Recent Updates Published About Favipiravir in COVID-19

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ABSTRACT
Due to its high transmission potential, COVID-19 disease has turned out to be a worldwide public health threat. As of May 2020, over 5M infections and 300,000 deaths had been reported globally. At the moment, there is limited research evidence from RCTs recommending certain drugs for the treatment of suspected or confirmed COVID-19 patients. However, a number of studies have proposed numerous antiviral agents as a potential treatment option based on experiments done on animal models infected with other viral diseases. One such drug is favipiravir. The purpose of this review, therefore, was to examine recent updates about favipiravir and its likely role in the treatment of coronavirus disease. As has been previously reported in literature, favipiravir acts as a broad-spectrum medication that prevents the multiplication of flavivirus, filovirus, poliovirus, arenaviruses, and rhinovirus. The drug has recently been reported in some studies as useful in shortening the time of clinical recovery for COVID-19 patients. The study guaranteeing the usefulness of favipiravir in the treatment of the virus has since been withdrawn temporarily. The analysis in the study was largely open-label and non-randomized. Even with its adverse pharmacokinetic profile and the inconclusive data regarding its usefulness in the management of COVID-19, China has authorized the drug as a suitable treatment of COVID-19 patients as of March 2020. Still, favipiravir has been included in a number of ongoing trials, together with other antiviral drugs, such as lopinavir/ritonavir.

INTRODUCTION
Currently, there is a worldwide outbreak of a novel type of coronavirus (COVID-19), which started from Wuhan, China. At the moment, the disease has spread to over 140 nations, including Korea, Japan, and Italy. Recently, the World Health Organization (WHO) announced that the virus has turned out into a worldwide health concern, resulting in profoundly serious respiratory tract infections in human beings (Zhai et al., 2020). As of May 2020, over 5,488,825 cases and 349,095 deaths had been reported globally resulting from COVID-19. According to the WHO, the pandemic is now a universal topic in global online conversations, with the term “covid” ranking as the second most used word in all English-language social media posts published in May, 2020 (WHO, 2020). Limited evidence exists from randomized controlled trials (RCTs) to suggest a particular treatment for patients with an alleged or long-established COVID-19 infection. Apart from supportive care through respirators, no universal medical therapy has been validated to date. Even so, the quick spread of COVID-19 has led to every cooperative effort against the virus (Zhai et al., 2020).
An examination of early transmission patterns of COVID-19 showed that the average incubation period of the disease was between 5.2 and 12.5 days. An advanced study used the history of travel together with the symptom onset of 88 confirmed cases and reported a mean incubation period of 6.4 days (95% CI, 5.6–7.7) (Zhai et al., 2020).

An infrequent case has also been reported where the incubation period was as high as 19 days. However, most experts suggest an average incubation period of 14 days (Zhai et al., 2020). Possibilities for such long incubation time could mean changes in the policies used to screen and control suspected COVID-19 cases.

Quick and accurate detection of COVID-19 is essential to controlling outbreaks within the community and in hospitals. Some of the methods being used to detect the virus at the moment include “reverse-transcription polymerase chain reaction (RT-PCR), reverse transcription loop-mediated isothermal amplification (RT-LAMP), and real-time RT-PCR (rRT-PCR).” A diagnostic criterion developed by the China National Health Commission shows laboratory examinations as being the standard assessments for COVID-19 disease. On most occasions, these test center examinations include nasopharyngeal and oropharyngeal swab tests. While useful, laboratory tests have proven to consume a lot of time and are largely affected by a scarcity and delay of commercial kits. Apart from this diagnostic approach, automated solutions designed for molecular diagnostics can accommodate many samples and can easily be scaled to keep pace with changing demands (Zhai et al., 2020).

