. High transmissibility rate of the causative virus – Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) – has led to immense strain and bottlenecking of the health care system. While noteworthy advances in vaccine development have been made amid the current global pandemic, most therapeutic agents are repurposed from use in other viral infections and are being evaluated for efficacy in COVID-19. Favipiravir, an orally administered drug originally developed in Japan against emerging influenza viral strains, has been shown to have widespread application and safety across multiple ribonucleic acid (RNA) viral infections. With a strong affinity toward the viral RNA-dependent RNA polymerase (RdRp), favipiravir could be a promising therapy against SARS-CoV-2, by targeting downstream viral RNA replication. Initial trials for usage in COVID-19 have suggested that favipiravir administration during initial infection stages, in individuals with mild to moderate infection, has a strong potential to improve clinical outcomes. However, additional well-designed clinical trials are required to closely examine ideal timing of drug administration, dosage, and duration, to assess the role of favipiravir in COVID-19 therapy. This review provides evidence-based insights and throws light on the current clinical trials examining the efficacy of favipiravir in tackling COVID-19, including its mechanism, pharmacodynamics, and pharmacokinetics.

Keywords: antiviral, COVID-19, favipiravir, influenza, SARS-CoV-2

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Introduction

SARS-CoV-2 and its anatomy

The coronavirus disease of 2019 (COVID-19) has infected over 242 million people, leading to over 4.9 million deaths worldwide, at the time of this publication.¹ It is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2),^{2,3} closely related to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV).^{3,4} SARS-CoV-2 is a single-stranded positive sense ribonucleic acid (RNA) virus, 50–200 nm in diameter, consists of four structural proteins (about 33% of viral

genome) – Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N).⁵ The S protein, comprising of S1 and S2 subunits, mediates viral entry into the host cell membrane *via* the human cell angiotensin converting enzyme 2 (ACE2) receptor.⁵ The remaining 67% of the viral genome encodes polyproteins and precursors that further cleave into 16 non-structural proteins (nsp), like the RNA-dependent RNA polymerase (RdRp), critical for viral life cycle – replication and host immune system regulation.⁶ RdRp complex like nsp-12, with assistance of other cofactor proteins (like nsp7-nsp-8 heterodimer), handles the viral replication and transcription process of the virus.^{6,7} Interestingly, across RNA viral classes,

Correspondence to:
Mana Rao
Essen Medical Associates,
2015 Grand Concourse,
Bronx, NY 10453, USA.
manarao@gmail.com
Kritika Srinivasan
Department of
Biomaterials and
Pathology, Vilcek Institute,
New York University
School of Medicine, New
York, NY, USA

various sequence motifs and tertiary structures of RdRps are conserved.^{4,7-11} These conserved RdRp motifs are essential for its catalytic function, hence useful as potential drug targets.^{4,12}

COVID-19 pathogenesis and symptoms

COVID-19 is a multisystemic viral disease and commonly affects the respiratory tract.¹³ SARS-CoV-2 is transmitted mainly through droplets and exhibits pulmonary tropism, which is attributable to ACE2 receptors being widely distributed across lung epithelial cells.¹⁴ Clinical manifestations in human hosts can be wide ranging from asymptomatic to symptomatic disease with potential for sudden symptom evolution.^{12,14} Symptoms of mild disease may include fever, myalgia, cough, fatigue, anosmia, dysgeusia, and shortness of breath while moderate-severe or critical illness may lead to prolonged hospitalization, cytokine storm, viral pneumonia, secondary bacterial or fungal pneumonia, arrhythmias, acute kidney injury, neurological illness, and so on.¹² The COVID-19 response in some individuals can lead to a complex immunological cascade leading to a cytokine storm with damage to multiple organs.^{13,15} Symptomatic disease could eventually lead to post-acute COVID-19 syndrome.^{16,17} The exact duration for which these symptoms persist after resolution of acute disease remains to be fully understood.

COVID-19 management

While COVID-19 prevention is largely associated with targeting viral spike and structural proteins by highly efficacious vaccination – generating robust humoral antibody response – hospitalization-associated patient management and therapy is critically symptom associated. Identification of clinical disease staging – clinical symptoms combined with laboratory and radiologic assessment – are critical for risk stratification, triage, and early therapeutic intervention of patients who progress to severe disease, requiring hospitalization.^{13,18} In hospitalized patients, mechanical ventilation, oxygen therapy, and symptomatic treatment have been the mainstay of therapy.¹⁹ While there is no clinically effective therapy for COVID-19 in singular, several therapeutic agents such as corticosteroids, antivirals, monoclonal antibodies, and convalescent plasma are currently being administered and evaluated, many a times,

in conjunction. Antivirals have a special role to play, repurposed through their role in other viral infections, preventing viral entry into the host cells and causing suppression of viral replication at various steps.²⁰ Some key antivirals of interest are listed in Table 1.

