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Review Article

Safety and Effectiveness of Favipiravir for Novel Coronavirus (COVID-19): A Rapid Review of Available Evidence

Mohammadreza Mobinizadeh [1], Morteza Arab-Zozani [2, *]

[1]National Institute for Health Research, Tehran University of Medical Sciences, Tehran, Iran
[2]Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran

*Corresponding author: Morteza Arab-Zozani, Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran. Email: arab.hta@gmail.com

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Abstract

Context: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared for the first time in December 2019 in Wuhan, China. Due to the lack of unified and integrated evidence for Favipiravir, this study was conducted to rapidly review the existing evidence to help evidence-based decision-making on the therapeutic potential of this drug in the treatment of COVID-19 patients.

Evidence Acquisition: This study is a rapid Health Technology Assessment (HTA). By searching pertinent databases, the research team collected relevant articles and tried to create a policy guide through a thematic approach. This rapid review was done in four steps: (1) Searching for evidence through databases; (2) screening the evidence considering eligibility criteria; (3) data extraction; and (4) analyzing the data through thematic analysis.

Results: After applying the inclusion criteria, four studies were finally found, including three review studies and a clinical trial that was temporarily removed by its publisher from the journal's website. After searching the sources mentioned in the articles, two ongoing clinical trials were found in China. Also, by searching the clinical trial website, www.clinicaltrials.gov, five clinical trials were found in the search. The result of the search in the clinical trial registration system in Iran showed a study that is in the process of patient recruitment. A limited number of other articles were found, mostly in the form of reflections from physicians or researchers and letters to editors who have predicted the drug's performance on SARS-CoV-2, which needs further clinical study to be approved.

Conclusions: With the available evidence, it is not possible to make a definite conclusion about the safety and efficacy of Favipiravir in the treatment of patients with COVID-19.

Keywords: Novel Coronavirus; COVID-19; Favipiravir

1. Context

COVID-19 appeared for the first time in December 2019 in Wuhan, China. The disease spread rapidly to countries such as Japan, South Korea, and Iran, and then to the globe such that it was declared a pandemic by the World Health Organization (WHO) (1, 2). Treatment of patients with the disease began instantly in many countries, but there is still no definitive cure for this disease. Therefore, researchers are trying to find a drug to treat the disease caused by the virus. Research has so far shown that more than 30 factors may have a potential effect on COVID-19, but there is no certainty about these treatment options, and that is why there is a need for more research and more clinical trials (3, 4).

Antiviral therapies such as interferon-alpha (IFN-α), lopinavir/ritonavir (Kaletra), chloroquine phosphate, ribavirin, and umifenovir (Arbidol) have been included in the latest version of China's guidelines for the prevention, diagnosis, and treatment of COVID-19. Although vaccination is the ultimate solution to overcome this disease, some of the above-mentioned treatments are waiting to be approved, including several broad-spectrum antivirals such as Favipiravir, remdesivir, chloroquine, and traditional Chinese herbal remedies (5-7).

Due to the lack of unified and integrated evidence for Favipiravir use, this study was conducted to rapidly review the existing evidence to help evidence-based decision-making on the therapeutic potential of Favipiravir in the treatment of COVID-19 patients.

2. Evidence Acquisition

This study is a rapid Health Technology Assessment (HTA). By searching pertinent databases, the research team collected relevant articles and tried to create a policy guide through a thematic approach. This rapid review was done in four steps: (1) Searching for evidence through databases; (2) screening the evidence considering eligibility criteria; (3) data extraction; and (4) analyzing the data through thematic analysis.

We searched several bibliographic databases, including PubMed, Cochrane library, and Google scholar using keywords including drug (Favipiravir OR Avigan) and disease (COVID-19 OR SARS-CoV-2 OR 2019-nCOV OR novel coronavirus) until 8 April 2020. We also searched the clinical trial sites (https://clinicaltrials.gov/ and https://irct.

ir) for capturing ongoing clinical trials. In addition, the references for the final articles were searched manually.

Studies that investigated the safety and effectiveness of Favipiravir in patients with COVID-19 alone and/or in comparison with other routine treatments or placebo were included in this study. Due to the limited number of studies in this field, all types of studies were included.

After reviewing the titles and abstracts, seven articles were included based on the eligibility criteria. These studies included three review studies, two commentaries, one communication article, and one clinical trial study whose full-text was temporarily removed by the publisher from the journal's website at the time of the search, but it is in the "In Press" status now. After searching the references of the final articles, the protocols of two undergoing clinical trials were also found. A search in clinical trial registry sites also revealed five studies that were in the process of patient recruitment. A study was also found on Iran's clinical trial registry site, which was a multicenter study and in the process of recruiting patients. It should be noted that other clinical trials in the country have received the permission of the National Committee for Ethics in Biomedical Research, but have not been registered in the above registry, so their details are not available.

Also, among the first seven articles, two articles were published as commentaries, which, based on the performance of this drug on other diseases, predicted its effectiveness in COVID-19. These articles are listed in the section under the heading "global predictions" and need to be confirmed by future human clinical studies.

3. Results

A summary of the included studies, along with the specifications of the clinical trials is shown in Tables 1 and 2.