No recent evidence from RCTs recommends any particular anti-SARS-CoV-2 treatment for those alleged or established to have COVID-19 disease (Zhai et al., 2020). While efforts to search for a coronavirus cure continue, it is important to acknowledge the progress that has been made in the development of antiflue therapies since the middle of the 20th century (Furuta et al., 2017). Over the years, researchers have developed antibiotics, vaccines, as well as anti-microbial agents believed to be effective in dealing with certain types of viruses. Popular antiviral agents proposed for the cure of COVID-19 include lopinavir (LPV), ribavirin, remdesivir, and favipiravir; which is the focus of this review paper. LPV has proven to stop the protease activity of coronavirus in vitro as well as animal studies. When used as an initial treatment, LPV/ritonavir resulted in a reduced death rate from 11% to 2.3%. However, the success of LPV and its potential use in treating COVID-19 is largely based on experience with SARS and MERS outbreaks. The other antiviral agent, Ribavirin is often used to treat numerous types of virus infections, such as hepatitis C virus, respiratory syncytial virus, and certain viral hemorrhagic fevers. Ribavirin targets the SARS-CoV-2 RNA-dependent RNA Polymerase (RdRp) model, making it as possible treatment choice for COVID-19. Next, remdesivir was developed to treat Ebola virus disease but shows a wide-spectrum antiviral activity against many other RNA viruses (Zhai et al., 2020). Of key concern to this review is pyrazinecarboxamide derivative T-705 (Favipiravir), an antiviral agent developed by Toyama Chemical Co., Ltd in 2002 (See Figure 1 for an illustration of the chemical structure of Favipiravir (T-705) (Furuta et al., 2017; Oesterich et al., 2014). Host enzymes convert pyrazinecarboxamide derivative T-705 to T-705-ribofuranosyl-5′-triphosphate, which either acts as nucleotide analog that discretely stops the virus-related RNA-dependent RNA polymerase or results in deadly mutagenesis. Favipiravir was invented by modifying pyrazine through a chemical approach. Primarily, the medication was designed to inhibit virus replication among influenza patients. However, it has shown to be valuable against all the other RNA viruses, for instance, arena – and bunyaviruses in vitro and in vivo, as well as noro- and flaviviruses. What this means is that favipiravir is a potential medication that can be used in the treatment of influenza infections and a wide range of other RNA viruses (Furuta et al., 2017; Oesterich et al., 2014). On average, 5 mg of the drug costs about $50 at the moment (Med Chem Express, 2020).

**MECHANISM OF ACTION**

Favipiravir’s mechanism of action has been described in various studies and is as follows (Furuta et al., 2017). The medication is designed to inhibit the multiplication of viral genome. The medication is activated once it is incorporated into the cells. However, the mechanism of interaction between favipiravir-RTP and RdRp molecule is yet to be adequately explained. The prevailing assumption is that favipiravir could easily be inappropriately incorporated in a promising viral RNA, or could act by attaching itself to polymerase domains, thereby stopping the combination of nucleotides for viral RNA duplication and transcription. Recent research has also shown that favipiravir had the ability to induce lethal mutagenesis during influenza infection. The medication also reduced viral titer either at a low or high multiplicity of infection in vitro (Furuta et al., 2017).
Existing Literature

Over time, an extensive literature has developed on the value of favipiravir in treating patients with Ebola virus. The prevailing hypothesis is that high doses of favipiravir have a potential impact on Ebola virus disease patients (EVD). To ascertain this hypothesis, studies have assessed the efficacy of the pyrazinecarboxamide derivative T-705 against Zaire Ebola virus. Most of the studies have been conducted in vitro and in vivo. The T-705 compound used in the study had been custom synthesized and mixed with dimethyl sulfoxide (DMSO) (Oestereich et al., 2014). The mixture was maintained at a concentration of 10 mg/ml and the resulting solution stored at temperatures of -20°C. As far as the findings of the study are concerned, T-705 proves to be the first effective therapeutic agent that can be used in the treatment of advanced cases of Ebola virus disease as demonstrated in an animal model. Based on the findings, the compound caused a reduction in viremia, amended the clinical and biochemical indications of the disease, and prevented lethal outcome in 100% of the animal models as long as treatment was started 6 days after infection. This duration was equivalent to 2-4 days prior to the time of death in the animal models used as controls for the study. Since the drug shows obvious effects in vivo, efficacy on other viruses within the same conditions seems possible. Despite these findings, there is still more that needs to be done to translate findings obtained from animal models into more realistic Ebola hemorrhagic fever (EHF) models, and eventually apply the findings in clinical practice (Oestereich et al., 2014).

