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Review Article

Use of Favipiravir Against Covid-19: A Review

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ABSTRACT

Coronavirus disease 2019 (COVID-19) emerged as a global challenge for the world healthcare community. The use of favipiravir against COVID-19 was studied in various studies but its efficacy and side effects remain uncertain. Therefore, we aimed to analyze the use of favipiravir in patients suffering from coronavirus. The literature search was done by using several databases including MEDLINE, Google Scholar, Web of Science, PubMed, and Science Direct. To ensure the credibility and accuracy of the included articles we include only those studies that were published in indexed journals. Furthermore, in this current review, we mainly include only those studies published from January 2015 to September 2021. We included all the review and research articles published in the English language. The review of currently available literature suggests the use of favipiravir showed both some utility and side effects in patients diagnosed with coronavirus-19. Moreover, the use of this antiviral drug may show a promising role in mild to moderate COVID-19 patients and it may reduce the need for prolonged hospital stay and mechanical ventilation. But there is still a need to confirm the side effects and favipiravir efficacy in the patients suffering from this fatal disease.

INTRODUCTION

In December 2019, the Coronavirus outbreak was the first report from Wuhan, China which was first reported on December 31, 2019, to the World health organization (WHO) regional office. And on 11th March 2020, it is declared a pandemic. Different actions such as restrictions on social gathering, lockdown, case detection, contact tracing, and quarantine of diagnosed patients are being used to reduce the spread of disease [1]. It was later termed as SARS-CoV-2 virus because it is similar to the severe acute respiratory syndrome coronavirus (SARS-CoVs) outbreak[2]. Coronaviruses are members of the Coronaviridae family [3]. SARS-CoV-2 is classified under the genus of beta coronaviruses [4]. There are seven species of coronavirus that can cause disease in humans. Some of them can cause only mild symptoms while some can result in serious illnesses[5]. The Coronaviruses have become one of the main reasons responsible for emerging respiratory disease outbreaks [6]. Although it is yet to be proved that SARS-CoV-2 has a probable zoonotic origin[7].To date, several studies investigated the use of favipiravir against coronavirus but the results remain uncertain thus it is the need of the hour to analyze all the published literature available that may provide us more definite conclusions.

METHODS

We searched all the relevant literature by using various databases including PubMed, Google Scholar, MEDLINE, and Science Direct till September 2021. We included both review and research studies published in the English language for the present study.

COVID-19 transmission and pathogenesis: The virus is transmitted by aerosol droplets which are produced during coughing, sneezing, or talking of an infected person. The spread can be through indirect contact with objects touched by infected persons [8]. It is enveloped, single-stranded RNA virus [9]. Coronaviruses contain structural

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proteins. Once inside the host, the virus gets attached to the cell membrane. The S protein is present on the surface of the virus[10, 11]. The current evidence suggests that the virus is mainly spread through respiratory droplets in humans [12]. It uses Angiotensin-converting enzyme 2 (ACE2) as its receptor which binds with the receptor-binding domain (RBD) of its S protein [13]. The ACE2 receptor is highly expressed in the lungs, kidneys, heart [14].

Clinical Manifestation: The incubation period of the disease is four to five days[15]. The patients suffering from COVID-19 presents with fever, cough, shortness of breath, and muscle ache [16]. In addition, vomiting, nausea, diarrhea, loss of appetite can be seen in patients affected. COVID-19 can also affect the liver which results in increased levels of alanine aminotransferase and aspartate transaminase [17]. In some cases, the body releases an increased amount of cytokines very rapidly which can lead to the death of the patient [18]. People of old age are at increased risk of mortality, whereas children are less affected[19, 20].

Therapeutic options for COVID-19: At present no specific treatment strategy is available for this virus. Suggested therapeutic strategies advice is to help relieve the symptoms and prevent any complications caused[21]. Because there is no specific treatment available it is necessary to look for an effective antiviral agent against COVID-19 and investigate its clinical outcome in detail. Another way is to check the existing treatments for the patients suffering from COVID-19infections. Different clinical trials are being conducted to check the effective treatment options.

Favipiravir: One of the anti-viral agents used against COVID-19 is favipiravir. Favipiravir is an antiviral agent developed by the Toyama Chemical Company in Japan[22]. Its mode of action is like the purine analog. It acts by inhibiting the RNA-dependent RNA polymerase (RdRp). After being administered into the human body favipiravir converts into an active form. This conversion occurs by the process of phosphoribosylation inside the cell. This active form will then act as a substrate by RdRp and inhibits the RNA polymerase activity[23].

Uses: Favipiravir is found to be effective against various RNA viruses e.g. arenavirus, bunyavirus, flavivirus, and filoviruses[24]. Favipiravir was approved as a treatment option for novel Coronavirus on 15 February 2020 in China [25]. A study has shown favipiravir results in a faster viral clearance rate in addition to improvement in chest imaging results. The same study also showed favipiravir to be more effective on COVID-19 patients as compared with lopinavir/ritonavir [26]. A study conducted in China in February 2020 showed that as compared to lopinavir/ritonavir favipiravir leads to faster viral clearance[27]. Its antiviral activity was reported against a clinical isolate SARS-CoV-2 in vitro but in increased concentration as compared to chloroquine and remdesivir [28]. Favipiravir proved to be a treatment option in another study [29]. In contrast to other studies, this drug showed no antiviral effect against this novel Corona virus[30].

Comparison with other drugs: According to a study remdesivir and chloroquine proved to be most effective among seven antiviral drugs tested. The other drugs which were investigated include favipiravir, ribavirin, penciclovir, nafamostat, and nitazoxanid. Favipiravir showed antiviral activity but at a higher concentration[28] Favipiravir was found to be more effective than arbidolin in terms of patient's recovery and take less time to relieve fever and cough[29].

Side effects: No significant effect of favipiravir on the QT/QTc interval has been documented except one study which quotes a mild elevation in QT interval in an Ebola patient[31]. An increase in blood uric acid is seen in patients receiving favipiravir medication [32]. Favipiravir also has a risk for teratogenicity [33]. Other side effects include mild diarrhea, an increase in transaminases levels, and a decrease in neutrophil count [34].

Clinical trials: Currently, approximately 28 different clinical trials are being conducted to check the efficacy of favipiravir against coronavirus disease 2019[35]. A clinical trial started by FUJIFILM Toyama Chemical Company at the end of March 2020 to check the safety and efficacy of favipiravir has entered Phase III [36]. Another clinical trial investigating favipiravir against CoVid-19 started by Glenmark pharmaceuticals in India has also entered phase three [37]. In Italy, a Phase III clinical study evaluating the efficacy and safety of this drug in COVID-19 patients is also under process[38]. In the recent report, a meta-analysis of clinical trials was performed by Hassanipour et al. and the results of this study suggested that after one week of hospitalization there is a significant improvement in the Favipiravir group as compared to the control group. But in terms of mortality, there is no significant beneficial effect in the general group of patients with moderate or mild COVID-19[39]. Similarly, in another meta-analysis research conducted by Manabe et al., the use of Favipiravir in mild to moderate COVID-19 patients exhibited significantly better viral clearance by seven days and clinical improvement within fourteen days [40]. Furthermore, a multi-center randomized study supported the promising role of Favipiravir in reducing the need for mechanical ventilation and hospital stay[41].

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CONCLUSION

Extensive human-based trials are further needed to determine the clinical effectiveness, the effective dose, time to treat the disease of favipiravir against the disease. The current clinical trials will give in detailed insight into the use of favipiravir against COVID-19. Also, favipiravir can be checked in combination with other drugs to check its synergistic effect against SARS-CoV 2.

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