

Favipiravir and COVID-19: A Simplified Summary

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ABSTRACT

A recent outbreak of coronavirus disease 2019 (COVID-19) caused by the novel coronavirus designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan, China, at the end of 2019 and then spread rapidly all over the world. However, there are no specific antiviral therapies for COVID-19, using the agents which approved or in development for other viral infections is one of the potentially quickest ways to find treatment for this new viral infection. Favipiravir is an effective agent that acts as a nucleotide analog that selectively inhibits the viral RNA dependent RNA polymerase or causes lethal mutagenesis upon incorporation into the virus RNA. In view of recent studies and discussion on favipiravir, in this mini review we aimed to summarize the clinical trials studying the efficacy and safety of favipiravir in patients with COVID-19.

Introduction

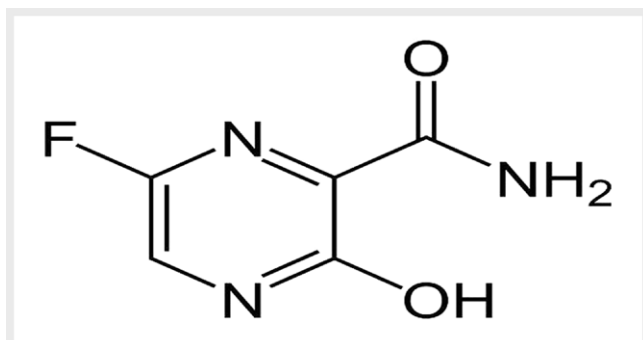
At the end of 2019, novel coronavirus pneumonia (NCP) emerged in Wuhan and had spread rapidly. The pathogen was confirmed new coronavirus, which was officially named coronavirus disease-19 (COVID-19) by the World Health Organization (WHO) [1]. The clinical characteristics of COVID-19 include fever, respiratory symptoms, dyspnea, cough and pneumonia [2–5]. Currently, there is no specific antiviral treatment for COVID-19. Therefore, identifying drug treatment options as soon as possible is critical for the response to the COVID-19 outbreak [6]. It has been revealed that SARS-CoV-2 has a genome sequence that is 75–80% identical to that of SARS-CoV, so, the existing treatment favipiravir for SARS and MERS may be helpful for developing COVID-19 therapeutics [7, 8]. Favipiravir, also known as T-705 was being developed in 2002 as an inhibitor of influenza virus replication [9]. The structures of favipiravir shown in ► **Fig. 1**. Favipiravir was approved for treatment

of novel influenza on February 15, 2020 in China [10]. This drug is currently undergoing clinic trials in treating COVID-19. Favipiravir is a type of RNA-dependent RNA polymerase (RdRp) inhibitor. It is converted by host enzymes to T-705- ribofuranosyl 5'-triphosphate and presumably acts as a nucleotide analog that selectively inhibits the viral RNA dependent RNA polymerase (► **Fig. 2**) or causes lethal mutagenesis upon incorporation into the virus RNA without cytotoxicity to mammalian cells [11–15]. Besides influenza virus [16], favipiravir has shown potent antiviral activity against other segmented negative-strand RNA viruses such as arena- and bunyaviruses in vitro and in vivo [17, 18]. In addition, favipiravir has also demonstrated activity against positive-strand RNA viruses such as noro- and flaviviruses [19, 20]. Therefore, favipiravir may have potential antiviral action on SARS-CoV-2, which is an RNA virus. It has been demonstrated that, as a prodrug, favipiravir effectively inhibits the SARSCoV- 2 infection in Vero E6 cells (ATCC-1586) [21]. On

February 14, a clinical trial on favipiravir for the treatment of COVID-19 initiated by the Clinical Medical Research Center of the National Infectious Diseases and the Third People's Hospital of Shenzhen achieved promising results. The preliminary results from a total of 80 patients (including the experimental group and the control group) indicated that favipiravir had more potent antiviral action than that of lopinavir/ritonavir. No significant adverse reactions were noted in the favipiravir treatment group, and it had significantly fewer adverse effects than the lopinavir/ritonavir group [7].