Table 1. A Summary of the Characteristics of the Included Studies

Title of the Study	Publication Year	Study Design
Experimental treatment with Favipiravir for COVID-19: An Open-Label Control study (8)	2020	Randomized clinical trial
Outcome reporting from protocols of clinical trials of coronavirus disease 2019 (COVID-19): A review (9)	2020	Review
A systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS, or COVID-19: Initial assessment (10)	2020	Systematic Review
Potential therapeutic agents against COVID-19: What we know so far (11)	2020	Review
Angiotensin receptor blockers as tentative SARS-CoV-2 Therapeutics (5)	2020	Commentary
Therapeutic options for the 2019 novel coronavirus (2019-nCoV) (12)	2020	Comment
Discovering drugs to treat coronavirus disease 2019 (COVID-19) (1)	2020	Communication
Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19)	2020	Study Protocol
Randomized, open-label, controlled trial for evaluating of the efficacy and safety of baloxavir marboxil, Favipiravir, and lopinavir-ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients	2020	Study Protocol

Table 2. A Summary of the Characteristics of Registered RCTs

Trial Title	Disease	Trial Arm	Country
Clinical study to evaluate the performance and safety of Favipiravir in covid-19	COVID-19	Drug: A, Favipiravir; B, placebo	Milano, Italy
A prospective study on corona virus disease 2019 patients whose nucleic acids changed from negative to positive	COVID-19	Drug: Favipiravir	Multicenter, China
Clinical Trial of Favipiravir tablets combine with chloroquine phosphate in the treatment of novel coronavirus pneumonia	Novel coronavirus Pnuemonia	Drug: A, Favipiravir tablets + chloroquine phosphate tablets; B, Favipiravir tablets; C, placebo	Beijing, Beijing, China
Favipiravir combined with tocilizumab in the treatment of corona virus disease 2019	COVID-19	Drug: A, Favipiravir combined with tocilizumab; B, Favipiravir C, tocilizumab	Multicenter, China
Various combination of protease inhibitors, oseltamivir, Favipiravir, and hydroxychloroquine for treatment of COVID19: A randomized control trial	Coronavirus infections	Drug: Oral	Bangkok, Thailand
Evaluation of safety and efficacy of hydroxychloroquine plus Favipiravir drug regimen in comparison with hydroxychloroquine plus Kaletra on the need for intensive care unit treatment in patients with COVID-19; a randomized, multicenter, parallel groups, open-label study	COVID-19	A: Favipiravir plus hydroxychloroquine; B, Kaletra plus hydroxychloroquine	Tehran, Iran

3.1. Clinical Trial Studies

According to Table 1, the only study that examined the effectiveness of Favipiravir was conducted by Cai et al. (8) The report of this study has been made unavailable by the publisher for reasons that have not yet been mentioned. The publisher has used the term "temporarily unavailable" for this article, but at the time of writing the article, the full text of this study is in the "In Press" status. This open-label control study examined the effects of Favipiravir (FPV) versus lopinavir (LPV)/Ritonavir (RTV) for the treatment of COVID-19. The sample size for this study was 80 confirmed patients, of whom 35 were in FPV and 45 were in LPV-RTV groups. The authors concluded that FPV showed better therapeutic responses to COVID-19 in terms of disease progression and viral clearance (8).

In addition, two trials are ongoing in China. In the first study (ChiCTR2000029600), patients were classified into three arms of 30 patients. These three arms included alpha-interferon, lupinavir-ritonavir + alpha-interferon, and favipirvir + alpha-interferon. In the second study (ChiCTR2000029548), patients were classified into three arms of 10 patients. These three arms included Baloxavir-marboxil, Favipiravir, and lopinavir-ritonavir.

Also, three review studies have summarized the antiviral drugs and their ongoing clinical trials on SARS, MERS, and COVID-19. It should be noted that other studies and reports were found in our search but did not have sufficient validity due to the lack of a peer-review process.

3.2. Global Predictions

This drug can block the proliferation of RNA viruses. Approved nucleoside analogs (Favipiravir and ribavirin), as well as nucleoside analogs (remdesivir and galidesivir), may have therapeutic effects for the treatment of COVID-19 (13, 14). Nucleoside analogs in the form of adenine-guanine derivatives target RNA-dependent RNA polymerase and inhibit the viral RNA production in a wide range of RNA viruses such as the COVID-19 virus. Favipiravir is a guanine analogs that has been approved for influenza treatment, and can also be used effectively in the treatment of diseases such as Ebola. The drug has been approved for the treatment of new influenza in China since 2020, and it is currently being used in several clinical trials to treat COVID-19 (15).

In 2014, Favipiravir, under the Avigan brand, received a PMDA license in Japan to cure new flu infections (16). Due to the teratogenic effects observed in Favipiravir animal studies, this drug can be recommended only in limited cases of influenza for which other drugs are not effective (17). According to clinicaltrials.gov (https://clinicaltrials.gov), there are nine clinical trials on this drug, including five for influenza indications, three for Ebola, and one for pharmacokinetic testing for liver failure. The drug has recently been approved in China for the treatment of influenza.

4. Conclusions

Although there are several experiences from the onset of the coronavirus crisis regarding the use of various drugs, especially antiviral drugs, and their effects on the coronavirus in different countries around the world, the effect of none of these drugs in terms of side effects and final effectiveness has yet been approved. Considering that only one study has been published on the effectiveness of Favipiravir, which has been measured by the review of its counterparts, and that other studies are in early stages and their results have not yet been published, it seems that more time is needed to conclude about the success of Favipiravir in the treatment of COVID-19.

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