One recent study used a sample of Ebola-virus-infected nonhuman primates (NHPs) to examine the efficacy of the antiviral properties of favipiravir. To begin with, the authors tested 100 mg/kg BID favipiravir, guided by pharmacokinetic studies. Based on the outcome of the experiment, the drug has no impact on survival and resulted in reduced plasma drug concentrations than anticipated, findings that were confirmed in a pharmacokinetic study carried out subsequently. Based on these findings, the authors carried out detailed pharmacokinetic studies in uninfected nonhuman primates using doses of 150 and 180 mg/kg BID. The resulting analyses showed that favipiravir had complicated nonlinear pharmacokinetics because of a concentration-dependent prevention of aldehyde oxidase, which refers to the key enzyme engaged in the metabolism of favipiravir. The outcome of the analyses also revealed that nonhuman primates could tolerate and experience a reduction in viremia with favipiravir doses of 150 and 180 mg/kg. The findings showed that favipiravir effectively subdued viral replication in a drug-concentration-dependent manner, and an rise in virus mutagenesis was observed over time. Specifically, the authors noted a reduction in the viral load levels at the 5th and 7th days in the treated animals, while there was no significant change among the untreated animals. In general, favipiravir concentrations above 70-80 μg/ml resulted in a reduction in the viral loads, lowered the infectivity of the virus, and prolonged sur-
vival (Guedj et al., 2018). Unfortunately, extrapolation to patients with Ebola virus disease is limited by the use of a lethal model and the fact that treatment in most patients starts several days after infection and visibility of symptoms. These findings support the likely role of favipiravir in human interventions. While the medication has an undesirable pharmacokinetic profile, recent information shows that the China has certified it to be marketed as a potential treatment of coronavirus disease, as of March, 2020 (Guedj et al., 2018; Jean et al., 2020).

Favipiravir promotes irrefutable recovery and lowers the risk of respiratory challenges. The medication has a tougher antiviral effect compared to LPV/r and can be used as a clinical problem reducing agent together with corticosteroids and hydroxychloroquine (Yousefi et al., 2020). A single study in Engineering recently reported the use of favipiravir in minor cases of COVID-19. The findings of the study revealed improved viral clearance and more regular radiological improvement when compared to other interventions, such as lopinavir/ritonavir combined therapy (Jean et al., 2020; Saber-Ayad et al., 2020). 1600mg of FPV were served two times each day on the first day and 600 mg two times each day from day 2 to 14. The prescription of FPV was compared to LPV/RTV of 400 mg/100 mg two times every day and interferon-α1b 60 mg two times each day (Yousefi et al., 2020; Lu et al., 2020). Under these study conditions, favipiravir has reported a shorter viral clearance time compared to the control arm. Favipiravir also showed a lot of improvements in chest imaging when likened to the control arm. Specifically, the improvement rate was found to be 91.43% for favipiravir compared to 62.22% for the control arm. Further analysis has also revealed that favipiravir attracts certain benefits associated with faster viral clearance. The study was largely open-label and non-randomized, but its manuscript has since been removed temporarily. The fact that the article documenting these findings has since been for the time being been removed by the publisher questions the suitability of favipiravir in treating COVID-19 (Yavuz and Ünal, 2020). Despite these findings, the medication is not appropriate for use when treating pregnant women because of teratogenicity and embryotoxicity among animals, and cannot be used to treat COVID-19 in this class of patients (Yousefi et al., 2020). Still, favipiravir has been incorporated in a number of trials together with other antiviral drugs, such as lopinavir ritonavir (Yousefi et al., 2020; Lu et al., 2020).

Some studies provide a more comprehensive description of therapeutic agents that can be used against COVID-19. One study describes Favipiravir as a guanine analogue that has the potential to inhibit RdRP of RNA viruses in a discriminating manner (Lu et al., 2020). The authors quote an in vitro study that showed the power of favipiravir in inhibiting SARS-CoV-2 in Vero E6 cells. They classify favipiravir among other likely therapeutic agents, like lopinavir/ritonavir, chloroquine, remdesivir, interferon, hydroxychloroquine, and ribavirin, among others. Additional clinical trials are being carried out at the moment to determine and confirm the effectiveness of these agents in the treatment of COVID-19 (Lu et al., 2020).