Studies of Favipiravir Conducted In Vitro

Nucleoside analogues in the form of adenine or guanine derivatives target the RNA-dependent RNA polymerase and block viral RNA synthesis in a broad spectrum of RNA viruses, including human coronaviruses. Favipiravir (T-705), a guanine analogue approved for influenza treatment, can effectively inhibit the RNA-dependent

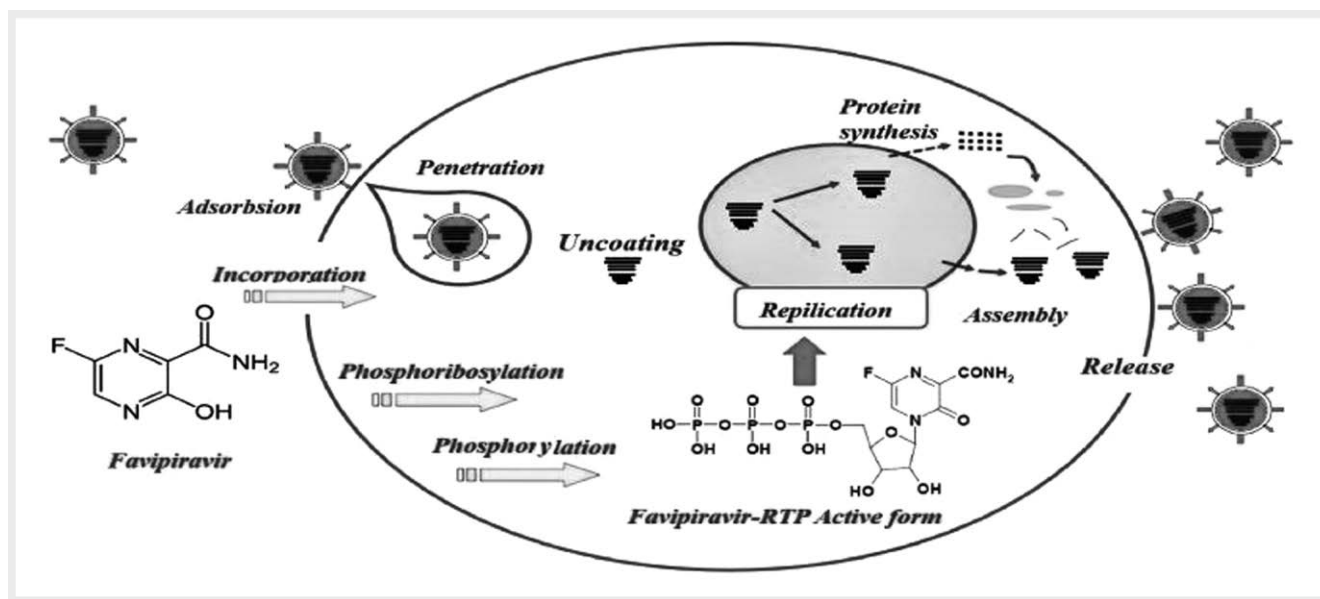


► **Fig. 1** Chemical structure of favipiravir (T-705) [16].

RNA polymerase of RNA viruses such as influenza, Ebola, yellow fever, chikungunya, norovirus and enterovirus [16], and a recent study reported its activity against 2019-novel corona virus. Chinese researchers who studied the effect of favipiravir in vitro (using Vero E6 cell line infected by SARS-CoV-2) found favipiravir to be effective in reducing viral replication (half-maximal effective concentration (EC50) = 61.88 μ M, half-cytotoxic concentration (CC50) > 400 μ M, selectivity index (SI) > 6.46) [21].

Clinical Trials

At least 18 different clinical trials for SARS-CoV-2 already registered in the Chinese Clinical Trial Registry (ChiCTR) and the International Clinical Trials Registry Platform (WHO ICTRP) propose to use favipiravir in the treatment of COVID-19 (► **Table 1**). For example, patients with 2019-nCoV are being recruited in randomized trials to evaluate the efficacy of favipiravir plus interferon- α (ChiCTR2000029600), favipiravir plus baloxavir marboxil (an approved influenza inhibitor targeting the cap-dependent endonuclease) (ChiCTR2000029544) and favipiravir plus Chloroquine Phosphate (ChiCTR2000030987). In a recent publication, Cai and colleagues found that favipiravir showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance indicate. They investigated the effect of favipiravir versus Lopinavir/Ritonavir on the treatment of COVID-19. They reported that favipiravir was independently associated with faster viral clearance and a higher improvement rate in chest imaging. Their findings suggested that favipiravir has significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance, as compared with Lopinavir/Ritonavir [7]. In the recent study Chen and colleagues compare the efficacy and safety of favipiravir and arbidol to treat COVID-19 patients on clinical recovery rate of day