Several clinical trials recruiting patients across the disease stages are trying to identify the most efficacious drug(s) for efficacious COVID-19 therapy, and retroviral therapies have been of most interest.^{21,23} Remdesivir has been used under emergency use authorization in several countries, demonstrating some efficacy in shortening recovery time in COVID-19 patients.²⁷ The combination of lopinavir with ritonavir showed some favorable outcome, but a clinical trial was discontinued due to side effects.¹⁹ Ribavirin, a guanine analog targeting viral RdRp was found to be ineffective in improving COVID-19 recovery outcomes, although in combination triple therapy with lopinavir and ritonavir, with interferon beta-1b, some improvement in efficacy was observed to decrease recovery in hospitalized patients with mild to moderate COVID-19.²⁵ In addition, singular therapy with umifenovir (arbidol) did not improve patient outcomes.²⁶ Favipiravir, similar in action to remdesivir, inhibits transcription and replication of multiple RNA viruses by targeting RdRp.²⁸

Favipiravir

Drug development and pharmacodynamics

In the process of viral replication, RdRp is a critical element, conserved across RNA viruses but absent in human cells, making it a promising antiviral target.¹² Favipiravir was developed by Toyama Chemical Company Limited and was first approved for clinical use in Japan in 2014, for novel and re-emerging influenza virus infections. It was discovered through a library screen of chemical candidates utilizing a plaque reduction assay.^{28,29} Understanding efficacy of favipiravir in COVID-19 is of particularly high interest,^{30,31} as it has been shown to have effective *in vitro* and *in vivo* antiviral activity against RNA viruses of multiple families – orthomyxoviridae, bunyaviridae, arenaviridae, filoviridae, rhabdoviridae, paramyxoviridae, flaviviridae, togaviridae, picornaviridae, and caliciviridae.^{22,32,33} Favipiravir is a pyrazine carboxamide derivative and is a prodrug;

Table 1. Repurposed antivirals being evaluated for therapeutic activity in COVID-19.

Drug	Mechanism	Primary application
Remdesivir	Targets viral proteases and RdRp	Hepatitis C, Respiratory Syncytial Virus (RSV), Human Immunodeficiency Virus (HIV), Ebola and Marburg viral disease ²¹
Favipiravir	Inhibits RdRp (purine nucleoside analog)	Multiple RNA viral diseases – Influenza, Ebola, Yellow fever, etc. ²²
Lopinavir and ritonavir	Inhibits viral proteases	HIV, SARS, MERS ²³
Molnupiravir	Competitive substrate of viral RdRp	Influenza, Chikungunya virus, Respiratory syncytial virus, Ebola, SARS, MERS ²⁴
Ribavirin	Acts on viral RdRp in replicating viral genome (guanine analog)	RSV, Hepatitis C, SARS, MERS ²⁵
Umifenovir	Inhibits fusion of viral S protein to ACE2	Influenza, SARS ²⁶

ACE2, angiotensin converting enzyme 2; HIV, Human Immunodeficiency Virus; MERS, Middle East Respiratory Syndrome; RNA, ribonucleic acid; RSV, Respiratory Syncytial Virus; SARS, Severe Acute Respiratory Syndrome.

its active metabolite, favipiravir ribofuranosyl 5' triphosphate (T-705 RTP), is formed by phosphorylation and is a nucleoside analog causing disruption of viral replication.^{29,33–35} It was observed that neither favipiravir nor favipiravir-ribofuranosyl-5'-monophosphate inhibited RdRp activity, instead the triphosphate metabolism of favipiravir to T-705 RTP lead to active influenza viral inhibition, through concentration dose-dependent studies.²⁸ Plaque reduction with time of addition assays were utilized to define the mechanism of action by exposing influenza infected cells to favipiravir. It was observed that plaque inhibitory activity was observed during the replication phase and not adsorption or release phase.²⁸ While competitive assays were used to investigate the mechanism of inhibition,²⁸ it was observed that the antiviral activity of favipiravir was significantly decreased in presence of natural purine nucleoside and not pyrimidine bases, thus indicating its mechanism of action as a pseudo purine, through RdRp.^{28,36} Although the precise interaction is not known, it is hypothesized that this active form either binds to the catalytic format of RdRp or gets misincorporated to the nascent growing viral RNA, leading to chain termination by ambiguous base-pairing, in turn causing abrupt break in viral replication^{36,37} (Figure 1). Sequencing of nucleoprotein clones revealed a higher mutation frequency and associated shift in the nucleotide profiles of

the nucleoprotein gene. In addition, no viable favipiravir-resistant mutants were observed, suggesting a 'virucidal' effect.^{28,34} The wide-spectrum activity of favipiravir may be associated with this misincorporation effect. The lethal mutagenesis and subsequent chain termination mechanism has been suggested against multiple RNA viral infections as well.^{34,35,38,39} One study indicated that binding of the T-705 RTP to RdRp may not lead to sufficient inhibition of norovirus activity.⁴⁰ Although, it may be possible that variable concentration and availability of the drug may be key in impacting the mechanism of action.³⁷ In addition, as this mechanism of action is vastly different to some other antivirals that inhibit cellular RNA or DNA synthesis – as with ribavirin and the neuraminidase inhibitors – favipiravir, instead, specifically acting on viral RdRp may be responsible for observed lower toxicity while being target sensitive and efficacious across multiple classes of RNA viruses.³⁶ At 50% inhibitory concentration, favipiravir was about 2650 times more selective for influenza RdRp, while lacking inhibition of human RNA or DNA synthesis.^{36,41}

Pharmacokinetics and safety

Favipiravir is metabolized mainly by aldehyde oxidase (AO) and partly metabolized to a hydroxylated form by xanthine oxidase (XO). A glucuronate

