

Favipiravir in Covid-19

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Abstract – The SARS-Cov-2 virus, emerged in December 2019 in Wuhan, China and has now spread to all parts of the world. Many research groups are carrying out intense research on drugs and vaccines to treat or prevent Covid-19. We have outlined aspects relating to Favipiravir, in treating RNA viral infections and its potential role in controlling SARS-Cov-2 infections.

Keywords –SARS-Cov-2, Covid-19, Favipiravir, Drugs.

The SARS-Cov-2 virus, an RNA virus emerged in December 2019 in Wuhan, China and has now spread to all parts of the world [1]. As of 06th April 2020, 1,244,421 cases have been reported with 68,976 deaths. Intense research on both drugs and vaccines to treat or prevent Covid-19 is being pursued by different research groups. We have outlined aspects relating to the mechanism of action of one of these drugs, Favipiravir, in treating RNA viral infections and its potential role in controlling SARS-Cov-2 infections.

Favipiravir (Trade name: Avigan) was developed by the Fujifilm Toyama Chemical Company and is licenced in Japan and China. It selectively inhibits RNA dependant RNA polymerase (RdRP), an enzyme needed for RNA viral replication within human cells. It functions as a purine analogue and is incorporated instead of guanine and adenine. The incorporation of a single molecule of Favipiravir terminates the elongation of viral RNA. The drug is converted intracellularly into its active phosphorylated form and is then recognised as a substrate by viral RdRP. It has a broad spectrum of activity towards RNA viruses (Influenza, Rhino, and Respiratory Syncytial Virus etc) but not against DNA viruses (such as Herpes) [2].

In 2014, Favipiravir was approved in Japan for use in the event of an outbreak of novel or re-emerging influenza viral infections, where other influenza antiviral drugs are either not or insufficiently effective. So far its production and distribution have been regulated by the Japanese Department of Health and the drug is not routinely available in pharmacies or hospitals. The Japanese and Taiwanese governments have built a stockpile of this medicine, with Japan having doses sufficient for two million persons. The drug is found to be well tolerated in healthy volunteers and in influenza virus infected patients. It is contraindicated for use in pregnancy because of teratogenic and embryotoxic effects noted in animals. An important feature is the lack of generation of resistance to Favipiravir among influenza viruses.

In Influenza, the beneficial effect has been attributed to a decrease in pulmonary viral load and TNF-alpha levels in the airways [3]. It was used for the post-exposure prophylaxis and treatment of patients with Ebola virus infections [4] and has also been used to treat humans with Lassa fever [5], Rabies [6] and Norovirus infections [7]. The approved Favipiravir dose for influenza in Japan is 1600mg twice daily on day 1 and 600mg twice daily for four more

days. For Ebola virus infection the dose is 6000mg on the first day and 2400mg for nine more days.

Wang et al [8] evaluated the antiviral efficiency of seven drugs (ribavirin, peniciclovir, nitazoxanide, nafamostat, chloroquine, remdesvir and favipiravir) against a clinical isolate of SARS-Cov-2 *in vitro*. High concentrations of Ribavirin, Peniciclovir and Famciclovir [Half maximal effective concentration (EC50) = 61.8 micromol/L, half cytotoxic concentration (CC50) >400 microM, selectivity index (SI) > 6.46] were required to reduce SARS-Cov-2 infection of Vero E6 cells (ATCC-1586) *in vitro*.

A few weeks ago, an official from the Science and Technology Ministry in China, stated that Favipiravir was clearly effective in the treatment of Covid-19. At this news briefing, it was stated that clinicians in Shenzhen had found patients taking Favipiravir to clear coronavirus RNA after a median of four days. The clearance period in the control group was 11 days.

Cai et al [9] examined the effects of Favipiravir vs Lopinavir/ritonavir for the treatment of Covid-19 in a non-randomised clinical trial. Thirty-five patients were treated with Favipiravir (Day 1: 1600mg twice daily; Days 2 – 14: 600mg twice daily) and 45 patients were treated with Lopinavir/ritonavir (Days 1-14: 400mg/100mg twice daily) and followed up to day 14 after treatment. They found Favipiravir to be independently associated with faster viral clearance and higher rates of improvement in chest imaging. Adverse effects from Favipiravir were rare and tolerable and none of the patients had to discontinue the medication.

Recently, Chen et al [10] carried out a prospective multicentre open labelled randomised superiority clinical trial of Favipiravir (116 patients) vs Umifenovir (120 patients) for Covid-19 patients in Wuhan, China. They found that in patients with moderate Covid-19 infections (who had not received any prior antivirals), Favipiravir showed superior efficacy in terms of the rate of clinical recovery at day 7 and a reduced the incidence of fever and cough. The clinical recovery rate at day 7 was 55.8% in the Umifenovir group and 71.4% in the Favipiravir group. All patients were eighteen years or older and the dose of Favipiravir used was 1600mg twice daily on day 1 and then 600mg twice daily for a further seven to ten days. The adverse effect profile of Favipiravir was reported as manageable.

Several other clinical trials of Favipiravir in Covid-19 patients have already started (ChiCTR2000029544, ChiCTR2000029548, ChiCTR2000029996,

ChiCTR2000030113, NCT04273763, NCT04310228). Some of the trials are using Favipiravir in combination with other antiviral or anti-inflammatory agents. The Fujifilm Toyama Company has increased production of this medication in collaboration with its national and international partners and announced a phase III clinical trial to evaluate its safety and efficacy in patients with Covid-19. A number of studies are still recruiting patients and further results on the use of Favipiravir in Covid-19 patients are expected to be released in May and June 2020. These results should help further clarify the role of Favipiravir in the treatment of Covid-19 patients.

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