► **Fig. 2** Schematic representation of the activation mechanism of favipiravir (Based on Furuta et al. [22]). Favipiravir is incorporated into cells and converted to favipiravir ribofuranosyl phosphates by host cell enzymes. The triphosphate form, favipiravir-RTP, inhibits the influenza viral RNA polymerase activity.

► **Table 1** Characteristics of clinical trials studying the efficacy and safety of favipiravir in patients with new coronavirus pneumonia (COVID-19).

| ID | Public title | Country | Recruiting Status | Type | Registration time |
|------------------------|---|--------------------|------------------------|----------------|-------------------|
| ChiCTR2000029544 | A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in novel coronavirus pneumonia (COVID-19) patients who are still positive on virus detection under the current antiviral therapy | China | Pending | Interventional | 2020/02/03 |
| ChiCTR2000029548 | 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 | China | Pending | Interventional | 2020/02/04 |
| ChiCTR2000029600 | Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) | China | Recruiting | Interventional | 2020/02/06 |
| ChiCTR2000030113 | Randomized controlled trial for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) with poorly responsive ritonavir/ritonavir | China | Recruiting | Interventional | 2020/02/23 |
| ChiCTR2000030254 | the Efficacy and Safety of Favipiravir for novel coronavirus-infected pneumonia: A multicenter, randomized, open, positive, parallel-controlled clinical study | China | Completed | Interventional | 2020/02/26 |
| ChiCTR2000030894 | Favipiravir Combined with Tocilizumab in the Treatment of novel coronavirus pneumonia (COVID-19) - A Multicenter, Randomized, Controlled Trial | China | Recruiting | Interventional | 2020/03/16 |
| ChiCTR2000030987 | A Randomized Controlled Trial for Favipiravir Tablets Combine with Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia (COVID-19) | China | Recruiting | Interventional | 2020/03/20 |
| ChiCTR2000033491 | Oral Favipiravir for Patients with Delayed SARS-Cov-2 viral RNA Clearance | China | Completed | Interventional | 2020/06/02 |
| EUCTR2020-001528-32-IT | Adaptive Randomized trial for therapy of Corona virus disease 2019 at home with oral antivirals | Italy | Recruiting | Interventional | 24/06/2020 |
| NCT04464408 | Favipiravir Therapy in Adults with Mild COVID-19 | Saudi Arabia | Not yet recruiting | Interventional | 28/06/2020 |
| JPRN-jRCTs041200025 | Phase II trial of combination therapy with favipiravir and corticosteroids for COVID-19 | Japan | Recruiting | Interventional | 01/07/2020 |
| EUCTR2020-002106-68-GB | FLARE: Favipiravir ± Lopinavir: A RCT of Early antivirals | United Kingdom | ongoing | interventional | 07/07/2020 |
| IRCT20150107020592N30 | Prophylactic Favipiravir for Healthcare Workers in COVID-19 Pandemic | Iran | Recruiting | interventional | 10/07/2020 |
| NCT04471662 | Nelfinavir and Favipiravir Combination in Newly Diagnosed COVID19 Egyptian Patients | Egypt | Not yet recruiting | Interventional | 13/07/2020 |
| NCT04474457 | Efficacy and Safety of Favipiravir in the Treatment of COVID-19 Patients Over 15 Years of Age | Turkey | Recruiting | Observational | 15/07/2020 |
| NCT04475991 | Safety and Efficacy of Maraviroc and/or Favipiravir vs Currently Used Therapy in Severe COVID-19 Adults | Mexico | Not yet recruiting | Interventional | 15/07/2020 |
| NCT04478448 | Bioequivalence Study of Favipiravir From Flupirava 200 mg Tablet (European Egyptian Pharmaceutical Industries, Egypt) Versus Avigan 200 mg Tablets (Man. by Toyama Chemical Co., Ltd Japan) | Egypt | Recruiting | Interventional | 16/07/2020 |
| NCT04501783 | Study of Efficacy and Safety of TL-FVP-t vs. SOC in Patients with Mild to Moderate COVID-19 | Russian Federation | Active, not recruiting | Interventional | 05/08/2020 |