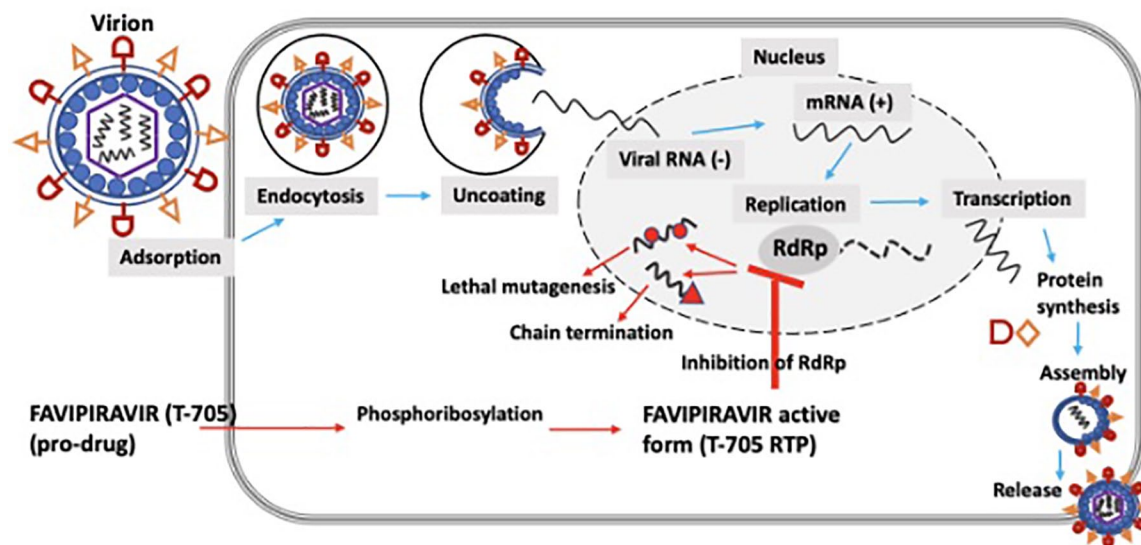


Figure 1. Schematic showing the mechanisms of action associated with favipiravir.

conjugate was observed in human plasma and urine as a metabolite other than the hydroxylated form. It is predominantly excreted into the urine as a hydroxylated form, with minimal unchanged drug. The pharmacokinetic profile of favipiravir has been studied through dose-escalated studies, with oral dosage for adults at 1600 mg twice daily on day 1 (loading dose), followed by 600 mg twice daily for 4 days, with the total duration of therapy being 5 days.²⁹ The maximum plasma concentration was achieved within 2 h after administration of a single dose, although plasma concentration quickly decreased, with half-life between 2 and 6 h.^{29,42} Interestingly, administration of multiple doses led to an increase in the time to maximum plasma concentration and half-life.⁴² Favipiravir is associated with dose- and time-dependent pharmacokinetics, possibly explainable by saturation of the main enzymatic pathway as it was shown to inhibit AO *in vitro*.^{29,42} In Ebola-infected patients, the favipiravir plasma concentration surprisingly decreased between treatments, potentially due to severe disease conditions or intrinsic properties of favipiravir metabolism.⁴³ In variable disease conditions, favipiravir bioavailability and the hepatic first pass can be altered, through an increase in the activity of the AO with temperature.^{32,43}

The literature suggests that favipiravir is a well-tolerated drug.³² The most frequently reported adverse effects of favipiravir when used for influenza treatment, are mild to moderate diarrhea, asymptomatic increase of blood uric acid and

transaminases, and a decrease in the neutrophil count.²⁹ In a study evaluating the inhibition properties of favipiravir against human and mouse norovirus RNA polymerases, it was found that favipiravir ribonucleoside triphosphate was recognized as a substrate of the human mitochondrial RNA polymerase, but did not result in inhibition of the DNA-dependent RNA polymerase nor cause mitochondrial toxicity in cells.^{32,40} Despite good tolerance observed, a major concern to safety of clinical favipiravir use is related to its teratogenic tendencies. In studies with fetal/embryo models of multiple animal species, teratogenicity was observed across all.⁴⁴ The exposure dosage causing teratogenicity was comparable with the proposed human use dosage. Therefore, it is strongly recommended that favipiravir not be administered to pregnant or possibly pregnant individuals.^{29,44} Due to this high risk of teratogenicity and embryotoxicity, favipiravir is conditionally marketed with strict regulation in Japan.³² Hence the clinical use of favipiravir is restricted to novel or re-emerging influenza viruses, only when that virus is resistant to other influenza antivirals, while being manufactured and distributed only upon request by the Minister of Health, Labor and Welfare in Japan.^{29,32}

Use in influenza

Early literature on favipiravir dates to 2001. Also known as T-705, favipiravir was tested *in vitro* for its antiviral properties against Influenza A, B, and C, against all of which it was found effective. It