A number of authors have explored the mechanism of action of favipiravir in an effort to understand its potential role in the treatment of COVID-19 (Jean and Hsueh, 2020). However, a more comprehensive description of the mechanism of action is evident in studies that examine the use of the medication on influenza patients. Some researchers have managed to evolve resistance of favipiravir by establishing an adequate size of the virus, while upholding selective pressure through constant exposure to the medication. Findings show that two mutations in the influenza A virus RNA polymerase must be joined together for strong resistance to be experienced. The primary mutation – K229R – prohibited the integration of favipiravir into the nascent Viral RNA. However, it is possible that favipiravir could demonstrate different nonmutagenic mechanisms of action. That means that the medication could operate as a chain terminator under particular circumstances. Alternatively, favipiravir could also result in long pauses as well as backtracking as evident in past studies examining the RdRP of poliovirus (Goldhill et al., 2018). Definitely, there is need for more research to ascertain whether the nonmutagenic mechanisms of the medication have an important role to play in inhibiting COVID-19 and other associated viruses.

The structural aspects of favipiravir have also been examined in recent in vitro and human studies seeking a viable treatment for COVID-19 patients. From these studies, it is clear that the antiviral activity of favipiravir reduces once purine nucleosides are present. In its mechanism of action, the prodrug first enters the cells that have been infected with the virus through endocytosis. Once in, the medication activates into favipiravir ribufuranosyl phosphates. Phosphoribosylation and phosphorylation play a key role to facilitate this process. The antiviral activity starts when the medication starts to discretely target the conservative catalytic domain of RNA-dependent RNA polymerase, by this means interfering with the process of nucleotide incorporation which happens during biological replication.
of RNA. The interference in the RNA replication process causes an upsurge in the number and regularity of transition mutations. Besides, the dysregulation in the replication of viral RNA causes the replacement of “guanine (G) by adenine (A), and cytosine (C) by thymine (T) or C by Uracil (U).” The replacement process instigates destructive mutagenesis in the RNA viruses. As of April 2020, there were close to eight current clinical trials being carried out in China and two others being run in Japan. The purpose of these clinical trials is to identify the usefulness of favipiravir in the treatment of SARS-CoV-2 (Wu et al., 2020).

Recent research data has also shown that cardiac comorbidities happen commonly among patients diagnosed with COVID-19. Emerging data shows that 19-33% of patients hospitalized with the disease experience contemporaneous cardiac injury. Patients with such cases may experience acute systemic inflammatory responses, hypoxia or microthrombi resulting in microvascular damage, and direct injury developing from severe SARS-CoV-2. Such patients stand an increased chance of succumbing to death. What’s more, it is not possible to fully exclude acute effects from pharmacotherapy. SARS-CoV-2 infection may also cause concomitant injuries to the heart, which can increase the risk of serious events from drugs that are generally considered safe. This could explain why some studies have reported prolonged QT interval as a result of using favipiravir (Naksuk et al., 2020). For instance, a recent study investigated the use of Favipiravir in the Ebolavirus that mostly affected West Africa (Chinello et al., 2017). The outcome of the study confirmed the prolongation of QTc interval during favipiravir therapy in an Ebolavirus patient. Until now, it is not yet clear from the study whether the occurrence and etiology of cardiac effusion contributed to the prolonged QTc in the patient. What is clear is that the prolonged QTc was noticed three days before the cardiac effusion was detected (Chinello et al., 2017).

Apart from cardiac comorbidities, patients with COVID-19 have many other concerns. These may include renal and hepatic dysfunction, drug-drug interaction, and availability of few resources to facilitate the monitoring of heart conditions. Because of these concerns, hospitals and clinics must establish the right administrative protocols before they can consider using favipiravir in the treatment of COVID-19 disease (Naksuk et al., 2020).

CONCLUSION

The purpose of the review was to analyze the recent published articles about favipiravir effects in COVID-19 patients. The results suggest that favipiravir could be a suitable antiviral drug against COVID-19. The medication’s mechanism of action relies on RNA chain termination and error catastrophe. However, it is clear from the review that most COVID-19 patients experience underlying cardiovascular disease and close to one-third of those hospitalized suffer from cardiac injury. Together, these studies support a possible role for high disease of favipiravir for future human interventions, as long as hospitals and clinics establish the right administrative protocols.

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Conflicts of Interest

Author has declared that no competing interests exist.

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