7. 120 patients were assigned to favipiravir group (116 assessed) and 120 to arbidol group (120 assessed). In full analysis set (FAS) cohort, for moderate patients with COVID-19, clinical recovery rate of day 7 was 55.86% in the arbidol group and 71.43% in the favipiravir group ($P = 0.0199$). For moderate COVID-19 patients and COVID-19 patients with hypertension and/or diabetes, the latency to fever reduction and cough relief in favipiravir group was significantly shorter than that in arbidol group (both $P < 0.001$), but there was no statistical difference was observed of auxiliary oxygen therapy or noninvasive mechanical ventilation rate (both $P > 0.05$) [23].

Discussion

The covid-19 has spread rapidly since its recent identification in patients with severe pneumonia in Wuhan, China. Currently, there is no specific antiviral treatment for COVID-19. Therefore, identifying drug treatment options as soon as possible is critical for the response to the COVID-19 outbreak [10, 24]. One of the potentially quickest ways to find treatment is to test substances already approved or in development for other viral infections. Favipiravir was discovered by chemical modification of a pyrazine analog initially screened by in vitro anti-influenza virus activity in cells [22]. Favipiravir is a selective and potent inhibitor of influenza viral RNA polymerase [25] and effective against all subtypes and strains of influenza viruses including ones sensitive or resistant to marketed neuraminidase and M2 inhibitors [26]. Favipiravir demonstrated anti-viral activities against other RNA viruses [27]. These data clearly suggest that favipiravir is a promising drug for the treatment of infections by not only influenza virus but also a wide range of RNA viruses. The research letter, written by a group of Chinese researchers, studied the effect of the influenza antiviral favipiravir in vitro, using Vero E6 cells infected by SARS-CoV-2 at a multiplicity of infection (MOI) of 0.05 demonstrated that favipiravir is effective in reducing viral replication, with half-maximal effective concentration (EC50) 61.88 μM [21]. Furthermore favipiravir, has been tested in clinical trials with Covid-19 patients in China. According to an open-label, non-randomized trial the results showed shorter viral clearance time than the control group that received lopinavir/ritonavir [7]. In addition another multicenter, open-labelled clinical trial reported that in moderate COVID-19 patients untreated with antiviral previously, favipiravir can be considered as a preferred treatment because of the higher clinical recovery rate of day 7 and more effectively reduced incidence of fever, cough besides some manageable antiviral-associated adverse effects [23]. However, data of the above studies indicate the efficacy of favipiravir, we need to wait for more clinically valid evidence to confirm the positive value of this antiviral agent for COVID-19 treatment. Furthermore, the adverse reactions of this drug should be kept in mind. In repeat-dose toxicity studies involving dogs, rats, and monkeys, notable findings after administration of oral favipiravir included: adverse effects on hematopoietic tissues such as decreased red blood cell (RBC) production, and increases in liver function parameters such as aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT) and total bilirubin, and increased vacuolization in hepatocytes. Testis toxicity was also noted [28]. Favipiravir is known to be teratogenic; therefore, administration of

favipiravir should be avoided in women if pregnancy is confirmed or suspected [25] and toxicity information regarding favipiravir in humans is not readily available so the Ministry of Health, Labor and Welfare granted conditional marketing approval with strict regulations for its production and clinical use [29].

Conclusion

Favipiravir might be crucial for ensuring an efficient treatment, decrease mortality and allow early discharge in relation to Covid-19. However more clinical studies are urgently needed to evaluate the efficacy and safety of this antiviral nucleoside for COVID-19 treatment.

Author Contributions

M Ghasemnejad-Berenji; literature review and writing the manuscript writing the original draft of the review article. S. Pashapour; literature review and revising the review article.

Conflict of Interest

The authors declare that they have no conflict of interest.

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