was also reported to have activity against oseltamivir and amantadine-resistant Influenza A. The Influenza A viral strains originally studied included H1N1, H2N2, and H3N2.⁴⁵ Selective viral RNA polymerase inhibition without inhibition of cellular RNA or DNA synthesis was reported as its proposed mechanism of action.³⁶ Takahashi *et al.*⁴⁶ reported that T-705 retained its efficacy against influenza-infected mice when compared with oseltamivir despite a delay of treatment initiation of up to 25-h post infection. Sidwell *et al.*⁴⁷ reported activity of T-705 against mice infected with avian H5N1 influenza. Antiviral drug regimens studied in mice yielded statistically significant protection against death at doses of or higher than 30 mg/kg/day given twice a day for 5 days. The effect of delaying therapy by up to 72 h after infection was also studied and Furuta *et al.* reported that T-705 retained its antiviral property in protecting mice against death at doses of 300 mg/kg/day given every 6 h for 5 days.^{41,48} Favipiravir resistance was first reported by Goldhill *et al.*⁴⁹ who stated that a K229R mutation in RdRp would confer drug resistance to favipiravir among pandemic 2009 H1N1 Influenza A viral strains. In one study, the combination of favipiravir with oseltamivir showed synergy at low doses in animal models infected with H1N1, H3N2, and H5N1 Influenza A viral strains.⁵⁰ Wang *et al.*⁵¹ found accelerated clinical recovery among patients with severe Influenza on favipiravir and oseltamivir combination therapy compared with oseltamivir alone.

The approved favipiravir drug regimen in Japan for the treatment of Influenza is 1600 mg (loading doses) on day 1 followed by 600 mg twice a day, with the total duration of therapy being 5 days.^{29,52} Other experimental clinical studies in influenza^{53–56} used a regimen of 1800 mg (loading doses) followed by 800 mg twice a day, for a total duration of therapy of 5 days. Evidence from clinical trials assessing over 2000 patients suggests that favipiravir is well-tolerated.^{51,53–56} Adverse drug reactions reported include elevation in serum uric acid levels, diarrhea, elevation of liver enzymes, and reduction in neutrophil count.⁵²

Use in other viral diseases

Viral hemorrhagic fevers

The causative agents of viral hemorrhagic fevers (VHFs) belong to *Arenaviridae*, *Bunyaviridae*,

Filoviridae, and *Flaviviridae* families of viruses, all of which are RNA viruses. Prominent VHFs caused by these viruses include Ebola viral disease and Yellow Fever among others. Favipiravir was trialed in rural Guinea during the Ebola virus disease (EVD) outbreak in 2014 as a multicenter proof-of-concept non-comparative trial. Nuanced conclusions were drawn about the efficacy of favipiravir as the trial was nonrandomized and all study participants received the drug given the public health crisis at the time. The authors reported that although favipiravir monotherapy may not be effective in patients with very high viremia, its clinical utility in intermediate to high viremia would merit investigation.⁵⁷ Another retrospective observational study on outcomes of patients treated with compassionate use favipiravir *versus* untreated patients showed a lower-case fatality ratio among those treated with favipiravir thereby conferring survival benefit.⁵⁸ Translational research on the efficacy of favipiravir against EVD done in macaques showed survival benefit among the infected animals that received ≥ 150 mg/kg of favipiravir. The authors observed inhibition of viral replication in a concentration-dependent manner and concluded that favipiravir plasma trough concentrations > 70 – 80 $\mu\text{g/ml}$ were linked to lower viral loads and improved survival.⁵⁹

Favipiravir has been tested *in vitro* against other etiological agents of VHFs including *Bunyaviridae* and *Arenaviridae*. Gowen *et al.*⁶⁰ studied the *in vitro* inhibitory effects of favipiravir (T-705) and ribavirin in monkey kidney Vero 76 cells against La Crosse virus, Punta Toro virus, sandfly fever virus, and rift valley fever virus (Bunyaviruses) and found that the drug inhibited the growth of the tested viral strains and was less toxic than ribavirin. The same authors examined the *in vitro* activity of favipiravir (T-705) against Junin virus, Pichinde virus, and Tacaribe virus (Arenaviruses) and found that the drug was highly active against the tested viral strains in cell cultures. The drug also afforded protection to hamsters infected with Pichinde virus and mice infected with Punta Toro virus.

Yellow fever is a VHF caused by the yellow fever virus (YFV), a flavivirus. The YFV distribution runs through tropical and subtropical Africa and South America. Clinical disease could be asymptomatic or may manifest with fever, chills, headache, myalgia, jaundice, bleeding, shock, and organ failure. The mortality rate of those with

severe symptomatic disease can be > 30%. Julander *et al.* found T-705 to be moderately effective against YFV in cell culture. It was also found to be an effective treatment in YFV infected hamsters conferring survival benefit among the infected animals treated with T-705.⁶¹

West Nile Virus

West Nile Virus (WNV) is a vector-borne (mosquito) disease caused by the West Nile Virus, a flavivirus. The spectrum of disease can vary from asymptomatic infection to mild febrile illness to severe viral meningitis or encephalitis. To date, there is no approved antiviral for the treatment of WNV. Morrey *et al.* studied the efficacy of orally administered favipiravir (T-705) among rodents infected with WNV and found the drug to be active against WNV. The drug's lack of activity past the second day on viral infection was attributed to either the lack of a standard drug regimen or insufficient bioavailability in the brain or lack of neuronal metabolism to convert favipiravir to T-705 RTP.⁶²

Nipah virus

Nipah virus is an emerging zoonotic infection caused by the Nipah virus which belongs to the *Paramyxoviridae* family of viruses. Outbreaks have been reported out of Malaysia, Bangladesh, and India periodically. Fruit bats are its natural reservoir, and the virus can be transmitted to humans either from bats or *via* an intermediate host such as pigs or *via* human-to-human transmission. Clinically, the disease manifests as viral encephalitis with features of respiratory compromise. To date, there is no approved treatment or vaccine for Nipah virus. The disease has a high mortality rate, ranging upward of 40%.⁶³ Favipiravir has shown *in vitro* activity against vero cells infected with Nipah virus and prevented viral replication.⁶⁴ Dawes *et al.*⁶⁴ also found benefit of favipiravir administration among hamsters infected with Nipah virus and reported that treated hamsters infected with the virus did not develop any signs of clinical disease.

Respiratory viral diseases (other than influenza and COVID-19)

Human metapneumovirus (hMPV) and RSV, previously classified under *Paramyxoviridae*, belong to the family *Pneumoviridae* and can cause

upper or lower respiratory tract disease in humans. Parainfluenza virus can cause similar disease and belongs to the *Paramyxoviridae* family of viruses. Favipiravir (T-705) demonstrated activity against all these viruses *in vitro* in a study done by Jochmans *et al.* The authors also reported *in vivo* drug activity in hamsters infected with hMPV.⁶⁵

Use in COVID-19

Early genomic sequencing of SARS-CoV-2 virion suggested over 90% homology, across several essential enzymes, with other coronaviruses, particularly those causing SARS and MERS.⁶⁶ In a quest for identifying effective therapy amid a catastrophic global pandemic, this knowledge helped trigger the 'repurposing' of multiple antiviral drugs including broad-spectrum antivirals and more specifically, drugs previously directed toward therapy of SARS, MERS, and other viral infections. The mechanism of action of favipiravir against SARS-CoV-2 is similar to that previously described in literature. After viral incorporation of T-705 RTP by RdRp, the nascent coronaviral RNA undergoes slowed RNA synthesis, chain termination, and viral mutagenesis, while evading the viral RNA repair mechanism. The SARS-CoV-2 RdRp has been described to have 10-fold higher activity than other viral counterparts, while simultaneously being prone to high nucleotide incorporation and error rates.⁶⁷ These processes significantly bottleneck the RNA replication by causing nucleotide shifts in an unbalanced viral environment with already low cytosine levels.⁶⁷ These critical hallmarks of the SARS-CoV-2 virion machinery make it vulnerable to RdRp inhibitors.

Alongside an effective vaccine, antivirals have a critical role in containing local spread of infection by curtailing viral load and shedding, at an early infection stage.⁶⁸ Studies suggest viral load in the upper and lower respiratory tracts in patients with mild infection peak in the early stage of infection, days 4 and 6, respectively, while in moderate-severely infected patients they peak in later stages, days 8 and 11.⁶⁹ Thus, the role of antivirals like favipiravir may be higher in mild-moderate infections at an early stage of the disease, to control the viral load, shedding, and infectivity rates,⁷⁰ to help reduce the burden of hospitalization and associated patient care on an already overwhelmed system.

An early study (February 2020) showed that favipiravir at higher concentrations (EC₅₀ = 61.88 μM)

was able to minimize viral infection in vero E6 cells *in vitro*.⁷¹ While these *in vitro* studies suggested a need for further evaluation, the efficacy of favipiravir in patients infected with COVID-19 was initially assessed through two separate clinical trials in China (February 2020).⁷² The inclusion criteria for both the trials included patients within the early stage of disease, from manifestation of symptoms and positive test result with reverse transcription polymerase chain reaction (RT-PCR), and patients with severe disease were excluded. In one of the trials, patients with COVID-19 were treated with a combination of favipiravir and alpha interferon ($n = 30$), while the other treatment arm was treated with lopinavir and ritonavir combination with alpha interferon.⁷² The second clinical trial assessed the efficacy of favipiravir against therapy with baloxavir marboxil.⁷² In addition, after initial approval of favipiravir for treatment of COVID-19 in China (February 2020), another study with 80 patients showed it had promise as an antiviral therapeutic, with lower side effects when compared with the lopinavir/ritonavir treatment arm.⁷³ While these initial studies showed some favorable results, there were safety concerns for use due to side effects like teratogenicity, prolongation of QTc interval and hyperuricemia as evidenced in use for other pathologies.⁷⁴ Interestingly, in a randomized controlled trial conducted on patients to receive either favipiravir or arbidol, with a primary outcome for recovery on day 7, favipiravir did improve latency to relief of cough and fever but did not improve clinical recovery rate, while the most frequently observed side effect was hyperuricemia.⁷⁵

Subsequently, other studies have been conducted to understand the efficacy of favipiravir in COVID-19. Studies have suggested that favipiravir could lead to viral clearance by day 7 and improve clinical outcome by 2 weeks when administered in early stages of infection.^{76,77} In one study, the median time to viral clearance was about 12.8 days in patients when favipiravir therapy was initiated on day 1, and increased to 17.8 days when therapy was started on day 6.⁷⁸ In addition, there were significant differences in duration of hospitalization, with need for oxygenation and mechanical ventilation, in patients with mild or asymptomatic infection when favipiravir therapy initiated late stage *versus* early. Thus, it may be important to initiate favipiravir therapy at an early stage of disease in asymptomatic or

mildly infected COVID-19 patients, to achieve reduction in viral load and disease progression.^{76,77} Importantly, dosing regimens could significantly change the clinical outcome of the patient, lower doses indicating to have lower association with better outcomes.⁷⁶ Comparison of multiple trials suggests that favipiravir may not have a significant beneficial effect on improving patient mortality rate in subjects with mild to moderate COVID-19, and this may be associated with the timeline of therapy initiation.⁷⁷ However, it is necessary to assess the favipiravir therapy initiation timeline, dosage, duration, and safety through trials with larger sample size.

The use of favipiravir on a compassionate or approved basis for the indication of COVID-19 treatment has been put through clinical trials across the globe. Table 2 summarizes key published clinical trials (including from preprint servers) to date. The drug was trialed in cases of asymptomatic and mild-moderate disease as well as in moderate-severe cases of COVID-19 pneumonia. While most trialed a regimen of 1600 mg loading dose (two doses) on day 1 followed by 600 mg twice daily, other regimens used 1800 mg loading dose (two doses) followed by 800 mg twice a day. The length of drug therapy with favipiravir was varied and ranged from 7 to 14 days. At the present time, favipiravir is not approved for use in COVID-19 by the United States Food and Drug Administration or its European counterpart, the European Medicines Agency. The formally recommended dose and duration of therapy remain awaited based on results of the ongoing clinical trials. However, it is noteworthy that 600 mg twice daily maintenance dose has been used to manage COVID-19 in some international markets.⁷⁹ Doi *et al.* studied the effect of early *versus* late favipiravir use among adolescents and adults with asymptomatic or mild COVID-19 and noted that viral clearance by day 6, which was their primary endpoint, was similar between the two groups. Secondary and exploratory endpoints, that is, viral load reduction by day 6 and time to defervescence were met in the early treatment arm.⁸⁰ Another group of researchers who studied the drug's efficacy *versus* supportive care alone, among patients with mild to moderate COVID-19, found shorter time to cessation of viral shedding with favipiravir but this was not statistically significant. The median time to clinical cure among symptomatic patients at baseline was reportedly significantly faster with favipiravir.⁸¹ Ivashchenko *et al.*

Table 2. Summary of published (including preprint) literature from favipiravir clinical trials to date.

Authors	Study period	Geographic region of study origin	Trial design	Patient population	Intervention	Favipiravir dose(s)	Duration of therapy	Primary outcome	Secondary outcome(s)	Results
Chen <i>et al.</i> ⁷⁵	February–March 2020	China	Prospective, randomized, open-label multicenter	Adults with COVID-19 pneumonia	Conventional therapy + umifenovir versus conventional therapy + favipiravir	1600/600	10 days	Clinical recovery on day 7	Latency to relief for fever and cough, the rate of auxiliary oxygen therapy or noninvasive mechanical ventilation	Favipiravir did not significantly improve the clinically recovery rate at day 7 compared with umifenovir. Significantly improved latency to relief for fever and cough
Lou <i>et al.</i> ⁷⁶	February 2020	China	Exploratory, single-center, open-label, randomized, controlled, 1:1:1	Hospitalized adults with COVID-19	Baloxavir, favipiravir, control (lopinavir/ritonavir, umifenovir, darunavir/cobicistat)	1600 or 2200/600	14 days	PCR negativity by day 14	Percentage of subjects with negative PCR by day 7, the incidence of mechanical ventilation by day 14, ICU admission by day 14, and all-cause mortality by day 14	Adding either baloxavir marboxil or favipiravir to the current standard treatment did not provide additional benefits
Doi <i>et al.</i> ⁸⁰	March–May 2020	Japan	Prospective, randomized, open-label	Adolescents and adults with asymptomatic or mild COVID-19	Early versus late favipiravir (day 1 versus day 6)	1800/800	10 days	Viral clearance by day 6	Change in viral load by day 6	Viral clearance by day 6 was not significantly different, associated with numerical reduction in time to defervescence
Udwadia <i>et al.</i> ⁸¹	May–July 2020	India	Randomized, open-label, parallel arm, multicenter, phase 3	Pts with mild-moderate COVID-19	Favipiravir plus supportive care versus supportive care alone	1800/800	14 days	Time to cessation of viral shedding (OP and NP swabs)	Time to clinical cure	Shorter time to cessation of viral shedding with favipiravir but not statistically significant. Median time to clinical cure among pts symptomatic at baseline was significantly faster with favipiravir

(Continued)

Table 2. (Continued)

Authors	Study period	Geographic region of study origin	Trial design	Patient population	Intervention	Favipiravir dose(s)	Duration of therapy	Primary outcome	Secondary outcome(s)	Results
Ivashchenko <i>et al.</i> ⁸²	April–May 2020	Russia	Adaptive, multicenter, open-label, randomized, Phase II/III	Hospitalized pts with moderate COVID-19 pneumonia	Favipiravir versus standard of care (HCQ/CQ & lopinavir/ritonavir)	1600/600, 1800/800	14 days	Elimination of SARS-CoV-2 by day 10	–	Proportion of pts who achieved negative PCR on day 5 on both dosing regimens of favipiravir was twice as high as in the control group ($p < 0.05$)
Zhao <i>et al.</i> ⁸⁴	February–March 2020	China	Multicenter, randomized 3:1:1	Adults with COVID-19 and increased IL-6	Favipiravir + Tocilizumab, favipiravir, tocilizumab	1600/600	7 days	Cumulative lung lesion remission rate	Improvement of clinical symptoms, changes in routine blood tests and IL-6, changes of oxygen therapy	Cumulative lung lesion remission rate at day 14 was significantly higher in combination group as compared with favipiravir group ($p = 0.019$), significant difference between tocilizumab and favipiravir ($p = 0.034$)
Khamis <i>et al.</i> ⁸⁵	June–Aug 2020	Muscat, Oman	Open-label, randomized controlled	Adults (18–75 years) hospitalized with moderate to severe COVID-19 pneumonia	Combination of favipiravir with inhaled interferon beta-1b versus hydroxychloroquine	1600/600	10 days	Time to clinical recovery, normalization of inflammatory markers and improvement in oxygen saturation	Deterioration of pneumonia, ICU admission rate and mortality within 14 days	No differences in overall length of hospital stay, ICU transfers, discharges, oxygen saturation at discharge, overall mortality and changes in the inflammatory markers at discharge
Solaymani-Dodaran <i>et al.</i> ⁸⁶	April–August 2020	Iran	Multicenter randomized open-labeled	Pts with PCR confirmed SARS-CoV-2 or GGOs on CT Chest, ages 16–100, oxygen saturation $< 93\%$ (moderate-severe cases)	Favipiravir + HCQ versus lopinavir/ritonavir + HCQ	1600/600	7 days	Number of ICU admissions	Length of hospital stay, in-hospital mortality, time to clinical recovery	No reduction in number of ICU admissions or intubations or in-hospital mortality compared with lopinavir/ritonavir. Time to clinical recovery and length of hospital stay similar in two groups

(Continued)

Table 2. (Continued)

Authors	Study period	Geographic region of study origin	Trial design	Patient population	Intervention	Favipiravir dose(s)	Duration of therapy	Primary outcome	Secondary outcome(s)	Results
Dabbous <i>et al.</i> ⁸⁷	April–May 2020	Egypt	Randomized, controlled, interventional, Phase 3	Mild-moderate COVID-19, NP swab PCR positive pts	Oseltamivir + HCQ versus favipiravir	1600/600	10 days	SARS-CoV-2 viral clearance on days 3, 7, and 14	Clinical outcomes on days 3, 7, and 14.	No statistically significant difference in PCR negativity between groups by day 7 and ~90% of both groups achieved viral clearance by day 14.
Dabbous <i>et al.</i> ⁸⁸	April–August 2020	Egypt	Multicenter, randomized, controlled	Mild-moderate COVID-19, ages 18–18, hospitalized pts	CQ versus favipiravir	1600/600	10 days	Mortality rate and need for mechanical ventilation	-	No statistically significant differences between two groups although lower length of stay in favipiravir arm

COVID-19, coronavirus disease of 2019; CQ, chloroquine; CT, computed tomography; HCQ, hydroxychloroquine; ICU, intensive care unit; NP, nasopharyngeal; OP, oropharyngeal; PCR, polymerase chain reaction; Pts, patients; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2. Retracted papers were excluded from the table. Ages 18–80, hospitalized pts.

observed statistically significant differences between favipiravir treatment groups compared with standard of care at the time (hydroxychloroquine or chloroquine or lopinavir/ritonavir); in terms of viral PCR clearance, Cai *et al.* suggested favorable radiographic outcomes in the favipiravir treatment arm compared with control (lopinavir/ritonavir) in addition to shorter median time for viral clearance.^{82,83} The optimal dosages and duration of drug therapy with favipiravir for COVID-19 remain indefinite. Further clinical trials with specific aims to guide these aspects of treatment are warranted.

Future directions

Table 3 summarizes publicly available information about ongoing favipiravir clinical trials.^{89–95} The GETAFIX, FLARE, COVERAGE, and VIRCO trials are focused on drug efficacy early in the treatment of COVID-19 and the COVERAGE trial will be looking specifically at geriatric patients. The PRINCIPLE trial collaborative group evaluated the use of azithromycin among adults 50 years of age or more with medical comorbidities and all adults above 65 years of age with COVID-19 and found that its use did not shorten the time to clinical recovery or reduce the risk of hospitalization.⁹⁶ Interim results of the PRINCIPLE trial also reported clinical utility of inhaled budesonide among patients with COVID-19 at risk for adverse outcomes.⁹⁷ The findings from the PRINCIPLE trial about favipiravir's clinical utility remain awaited. Bosaeed *et al.*⁸⁹ have proposed a multicentric randomized controlled trial to evaluate efficacy of favipiravir and hydroxychloroquine combination in comparison with control. Hassaniazad *et al.*⁹⁰ also published about an upcoming single-center, randomized, open-label clinical trial among moderately ill patients with COVID-19 evaluating the safety and efficacy of favipiravir and interferon beta-1a combination in comparison with lopinavir/ritonavir and interferon beta-1 combination.

Conclusion

Favipiravir, among other drugs, has gained prominence since 2020 because of the COVID-19 pandemic and its versatility as a broad-spectrum antiviral that inhibits RdRp and targets viral replication. While its utility has shown benefit in a few clinical trials, others yielded mixed results.

Table 3. Summary of ongoing favipiravir clinical trials.

Name of trial, authors, and region	Trial design	Participants	Intervention & comparator	Outcome
FACCT A Trial of Favipiravir and Hydroxychloroquine combination in Adults Hospitalized with moderate and severe COVID-19 Bosaeed <i>et al.</i> ⁸⁷ Saudi Arabia	Open-label, multicenter, randomized controlled clinical trial	<ul style="list-style-type: none"> Age 18 and above Male or nonpregnant female PCR positive Moderate or severe COVID-19 Within 10 days of disease onset 	Favipiravir (1800/800) × 10 days + HCQ × 5 days versus standard of care	Time to clinical improvement Other outcome: Time to PCR negativity
Evaluation of the efficacy and safety of favipiravir and interferon compared with lopinavir/ritonavir and interferon in moderately ill patients with COVID-19 Hassaniyazad <i>et al.</i> ⁹⁰ Iran	Phase 3, single-center, randomized, open-label, controlled trial	<ul style="list-style-type: none"> Age 20 and above PCR positive Moderate COVID-19 pneumonia on CT or CXR requiring hospitalization Hospitalized ≤ 48h 	Favipiravir (1600/600) × 5 days + IFN beta-1a versus lopinavir/ritonavir + IFN beta-1a	Viral load in NP swab samples assessed by PCR after 7 days and clinical improvement of fever and O ₂ saturation within 7 days
GETAFIX Glasgow Early Treatment Arm Favipiravir for adults with early stage COVID-19 Hanna <i>et al.</i> ⁹¹ United Kingdom	Multi-center, open-label, phase II/III randomized trial	<ul style="list-style-type: none"> Age 16 and above Exhibiting symptoms Positive for SARS-CoV-2 Point 1, 2, 3, or 4 on the WHO COVID-19 ordinal severity scale at time of randomization (asymptomatic with positive valid COVID-19 test, symptomatic independent, symptomatic assistance needed, hospitalized, with no oxygen therapy) Have ≥ 10% risk of death if admitted to hospital Able to swallow oral medication 	Favipiravir (1800/800) × 10 days + standard of care versus standard of care alone	Drug efficacy
COVERAGE Home Treatment of Older People with Symptomatic COVID-19 Duvignaud <i>et al.</i> ⁹² France	Multicenter, randomized, controlled clinical trial 1:1:1:1 Arm 1: Control Arms 2–5: Treatment	<ul style="list-style-type: none"> Age 65 and above Positive NP swab PCR Symptom onset within 3 days No hospitalization 	(1) HCQ (2) Imatinib (3) Favipiravir 200 mg, 12 tablets BID on day 0, 6 tablets BID from days 1–9 (4) Telmisartan Comparator: AZINC Forme et Vitalité®, 1 capsule BID for 10 days	Efficacy of drugs to prevent hospitalization/death in seniors > 65 years of age with recent COVID-19
VIRCO An adaptive randomized placebo-controlled phase II trial of antivirals for COVID-19 infection McMahon <i>et al.</i> ⁹³ Australia	Randomized, placebo-controlled phase II clinical trial	<ul style="list-style-type: none"> Age ≥ 18 years PCR positive within 5 days Within 5 days of symptom onset 	Favipiravir (1800/800) × 14 days versus placebo	Drug efficacy based on time to PCR negativity within 14 days. Other outcome measures: Drug safety, clinical benefit, effect on biomarkers of inflammation and immune system activity
FLARE Early antiviral treatment in outpatients with COVID-19 Brown <i>et al.</i> ⁹⁴ United Kingdom	Phase IIA, randomized, double-blind, placebo-controlled trial	<ul style="list-style-type: none"> Ages 18–70 Symptoms of COVID-19 disease within the first 5 days of symptom onset OR symptoms of COVID-19 and tested positive for within the first 7 days of symptom onset OR no symptoms but tested positive within the last 48h 	1:1:1:1 (1) Favipiravir (1800/400 QID) + lopinavir/ritonavir × 7 days (2) Favipiravir + lopinavir/ritonavir placebo (3) Favipiravir placebo + lopinavir/ritonavir (4) Favipiravir placebo + lopinavir/ritonavir placebo	Upper respiratory tract viral load on day 5
PRINCIPLE Platform Randomized trial of Interventions against COVID-19 in older people Hayward <i>et al.</i> ⁹⁵ United Kingdom	Open-label, multi-arm, prospective, adaptive platform, randomized clinical trial in community care	<ul style="list-style-type: none"> Symptoms of possible COVID-19 with a positive SARS-CoV-2 test – Within the last 14 days Age ≥ 65 years OR Patients aged ≥ 50–64 years with comorbidities 	Favipiravir/ivermectin/HCQ/azithromycin/doxycycline/inhaled budesonide versus standard of care	Time to recovery/hospitalization/death within 28 days

BID, twice a day; COVID-19, coronavirus disease of 2019; CT, computed tomography; CXR, chest X-ray; HCQ, hydroxychloroquine; IFN, interferon; NP, nasopharyngeal; PCR, polymerase chain reaction; QID, four times a day; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; WHO, World Health Organization.

The drug's full potential as a therapy for COVID-19 remains to be determined, including its optimal timing of administration, dosage, and duration of therapy. It is fairly well-tolerated with a major safety concern being its teratogenic potential. Adverse drug reactions among patients included hyperuricemia, QTc interval prolongation, and elevation in hepatic enzymes. Finally, favipiravir's prospect as a post-exposure prophylactic agent in COVID-19 remains to be tested.

Author contributions

KS: Conceptualization, manuscript preparation, review and editing.

MR: Conceptualization, manuscript preparation, review, editing and submission.

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ORCID iDs

Kritika Srinivasan  <https://orcid.org/0000-0003-2877-3542>

Mana Rao  <https://orcid.org/0000-0002-2516-2079>

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